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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)

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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.*

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ORIGINAL ARTICLE

Case Control Study

Resting energy expenditure in cirrhotic patients with and without hepatocellular carcinoma

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Abstract

BACKGROUND

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

AIM

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

METHODS

This is a prospective observational study evaluating the REE of 118 patients, 33 with cirrhosis and hepatocellular carcinoma and a control group of 85 patients

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).

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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.

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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-

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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.

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ORIGINAL ARTICLE

Case Control Study

Increased colon transit time and faecal load in irritable bowel syndrome

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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

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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.

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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).

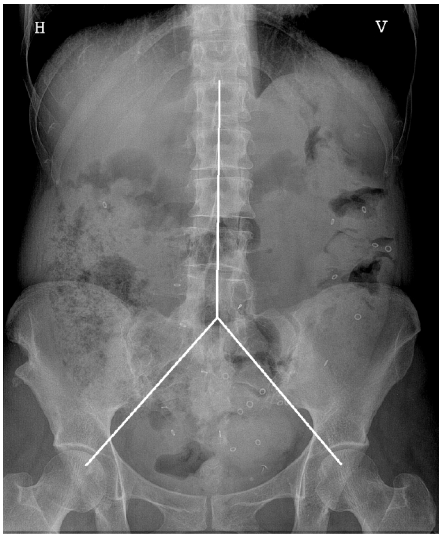

Figure 1 Colon transit study in an irritable bowel syndrome patient. Patient ingested 24 markers, and an X-ray was acquired at 48 h. From the X-ray, we counted the number of markers in each segment: 2 + 8 + 10 = 20; faecal load score: 2 + 2 + 1 = 5 (see text).

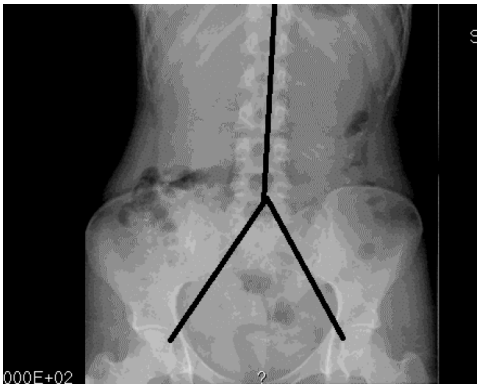

Figure 2 Colon transit study in a healthy control. Subjects ingested the 24 markers for 6 d, and an X-ray was acquired on day 7. From the X-ray we counted the number of markers in each segment: 11 + 6 + 1 = 18; faecal load score: 2 + 1 + 1 = 4 (see text).

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.

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ORIGINAL ARTICLE

Retrospective Study

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

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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

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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.

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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.

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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.

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ORIGINAL ARTICLE

Retrospective Study

Histopathological evaluation of long-term tenofovir disoproxil fumarate treatment in patients with hepatitis be antigen-negative chronic hepatitis B

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Institutional review board statement: This retrospective study was organised in accordance with the Helsinki Declaration. Local ethics committee approval was obtained (No. 11.03.2020-52/756).

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Abstract

BACKGROUND

Hepatitis B virus is a universal health problem. There are approximately 250 million people living with hepatitis B worldwide, and approximately 600000 of these people die every year due to the virus.

AIM

To compare the pretreatment and post-treatment histopathological results of patients with hepatitis be antigen (HBeAg)-negative chronic hepatitis B (CHB) who had been receiving tenofovir disoproxil fumarate (TDF) treatment at our clinic for at least 5 years.

METHODS

Patients with HBeAg-negative CHB who were being treated with TDF (245 mg/d) were included in the study. Liver biopsies of patients before TDF treatment and liver biopsies after 5 years of TDF treatment were retrospectively compared.

RESULTS

A total of 50 HBeAg-negative CHB patients were included in the study (mean age: 47.9 ± 10.4 years, men: 27.54%). Histological improvement was observed in 78% (39) of the patients after 5 years of treatment. After the 5 years of treatment, the mean Ishak score of the patients was 1.3 ± 1.3, and the mean histologic activity index score was 4.1 ± 2.8. A 1.53 point reduction in Ishak fibrosis score was detected after long-term TDF treatment.

CONCLUSION

Liver biopsies after 5 years of TDF treatment revealed a significant histological response and a regression of the necroinflammatory score compared to pretreatment liver biopsies. To better understand the effects of antiviral treatments on the improvement of liver histology, long-term studies involving larger numbers of patients are needed.

Key Words: Hepatitis B; Tenofovir; Chronic hepatitis; Biopsy; Liver; Fibrosis

Core Tip: Hepatitis B virus is a universal health problem. There are approximately 250 million people living with hepatitis B worldwide, and approximately 600000 of these people die every year due to the virus. Viral suppression with treatment can also lead to histological healing. In the current study, we aimed to compare the pretreatment and post-treatment histopathological results of patients with hepatitis be antigen-negative chronic hepatitis B who have been receiving tenofovir disoproxil fumarate (TDF) treatment at our clinic for at least 5 years. Liver biopsies after 5 years of TDF treatment revealed a significant histological response and a regression of the necroinflammatory score compared to pretreatment liver biopsies.

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INTRODUCTION

Hepatitis B virus (HBV) is a universal health problem. There are approximately 250 million people living with hepatitis B worldwide, and approximately 600000 of these people die every year due to the virus. The treatment of chronic HBV infection depends on many factors including clinical variables (*e.g.*, liver inflammation and/or the presence or absence of cirrhosis), the patient's immunological response to infection [*e.g.*, hepatitis be antigen (HBeAg) status], risk factors for the rapid progression of the disease (*e.g.*, age > 40 and family history of hepatocellular carcinoma), and virological factors (*e.g.*, HBV viral load and genotype). Treatment strategies for chronic hepatitis B (CHB) typically include pegylated interferon or nucleos(t)ide analogues (*e.g.*, entecavir and tenofovir). Interferon is recommended primarily for young patients with compensated liver disease who do not want to undergo long-term treatment[1-4].

For HBeAg-negative CHB patients, the predicted response to treatment is less accurate. Treatment should be started immediately after the diagnosis of HBeAg-negative CHB, because untreated spontaneous remission is rarely seen in this group. The aim of treatment in patients with CHB is to reduce the mortality and morbidity associated with the disease and to increase the quality of life and the lifetime of the patient by preventing complications such as cirrhosis, liver failure and hepatocellular carcinoma that may occur with the progression of the disease. The main goal in therapy is to achieve the long-term suppression of HBV deoxyribonucleic acid (DNA) replication. Viral suppression with treatment can also lead to histological healing. Recent studies have found histological improvements in sexually transmitted disease patients who received antiviral therapy[2-9].

In the current study, we aimed to compare the pretreatment and post-treatment histopathological results of patients with HBeAg-negative CHB who have been receiving tenofovir disoproxil fumarate (TDF) treatment at our clinic for at least 5 years.

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MATERIALS AND METHODS

Study design and patient population

Patients with HBeAg-negative CHB who received TDF treatment (245 mg/d) were included in this study. Patients were included in the study if they were over 18 years, had received antiviral treatment for at least 5 years, came to the outpatient control regularly, underwent liver biopsy before and after treatment, and had available laboratory parameters. Patients were excluded if they were HBeAg-positive, were previously treated with interferon or another antiviral, had a treatment incompatibility, or had been receiving treatment for less than 5 years. Patients were also excluded in cases of human immunodeficiency virus, hepatitis C or hepatitis D co-infection were detected. Elecsys instrument (Roche Diagnostics, Italy) was used to detect HBsAg, anti-HBs, HBeAg and anti-HBe. The real-time polymerase chain reaction AmpliPrep/COBAS TaqMan HBV test 2.0 (Roche Molecular Systems, NJ, United States) was used to quantify HBV DNA. Liver biopsies of patients were evaluated by an experienced pathologist.

Definitions of treatment responses

In our hospital, patients are followed up in the hepatology outpatient clinic according to the 2017 hepatitis B European Association for the Study of the Liver guidelines. According to these guidelines, a decrease in necroinflammatory activity [indicated by a ≥ 2 point decrease in the histologic activity index (HAI) or in the Ishak system] without worsening fibrosis compared to the pretreatment histological findings is determined as histological response. The virological response in patients who receive NA treatment is defined as undetectable by a sensitive polymerase chain reaction assay when HBV DNA is below the 10 IU/mL limit of detection. Serological responses for HBsAg are HBsAg loss and the development of anti-HBs. Normalisation of alanine aminotransferase (ALT) levels based on the ULN (40 IU/L) is determined as biochemical response.

Statistical analysis

The data are presented as the mean, median, standard deviation and percentage. All analysis was performed using IBM Statistic Package for Social Science Statistics, V.20.0 (IBM Corp., Armonk, NY, United States). The Kolmogorov–Smirnov test was used to assess normality of quantitative variables. Differences in the variables pre and post treatment were analysed by the Wilcoxon test within groups. All tests were two-tailed, and $P < 0.05$ was considered to be statistically significant.

Ethical approval

This retrospective study was organised in accordance with the Helsinki Declaration. Local ethics committee approval was obtained (No. 11.03.2020-52/756).

RESULTS

Demographic characteristics of the study population

A total of 50 HBeAg-negative chronic HBV patients were included in the study. The demographic characteristics of the patients are presented in Table 1. The baseline mean HAI score of the patients was 7.2 ± 3.2, and the mean baseline Ishak fibrosis score was 2.2 ± 1.4. The average time from the start of treatment to liver biopsy was 60.8 ± 9.7 wk. All patients were treated with tenofovir disoproxil fumarate (245 mg/d).

Histological response

All biopsy samples were evaluated by a pathologist specialising in liver diseases. Histological improvement was observed in 78% (39) of the patients after 5 years of treatment. After 5 years of treatment, the mean Ishak score of the patients was 1.3 ± 1.3, and the mean HAI score was 4.1 ± 2.8. A 1.53 point reduction in Ishak fibrosis scores after long-term treatment was obtained. The long term treatment (60 wk) resulted in most of patients with no or minimal necroinflammation, as assessed by HAI score (Figure 1), and no or minimal fibrosis, as defined by Ishak classification (Figure 2).

Eleven patients had advanced fibrosis or cirrhosis (Ishak score ≥ 4) before the treatment. After long-term treatment, all patients demonstrated at least a 1 point reduction in the Ishak fibrosis score, with a median reduction of 2.9 points from pre-

Table 1 Demographics of the patients before and after treatment

		mean ± SD	*P* value
Age		47.9 ± 10.4	
Male		27 (54%)	
Treatment period (wk)		60.8 ± 9.7	
AST	BT	82.3 ± 218.6	< 0.001
	AT	23.7 ± 14.1	
ALT	BT	74.3 ± 118.1	< 0.001
	AT	23.7 ± 14.1	
T.Bil.	BT	0.8 ± 0.4	0.024
	AT	0.8 ± 1	
Albumin	BT	3.9 ± 0.7	> 0.5
	AT	4 ± 0.8	
Creatine	BT	1 ± 1.98	> 0.5
	AT	0.8 ± 0.2	
PLT	BT	208000 ± 55000	0.007
	AT	238000 ± 78000	
Ishak score	BT	2.2 ± 1.4	0.002
	AT	1.3 ± 1.3	
HAI score	BT	7.2 ± 3.2	< 0.001
	AT	4.1 ± 2.8	

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; PLT: Platelets; HAI: Histology activity index; BT: Before treatment; AT: After treatment.

treatment values

Virological response

At the time of post treatment biopsy, 100% of the patients (50/50) had an HBV DNA level < 300 copies/mL; therefore, genotypic testing for resistance was not performed.

Serological response

All patients were HBeAg-negative. After long-term tenofovir treatment, two of the 50 patients showed HBsAg seroconversion.

DISCUSSION

Many studies have shown a statistically significant and consistent correlation between the viral load level or viral load change and the histological grade and biochemical and serological responses over the course of chronic HBV.

With antiviral therapy, viral replication is brought under control, thereby suppressing necroinflammatory activity in the vast majority of patients. In this way, progressive liver damage is avoided, and there is a decreased risk of hepatocellular carcinoma. Untreated spontaneous recovery is rare in patients with HBeAg-negative CHB. Therefore, after the diagnosis is made, non-cirrhotic patients who meet the criteria should immediately begin treatment and continue it until HBsAg seroconversion occurs. Entecavir and tenofovir are frequently used for this treatment because of their low resistance profile. In patients with hepatitis B with cirrhosis, lifetime treatment is recommended[2-9].

According to recent studies, tenofovir and entecavir are frequently used in cirrhotic and non-cirrhotic patients with CHB, and these drugs have been shown to be safe and effective. These two molecules are frequently used owing to their low resistance

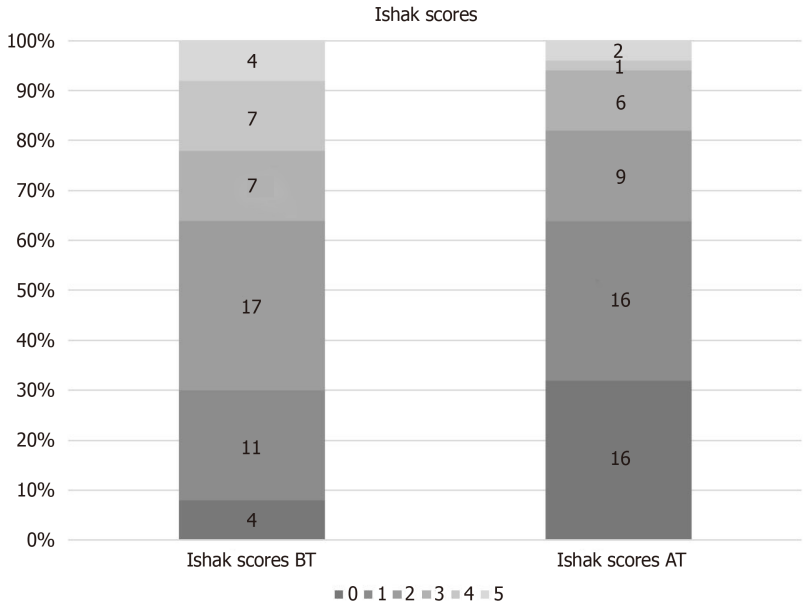

Figure 1 Ishak scores of the patients before and after treatment. BT: Before treatment; AT: After treatment.

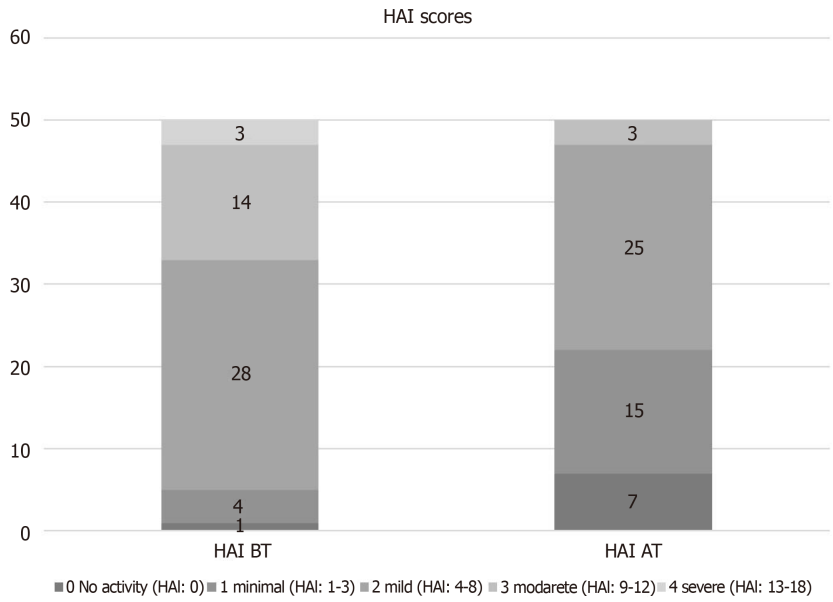

Figure 2 Histology activity index scores of the patients before and after treatment. HAI: Histologic activity index; BT: Before treatment; AT: After treatment.

profiles[9-11]. According to initial studies, tenofovir treatment results in fibrosis improvement, including cirrhosis regression, in the majority of patients. In one study, 51% of the 348 patients with paired biopsies (at baseline and at week 240) showed fibrosis regression in their follow-up biopsy. Interestingly, 71 of 96 patients (74%) with Ishak stage 5 or 6 were found to have no cirrhosis at week 240[12]. In their review, Pol *et al*[13] reported the safety and efficacy data from two real-world cohorts in the United Kingdom and Europe (362 NA-naïve patients, follow up time: 9-28 mo). In this report, virological suppression was detected in 80%-89% of patients; breakthrough was detected in 2% of patients without any corresponding resistance mutations. HBeAg seroconversion was seen in 7%-18% of patients, and HBsAg loss occurred in 2% of the European cohort. ALT normalisation was detected in 87% of patients by week 30 wk. Pan *et al*[14] reported the real-world safety and efficacy of TDF (90 Asian–American patients, 48 wk period). Ten percent of the patients had a prior treatment history with lamivudine or adefovir. The authors detected virological suppression in 82% of patients, HBeAg seroconversion was detected in 12% and ALT normalisation was

detected in 66% of the patients by the end of follow up. No TDF resistance was detected, and the treatment was considered well-tolerated. In the study conducted by Buti *et al*[15], after 5 years of tenofovir treatment, improvement in the Knodell score (≥ 1 point decrease) was found in 93.8% of cirrhotic patients and in 90.8% of non-cirrhotic patients, and no difference was found between the groups. A similar histological response with tenofovir treatment, regardless of the presence of cirrhosis, has been reported[15]. In a study, Tatar *et al*[16] reported remarkably good HBV DNA suppression, good biochemical response rate and improvement of liver necroinflammation in 52 CHB patients who were terated with TDF (The mean follow-up: 33 ± 11 mo). In accordance with these studies, our results showed HBV DNA to be negative in 100% of the patients after treatment; 38 (76%) had an improved Ishak fibrosis score, 34 (68%) had an improved necroinflammatory score (≥ 2 point improvement of HAI score), and HBsAg seroconversion was detected in 2 patients.

Some studies have reported a strong histological response and fibrosis regression in patients with advanced fibrosis/cirrhosis. In a study with patients who received tenofovir treatment for 5 years, a decline in fibrosis score was observed in 51%. The authors stated that this rate increased to 74% in patients with Ishak fibrosis scores of 5 and 6 before treatment, and histological improvement was greater than 91% in those with Ishak fibrosis scores >2[12]. In our study, 11 of the 50 patients had advanced fibrosis or cirrhosis (Ishak score ≥ 4) at baseline. After long-term tenofovir therapy, all 11 patients demonstrated at least a 1 point reduction in the Ishak fibrosis score, with a median reduction from baseline of 2.9 points.

This study is limited by its retrospective nature, which did not allow for the initial data to be diversified. Many pretreatment demographic characteristics that could affect the response to treatment could not be verified, and the effect of these factors on the treatment response could not be investigated.

CONCLUSION

Compared to the initial liver biopsies, the liver biopsies performed at least 5 years after the initiation of TDF treatment revealed a significant histological response and regression of the necroinflammatory score. These promising findings should be verified in a larger population by conducting a multicentre, prospective study.

ARTICLE HIGHLIGHTS

Research background

Hepatitis B virus is a universal health problem. There are approximately 250 million people living with hepatitis B worldwide, and approximately 600000 of these people die every year due to the virus. Viral suppression with treatment can also lead to histological healing.

Research motivation

Recent studies have found histological improvements in sexually transmitted disease patients who received antiviral therapy.

Research objectives

In the current study, we aimed to compare the pretreatment and post-treatment histopathological results of patients with hepatitis be antigen (HBeAg)-negative chronic hepatitis B (CHB) who have been receiving tenofovir disoproxil fumarate (TDF) treatment at our clinic for at least 5 years.

Research methods

Patients with HBeAg-negative CHB who were being treated with TDF (245 mg/d) were included in the study. Liver biopsies of patients before TDF treatment and liver biopsies after 5 years of TDF treatment were retrospectively compared.

Research results

A total of 50 HBeAg-negative CHB patients were included in the study (mean age: 47.9 ± 10.4 years, men: 27.54%). Histological improvement was observed in 78% (39) of the patients after 5 years of treatment. After the 5 years of treatment, the mean Ishak score

of the patients was 1.3 ± 1.3, and the mean histologic activity index score was 4.1 ± 2.8. A 1.53 point reduction in Ishak fibrosis score was detected after long-term TDF treatment.

Research conclusions

Liver biopsies after 5 years of TDF treatment revealed a significant histological response and a regression of the necroinflammatory score compared to pretreatment liver biopsies.

Research perspectives

These promising findings should be verified in a larger population by conducting a multicentre, prospective study.

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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.*

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SYSTEMATIC REVIEWS

Overview of drug induced liver injury in Brazil: What is the role of public health policy on the evidence?

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Abstract

BACKGROUND

Adverse drug reactions are responsible for increased costs and morbidity in the health system. Hepatotoxicity can be induced both by non-prescription drugs and by those used for chronic diseases. It is the main cause of safety-related drug marketing withdrawals and could be responsible for irreversible and fatal injuries.

AIM

To identify and to summarize Brazilian studies reporting the drug-induced liver injury.

METHODS

A systematic review of Brazilian studies was carried out until June 2020. It was found 32 studies, being 10 retrospective cohorts, 12 prospective cohorts, 5 cross-sectional, 3 case-control, one case series and one randomized clinical trial. In most studies were investigated tuberculosis patients followed by other infectious conditions like human immunodeficiency virus (HIV) and hepatitis C virus. The hepatotoxicity ranged from one to 57%, led by isoniazid, rifampicin, and pyrazinamide. Few studies reported algorithm to assess causality. In most studies, there were moderate outcomes and it was necessary drug interruption. However, few severe outcomes, such as chronic liver damage and liver transplantation were reported.

RESULTS

Twenty-two different criteria for hepatotoxicity were found. The great heterogeneity did not allow a meta-analysis. Standardization of parameter of drug-induced liver injury and greater effort in pharmacovigilance could contribute to learn more about drug-induced liver injury (DILI)'s epidemiology in

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Brazil.

CONCLUSION
The development of strategic public health policies seems to have an influence on the DILI scientific evidence in Brazil due to main studies are in HIV and tuberculosis line care, two strategic health policies in Brazil.

Key Words: Chemical and drug-induced liver injury; Pharmacovigilance; Pharmaco-epidemiology; Adverse effects; Infectious disease medicine; Hepatotoxicity

Core Tip: Hepatotoxicity is the main cause of safety-related drug marketing withdrawals and could be responsible for irreversible and fatal injuries. A systematic review of Brazilian studies was found 32 studies and the hepatotoxicity ranged from one to 57%, led by isoniazid, rifampicin, and pyrazinamide. Few studies reported algorithm to assess causality and twenty-two different criteria for hepatotoxicity were found. Standardization of parameter of drug-induced liver injury and greater effort in pharmacovigilance could contribute to learn more about drug-induced liver injury's epidemiology in Brazil.

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INTRODUCTION

Drug-induced liver injury, also known as drug-induced liver injury (DILI), is the main cause of discontinuation of new drug research and for their withdrawal from the market during the marketing period[1]. Some mechanisms have been described according to the drug, but these are not fully known yet[2]. Identification is a challenge due to the diversity of drugs with hepatotoxic potential, the lack of symptoms specificity, and the absence of specific biomarkers for DILI in the clinical practice[3]. In France and Iceland, incidences of 13.9/100000 and 19.1/100000 inhabitants/year were identified, respectively, in the general population[4,5]. DILI manifests itself through elevation of hepatic transaminases, in addition to alteration of hepatic function markers, and may vary from asymptomatic presentation to hepatic encephalopathy[6]. Detection is done by exclusion of other causes along with the use of a drug with hepatotoxic potential. The Russel Uclaf Causality Assessment Method (RUCAM) algorithm is the most accepted tool to aid in DILI detection[7]. Some risk factors have been described, such as gender, age, lifestyle, but the huge diversity of drugs hinders generalization; it is believed that individual characteristics, drug properties, and genetic, metabolic and immunological factors have an important impact on the development of idiosyncratic DILI[6].

Idiosyncratic reactions may occur at therapeutic doses with a latency of 5 to 90 d after the use of the drug. The drugs most commonly associated with this type of reaction are antimicrobials, with many cases for amoxicillin associated with clavulanate[5,8-10]. In prospective studies published in 2005 and 2013, the drugs most frequently related to DILI were erythromycin, sulfamethoxazole/trimethoprim, diclofenac, isoniazid, and ibuprofen[5,8,11]. When DILI is not detected early, it may progress to acute liver failure, rapidly leading to death. However, when well managed it evolves favorably with the suspension of medication and support measures for the symptoms[12]. Different treatment strategies are adopted, but with little evidence of efficacy. The use of corticosteroids has been the most frequent practice. In addition, N-acetylcysteine is used in cases of acute hepatic impairment induced by medication, but, except for paracetamol, it has limited efficacy[13]. In the presence of cholestasis, ursodeoxycholic acid and cholestyramine are reported in the management[14]. In

Japan, a compound consisting of L-cysteine, glycine and Glycyrrhiza glabra is routinely used in DILI intoxications[15]. Silymarin, used preventively along with tuberculostatics, has presented good results, but these are still preliminary[16,17]. In the most acute cases, plasma exchange, among other extracorporeal therapies, are alternatives to avoid transplantation[13,18].

The notification and diagnosis of the cases as well as the knowledge and involvement of health professionals regarding the hepatotoxicity of the drugs are of great importance for the early detection and reduction of damages to the patients affected by DILI[19-21]. In this context, this paper aims to identify Brazilian studies with data on drug-induced hepatotoxicity in order to know the profile of DILI in Brazil.

MATERIALS AND METHODS

A systematic review of published Brazilian studies of drug-induced liver injury was performed. The databases searched were PubMed, Scielo, Science Direct and the Brazilian thesis bank. The search strategy combined the descriptors for DILI with Brazil in Portuguese and English as follows: (Hepatotoxicity or drug-induced liver injury or liver injury or hepatotoxic adverse drug) and (Brasil or Brazil or Brazilian). There was no limitation by language, year of publication or study design. Other sources of access to the studies were used, such as contact with authors and references. The last search was performed in June 2020.

The eligibility of the studies was defined by the identification or suspicion of DILI due to drug or plant use and by being Brazilian studies. In order organize the results, case reports were excluded from this publication.

The selection of the studies was performed by two independent reviewers and in three sequential stages by reading the title, the abstract and the full text. A third reviewer resolved the disagreements. Data extraction are doing independently, the following variables were analyzed: Age; gender, comorbidities; local; and design; sample size; suspected drugs; HIV, tuberculosis (TB) or HCV infection; use of algorithm to support diagnosis; classification criteria for hepatotoxicity; outcomes related to DILI; frequency of DILI.

All Brazilian DILI cases reports are included. Risk of bias in individual studies aren't available and we didn't perform a summary of measures or a sensitivity or subgroup analyses.

RESULTS

Initially, 441 studies were found. After excluding case reports and duplicates and including gray literature, 32 studies were included as can be seen in Figure 1. The selected studies comprised 29 articles, 2 dissertations, and one monograph.

Table 1 presents some data from the studies included in this review. The publication date of the studies ranged from 1989 to 2015. Among the Brazilian states, Rio Grande do Sul, Rio de Janeiro and São Paulo accounted for 62% of the studies. Regarding the studied population, the average age was 37.9 years. In studies that DILI was analyzed by gender (n = 8), on average 55% of all patients who developed DILI were men.

Concerning the study design, we identified cohort studies (n = 22), 10 retrospective and 12 prospective, cross-sectional (n = 5), case-control (n = 3), case series (n = 1) studies and randomized clinical trial (n = 1). The studies were performed in outpatient (45%) and hospital settings (55%).

Analyzing the populations, 24 studies investigated patients under treatment for tuberculosis, 7 of them had patients co-infected with HIV, of which 5 had HIV and HCV. We identified studies with patients under treatment for acute myeloid leukemia (n = 2), metabolic syndrome (n = 1), colorectal cancer (n = 1), rheumatoid arthritis (n = 1), ulcerative colitis (= 1) and other unspecific severe disease (n = 1).

The main drugs associated with DILI were: Rifampicin, Isoniazid, and Pyrazinamide (RHZ), Nevirapine; Azathioprine; Fluorouracil; Methotrexate; Leflunomide; Tretinoin; Amphotericin B deoxycholate; and Propylthiouracil.

In four studies, causality algorithms were used to identify the drug responsible for hepatotoxicity. The Naranjo algorithm used generically for adverse drug reactions was used in one study[22-24]; RUCAM, used specifically in liver injury by drugs, was used in tree studies[25-27]. In addition, 22 different criteria for DILI determination were identified, categorized and summarized in Table 2.

Table 1 Summary of published Brazilian studies on drug-induced hepatotoxicity data

Ref.	Year	Place	State	Design	*n*	Class or medication	Use of algorithm	Frequency of DILI
Silva *et al*[22]	2019	Ho	BA	Cross-cut	306	MTX	No	2.0%
Alves *et al*[59]	2011	Ho	SC	Cross-cut	71	MTX/LEF	No	11.0%
Carvalho *et al*[74]	2014	A	RJ	Cross-cut	219	Azathioprine	No	2.7%
de-Medeiros *et al* [75]	1998	Ho	PR	RCT	37	Tretinoin	No	16.0%
Werner *et al*[61]	1989	Ho	SP	PC	389	Propylthiouracil	No	1.3%
Santos *et al*[63]	2013	Ho	RS	RC	185	5-Fluorouracil	No	57.8%
Uehara *et al*[76]	2005	Ho	SP	RC	12	Amphotericin B	No	30.0%
Magalhães[26]	2015	Ho	BA	Case series	31	Multiple	RUCAM	NA
Prado *et al*[27]	2019	A	BA	PC	149	Nimesulide, budesonide and valacyclovir	RUCAM	2.0%
Antonello *et al*[55]	2014	Ho	RS	PC	65	ARV	No	45.0%
Tovo *et al*[47]	2006	Ho	RS	PC	CI 385 MI 198	ARV	No	CI 57.8% MI 13.0%
Kondo *et al*[49]	2008	A	PR	RC	157	Nevirapine	No	4.0%
Gil *et al*[48]	2007	A	SP	Cross-cut	152	Tuberculostatic ARV and sulfonamides	No	19.7%
Tomich *et al*[77]	2015	Ho	SP	RC	149	Tuberculostatic, ARV among others[1]	No	22.1%
Santos *et al*[23]	2019	Ho	RJ	PC	45	Tuberculostatic	No	13.0%
Heinrich[24]	2014	A	MS	PC	100	Tuberculostatic	NARANJO	11.1%
Monteiro *et al*[25]	2012	A	RJ	PC	177	Tuberculostatic	RUCAM	33.3%
Gusmão Filho *et al* [43]	2001	Ho	PE	RC	52	RHZ/ RHE/	No	35.6%
Lima Mde *et al*[65]	2012	Ho	PE	Control case	156	RHZ and RHZE	No	26.9%
Zaverucha-do-Valle *et al*[41]	2014	A	RJ	RC	131	RHZ	No	26.7%
Coca *et al*[73]	2010	Ho	MG	Control case	162	RHZ	No	H^3 56.2% and H^4 10.4%
de Castro *et al*[44]	2010	A	RJ	PC	154	RHZ	No	19.5%
Nader *et al*[45]	2010	Ho	RS	RC	534	RHZ	No	8.8%
Vieira *et al*[78]	2008	A	SP	RC	297	RHZ	No	8.1%
de Souza *et al*[79]	1996	Ho	MG	PC	1096	RHZ	NI	6.0%
Fernandes *et al*[68]	2015	Ho	PA	PC	220	RHZ/RH	No	14.1%
Brito *et al*[64]	2014	A	RS	PC	245	RHZ/RH	No	6.1%
Schultz *et al*[46]	2014	Ho	RS	RC	69	Rifampicin	No	33.3%
Santos *et al*[53]	2013	A	PA	PC	270	Isoniazid	No	6.5%
Teixeira *et al*[52]	2011	A	RJ	Control case	167	Isoniazid	No	16.0%
Szklo *et al*[67]	2007	A	RJ	RC	40	SEO3[2]/EO9[2]	No	12.5%
Picon *et al*[66]	2002	A	RS	PC	78	SHE3[2]/HE3[2]/H3[2]	No	1.3%

[1]Sulfa drugs, statins, imidazole, anticonvulsant, nonsteroidal.
[2]Months.
H^3 transaminases > 1.25 to 2.5 × upper limits of normality.
H^4 transaminases > 2.6 to 5 × upper limits of normality. RUCAM: Causality algorithm; ARV: Antiretrovirals; MTX/LEF: Methotrexate/leflunomide; NA:

Not applicable; CI: Human immunodeficiency virus and hepatitis C coinfected; PC: Prospective cohort; RC: Retrospective cohort; MI: Monoinfected for human immunodeficiency virus; DILI: Drug-induced liver injury; RCT: Randomized clinical trial; R: Rifampicin; H: Isoniazid; Z: Pyrazinamide; S: Streptomycin; and ethambutol. O: Ofloxacin, Ho: Hospital; A: Ambulatory.

Table 2 Criteria used for the definition of liver injury

Criteria applied for liver injury definition	Ref.	Condition
Elevated ALT	Tovo *et al*[47], 2006	HIV/HCV
ALT > 2 × ULN	Monteiro *et al*[25], 2012	TB
ALT > 2.5 × ULN	Zaverucha-do-Valle *et al*[41], 2014; Kondo *et al*[49], 2008	TB/smoker; HIV
ALT > 3 × ULN	Fernandes *et al*[68], 2015; Santos *et al* [53] 2013;	TB; TB
ALT or AST > 2 × ULN	Alves *et al*[59], 2011; de Castro *et al* [44], 2010	AR; TB/HBV
ALT or AST > 3 × ULN	Heinrich[24], 2014; Vieira *et al*[78], 2008; Uehara *et al*[76] 2005	TB/ indigenous; TB; IMQ
ALT or AST > 3 × or BT > 1.5 ×	**Schultz *et al*[46]**, 2014	TB/TX
ALT > 3 × ULN; BT > 2 ×	Brito *et al*[64], 2014; Nader *et al*[45], 2010	TB/HCV
ALT or AST > 3 × ULN; BT > 2 ×	**Lima Mde *et al*[65]**, 2012; Picon *et al* [66], 2002	TB/HIV; TB
ALT ≥ 5 × LSN ou FA ≥ 2 × LSN ou ALT ≥ 3 × ULN e BT ≥ 2 × LSN	Prado *et al*[27], 2019	Gastro-hepatology conditions
(1) ALT > 3 × lower limit of normality; (2) ALT > 3 × ULN; (3) ALT > 3 × ULN and BT > 2 × ULN	Coca *et al*[73], 2010	TB/HIV
ALT or AST: (1) 1.25 a 2.5 × ULN; (2) 2.6 a 5 × ULN; (3) 5.1 a 10 × ULN; (4) > 10 × ULN	Antonello *et al*[55], 2014	HIV
ALT or AST: (1) 1.25 a 2.5 × ULN; (2) 2.6 a 5 × ULN; (3) 5.1 a 10 × ULN; (4) > 10 × ULN or BT – (1) 1.1 a 1.5 × ULN; (2) 1.6 a 2.5 × ULN; (3) 2.6 a 5.0 × ULN; (4) > 5.0 × ULN	Tomich *et al*[77], 2015	TB/HIV
Altered ALT or AST (hepatotoxicity) and ALT or AST > 5 × (hepatitis)	Gusmão Filho *et al*[43], 2001	TB/children
ALT or AST > 3 × ULN and hepatitis syndromes	Teixeira *et al*[52], 2011	TB
AST > 3 × ULN and hepatitis syndromes	Szklo *et al*[67], 2007	TB/previous liver injury
Altered ALT, AST, AP or BT	de Souza *et al*[79], 1996	TB
Increase in liver function tests	de-Medeiros *et al*[75], 1998	LMA
Histological assessments	Santos[63], 2013	QT/HPTC
AST or ALT: (1) 1.1-4.9 × ULN; (2) 5.0-9.9 × ULN; (3) 10.0-15.0 × ULN; (4) > 15.0 × ULN	Gil *et al*[48], 2007	HIV/child/adolescent
ALT > 2 times ULN or the ALT/AP ratio ≥ 5 or AP > 2 times ULN ALT/AP ratio ≤ 2 or ALT > 2 times ULN and ALT/AP ratio between 2 and 5	Magalhães[26], 2015	Several
ALT ou AST > 2 × LSN e BT > 1.3 mg/dL	Santos *et al*[23], 2019	TB
NI	Silva *et al*[22], 2019; Carvalho *et al*[74], 2014; Werner *et al*[61], 1989	IBD; Ulcerative colitis; Grave's disease

ALT: Alanine methyltransferase; ULN: Upper limits of normality; AST: Aspartate methyltransferase; BT: Total bilirubin; AP: Alkaline phosphatase; NI: Not identified; TB: Tuberculosis; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; HBV: Hepatitis B virus; IMQ: Immunosuppressed by chemotherapy; TX: Transplantation; QT: Chemotherapy; HPTC: Hepatectomy; IBD: Inflammatory bowel disease.

Concerning studies evaluating DILI-related outcomes (n = 16), only one did not require drug suspension or dose adjustment; one case progressed to chronic hepatitis and one reported the need for liver transplantation according to data presented in Table 3. A summary of the Brazilian studies and their findings is shown in Table 4.

Table 3 Main outcomes related to drug-induced liver injury in Brazilian studies

Ref.	DILI outcomes	Medications
Santos *et al*[23], 2019	6 Cases were resolved after the suspension of medications	Tuberculostatic
Magalhães[26], 2015	21 Cases were resolved after the suspension of the substance, but without the use of medications; 9 cases were resolved with the suspension of the substance associated with medications; 1 case with acute hepatic failure, requiring liver transplantation	Isoniazid, valproic acid, amitriptyline, cyclosporine, clozapine, dasatinib, imatinib, ACO, simvastatin, melphalan, and others
Antonello *et al* [55], 2014	There was no need to suspend or change the treatment	ARV
Kondo *et al* [49], 2008	7/157 Patients (4.4%) were hospitalized and, after discontinuation of Nevirapine, all presented clinical and laboratory improvement	Nevirapine
Brito *et al*[64], 2014	Changed therapeutic regimen in all who developed DILI 15/245 (6.1%)	RHZ
Lima Mde *et al* [65], 2012	Drug maintenance 26/156 (16.6%), temporary interruption 12/156 (7.7%), treatment change 11/156 (7%), suspension of medications TB 7/156 (4.5%)	RHZ, RHZE
Coca *et al*[73], 2010	Medication suspended in 7/30 (23.3%) HIV and 15/132 (11.4%) non-HIV	RHZ
Vieira *et al*[79], 2008	There was a need to modify the treatment regimen in 11/24 (45%) of the patients	RHZ
Picon *et al*[66], 2002	RHZ: 45 cases changed treatment; SHM: 1 case changed treatment	RHZ, SHM
Gusmão Filho *et al*[43], 2001	3/52 (5.76%) Required replacement of the medication. In 16/52 (30.7%) there was no need for intervention and in other 13/52 (25%) only the doses of Isoniazid and Rifampicin were changed	RHZ, RHE
de-Medeiros *et al*[75], 1998	Medication was suspended and 1/37 (2%) patient was excluded from the RCT	Tretinoin
Alves *et al*[59], 2011	Medication doses were temporarily reduced	MTX
Prado *et al*[27], 2019	The culprit drug was discontinued, and drug therapy was not necessary to resolve the problem in 3 patients	Nimesulide, budesonide, valacyclovir
Werner *et al* [61], 1989	There was clinical and laboratory Improvement with the suspension of the medication in 4/389 (1%) and 1/389 (0.25%) evolved to chronic hepatitis	Methimazole, Propylthiouracil

DILI: Drug-induced liver injury; R: Rifampicin H: Isoniazid; Z: Pyrazinamide; S: Streptomycin; and E: Ethambutol; RCT: Randomized clinical trial; MTX: Methotrexate; ARV: Antiretroviral; ACO: Oral contraceptives.

DISCUSSION

Some systematic reviews about DILI[28-31] can be found in the literature, but none in the Brazilian studies. The hepatotoxicity frequency ranged from one to 57%; however, as these studies investigate specific populations, these data do not allow to infer the frequency of DILI or to generalize the findings. The drugs with the highest number of reports were those with known hepatotoxic potential, such as isoniazid, pyrazinamide, and rifampicin, nevirapine[9].

The low incidence of DILI makes it difficult to develop prospective cohort studies, which would be more robust in verifying the causality between the drug and liver damage. In this review, one-third of the studies were prospective. The low frequency of clinical trials with hepatotoxicity data, attributed to the low number of clinical trials exclusively in the Brazilian population, is noteworthy. Clinical trials are not the best study design to assess drug safety, in addition to involving the potential of conflict of interests. Therefore, the cohort study is the ideal design for detecting ADRs, since it frequently reveals toxicities undetected in clinical trials.

Pharmacovigilance studies may be alternatives for better knowledge about DILI, but when coming from spontaneous reports they have the underreporting bias[32]. A Brazilian study found only ten cases of hepatotoxicity by herbal medicines from notification data of the regulatory agency, in a 10-year interval. Two cases developed acute liver failure and died, both of which reported the use of kava[33]. Liver transplantation was recently performed by kava in Brazil[34]. Through RUCAM it was considered probable, therefore it was possible to exclude extrinsic toxicity and contaminants after performing chemical analyses of the drug used. In this way, the

Table 4 Summarization of the Brazilian studies according to the drugs evaluated

Ref.	Drugs	Summary of Brazilian researches
Santos *et al*[23], 2019	Tuberculostatics	Patients with the *CYP2E1* variant genotype or Null GSTT1 showed higher risk of presenting DILI. Individuals with both genotypes had no increased risk compared to individuals with one genotype
Prado *et al*[27], 2019	Nimesulide, budesonide, valacyclovir	The present prospective study allowed reporting new cases of DILI in 2% outpatients. It also allowed estimating the incidence of hepatotoxicity induced by allopathic medicines, which are standardized by public healthcare authorities
Silva *et al*[22], 2019	MTX	The frequency of drug hepatotoxicity was about 2% of hepatobiliary disorders in inflammatory bowel disease patients
Fernandes *et al* [68], 2015	RHZ	An association founded between the 516 TT polymorphism and drug-induced hepatotoxicity
Tomich *et al*[77], 2015	Tuberculostatics ARV, sulfonamide drugs, statins, imidazoles anticonvulsants, non-steroidal anti-inflammatory	In HIV patients admitted to a tertiary hospital, it was found a high incidence (22.1%) of severe DILI. The use of anti-tuberculosis drugs and baseline liver injury were independent factors associated with severe DILI during a hospital stay
Magalhães[26], 2015	Various	Hepatotoxicity caused by a wide variety of medicines, plant supplies, and dietary supplements. Anti-infectives and chemotherapeutics were responsible for most reactions, in 41% and 19% of cases, respectively. There is a shortage of records in information records to evaluate the causality of reactions
Antonello *et al* [55], 2014	ARV	The coinfected patients are at an increased risk for developing hepatotoxicity, but the clinical and immunological benefits of highly active antiretroviral therapy are higher than the risk of hepatotoxicity and rarely justify discontinuation of therapy
Heinrich[24], 2014	Tuberculostatics	Age over 60 year old, the time after the start of treatment (15 d) and being indigenous (Brazilian native American) are risk factors for the development hepatotoxicity during treatment of TB
Zaverucha-do-Valle *et al*[41], 2014	RHZ	The anti-TB drugs interactions with smoking on hepatotoxicity, as well as the *NAT2* phenotype, may require adjusting therapeutic regimen dosages or alarm in case of adverse event developments
Schultz *et al*[46], 2014	Rifampin	The use of rifampin at daily doses of 600 mg or higher and lung transplantation founded to be an independent risk factor for liver toxicity in solid organ transplants recipients. Kidney transplantation appeared as a protective factor. Mortality was higher in the patients who had hepatotoxicity (43.5%), compared with those who did not
Brito *et al*[64], 2014	RHZ	Clinical (HIV, female and extrapulmonary TB) and genetic characteristics (*CYP2E1* without any mutations, having *NAT2* slow acetylator profile) are at higher risk of developing DILI in this population. Genotyping for glutathione S-transferase *GSTM1* and *GSTT1* showed no influence on drug response
Santos *et al*[53], 2013	5-fluorouracil	Patients exposed to chemotherapy have a 2.2-fold increase in the risk of developing hepatic steatosis
Santos *et al*[63], 2013	Isoniazid	Large-scale screening for *NAT2* and *CYP2E1* genotypes can prove useful in predicting the risk of adverse effects
Monteiro *et al* [25], 2012	Tuberculostatics	*GSTM1* and *GSTT1* null genotypes do not seem to play important roles in DILI in Brazilians. However, there was evidence that *GSTM1* polymorphisms were possibly related to the intensity of toxicity. Active HBV and initial high ALT could predict DILI
Lima Mde *et al* [65], 2012	RHZ, RHZE	The absence of hepatotoxicity was a protective factor against death. Coinfection with the B and C hepatitis virus and a T CD4+ cell count below 200 cells/mm^3 were independent risk factors for hepatotoxicity in these patients
Teixeira *et al* [52], 2011	Isoniazid	Slow acetylators had a higher incidence of hepatitis than intermediate/rapid acetylators. Slow acetylation status was the only independent risk factor for the occurrence of anti-TB drug-induced hepatitis during anti-TB treatment with INH-containing schemes in Brazilian individuals
Alves *et al*[59], 2011	MTX, Leflunomide	There was no difference between the elevation of aminotransferases in patients treated with MTX alone or with combined therapy
Coca *et al*[73], 2010	RHZ	Depending on the definition of drug-induced hepatitis, HIV infection may or may not be associated with hepatotoxicity. The impact that minor alterations in the definition had on the results was impressive. The emergence of new symptoms after initiating antituberculosis therapy could not be attributed to hepatotoxicity in over one-third of the cases
Nader *et al*[45], 2010	RHZ	The anti-HIV drugs and high doses of isoniazid were considered independent risk factors for hepatotoxicity due to RHZ regimen in this study. Though univariate analysis showed that anti-HCV drugs was associated with the outcome, it was not identified as an independent risk factor for hepatotoxicity related to the use of RHZ when the analysis controlled to HIV
de Castro *et al* [44], 2010	RHZ	Active HBV, indicated by the detection of surface antigen HBV, could predict hepatotoxicity, although with low precision

Vieira *et al*[78], 2008	RHZ	The frequency of adverse effects related to the treatment of tuberculosis with RHZ was 49.1% in this group of patients. However, in most cases, there was no need to modify the treatment regimen due to adverse effects
Kondo *et al*[49], 2008	Nevirapine	There was no correlation between high CD4 counts and adverse events when skin and hepatic reactions were analyzed together. However, hepatotoxicity occurred only in pregnant women with a CD4 count of ≥ 250 cells/μL
Szklo *et al*[67], 2007	SEO3/EO9	In this series of TB patients with serious liver injury, 3SEO/9EO was well tolerated, and it was effective in 85% of patients when used under routine clinical care conditions
Gil *et al*[48], 2007	tuberculostatics, ARV, sulfonamide drugs	One-fifth of patients experienced mild hepatotoxicity, attributed to antituberculosis agents and sulfonamides. Our results suggest that the ARV was well tolerated
Tovo *et al*[47], 2006	ARV	There was no difference between the groups concerning the type of ARV used, as well as cases of hepatotoxicity attributed to PI. There was no difference concerning tolerability to PI between the two groups
Picon *et al*[66], 2002	SHE3/HE3/H3	Streptomycin, isoniazid, and ethambutol regimen may be recommended as an alternative for the treatment of tuberculosis whenever the RHZ regimen cannot be indicated
de Souza *et al* [79], 1996	RHZ	Liver changes characterized as of small and medium intensity translated as pure cholestasis or hepatocanalicular hepatic reactions. Possibly Rifampicin was important in this evolution, acting as a potentiator of the actions triggered by isoniazid and pyrazinamide
Werner *et al*[61], 1989	Propylthiouracil	The adverse effects of thionamide drugs were similar in both high- and low-dose regimens. These undesirable effects demand a strict follow-up, as well as the high dose regimen for Graves' disease treatment particularly advised for patients with severe symptoms

TB: Tuberculosis; TBD: Tuberculostatic drugs HIV: Human immunodeficiency virus; DILI: Drug-induced liver injury; NAT2: N-acetyltransferase 2; MTX: Methotrexate; HCV: Hepatitis C virus; RHZ: Rifampicin, isoniazid and pyrazinamide; HBV: Hepatitis B virus; ARV: Antiretroviral; PI: Protease inhibitors; SEO3: Streptomycin, ethambutol and ofloxacin for 3 mo; SO9: Streptomycin and ofloxacin for 9 mo; SHE3: Streptomycin, isoniazid, and ethambutol for 3 mo; HE3: Isoniazid ethambutol for 3 mo; H3: Isoniazid for 3 mo.

pharmacovigilance studies associated with the appropriate technical support should be stimulated to facilitate the detection and elucidation of the cases.

The DILI studies were concentrated in the southern and southeastern regions of Brazil. In addition, most of the studies were conducted by research groups linked to academic centers. In Brazil, the continental dimension, the large population, and the great cultural diversity make it difficult to carry out a single representative study in the country. For this reason, it is important to encourage further regional studies.

Most Brazilian studies on drug-induced liver injury investigate population groups using drugs for the treatment of infection and chronic diseases–whose ambulatory therapy is provided by the Unified Health System–such as Tuberculosis, HIV, Rheumatoid Arthritis, Ulcerative Rectocolitis, and Acute Myeloid Leukemia. Public health policies like specialized care offered by these lines of care, and the clinical protocols and therapeutic guidelines are technologies that seem to be effective in the prevention and the management of these ADRs. Whereas the hepatotoxic potential is foreseen in the guidelines, a structured information technology and resources for monitoring pharmacotherapy are required for the operations of these services. The well-structured care line makes it possible to gather a large volume of data at the national level. Professional performance in the care lines also plays a role in training and research, enabling the formation of research groups. This impulse in scientific production seems to be able to influence the existing evidence at the national level.

Some risk factors were associated to DILI such as previous liver disease, immune dysfunction, diabetes, hypertension, alcohol consumption, gestation, female age, advanced age, polymedicine, dose and lipophilicity of the drug, among others[1,35,36]. The female gender was associated with the occurrence of hepatotoxicity with tuberculostatic drugs[10,37-39], but Brazilian studies, as well as in a Peruvian study[40], have shown a lower frequency of DILI in women. In the population with TB, unexpectedly, a higher prevalence of DILI was found in nonsmoking patients when compared to smokers; however, it was argued that the genetic profile of the sample could have influenced the result[41]. No further development of DILI in advanced age was found, unlike in international studies[5,10,42], but it is suggested that the specificity of the populations studied cannot be comparable. A differential factor in Brazilian studies is the frequent profile of infectious diseases. American and European studies generally present populations with chronic diseases. Therefore, the frequency of DILI related to certain drugs may change regionally according to the characteristics of the populations studied and the profile of drug use. Some authors have studied specific populations taking tuberculostatic drugs, such as Brazilian native Americans[24], children[43], hepatitis

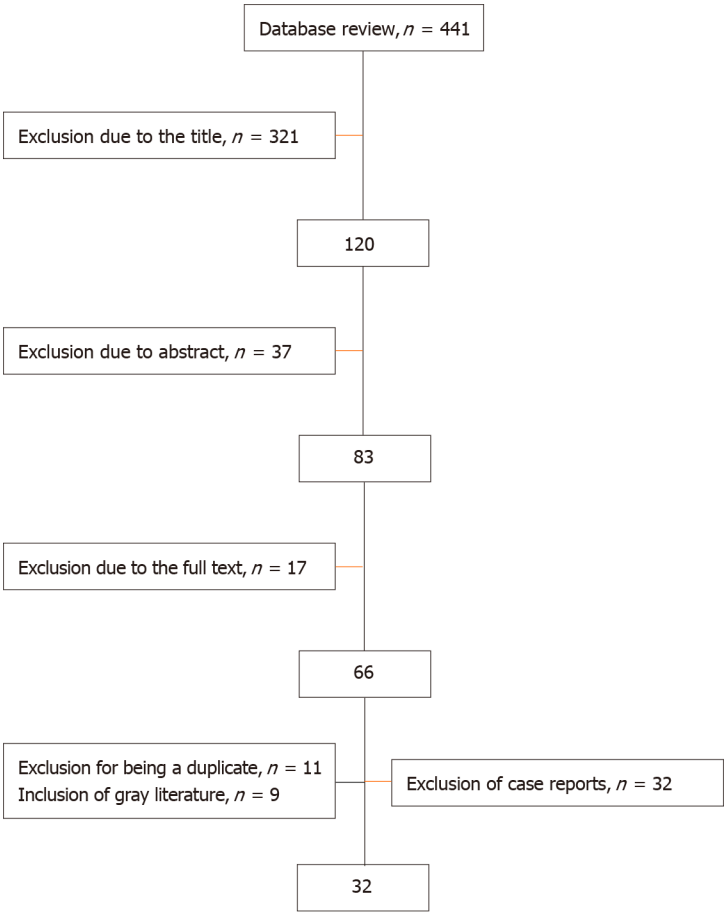

Figure 1 Flowchart of studies selection about drug-induced liver injury published in Brazil.

B[44], hepatitis C[45], solid organ transplanted patients[46], smokers[41], HCV/HIV coinfected[47], and antiretroviral (ARV) in children and adolescents[48] and nevirapine in pregnant women[49].

This review found that when patients using RHZ were analyzed the frequency ranged from 6% to 14%; however, some characteristics such as HIV infection, alcohol use, and polypharmacy were present and may have contributed to the frequency found. Some studies were developed from the analysis of drugs prescription. The DILI frequency by the drug was estimated. The number of prescriptions by a number of exposed users further the DILI frequency. In a study of hospitalized patients, the risk of developing DILI for erythromycin was 14 per 100000 prescriptions, penicillin had a risk of 10.9 per 10000 users of the drug[50]. Another study found DILI risk around 1 per 1000 users for chlorpromazine, azathioprine, and sulfasalazine[51]. Two Brazilian studies attributed RHZ hepatotoxicity more specifically to isoniazid[52,53]. In a United Kingdom study, Isoniazid, together with chlorpromazine, was associated with a DILI risk of 100/100000 users[54].

Considering the ARVs, nevirapine, abacavir, and ritonavir are the main hepatotoxic agents[47,55]. The information regarding the hepatotoxicity of ARVs is known and presented in the Brazilian clinical protocol for the management of HIV in adults. In addition, in the mentioned protocol there is a classification of the severity of hepatotoxicity according to the levels of transaminases[56,57]. In relation to TB treatment, the most reported was the basic regimen with RHZ for 2 mo, followed by Rifampicin and Isoniazid for 4 mo. Since 2009, ethambutol has been added to this treatment regimen. Known as a quadruple regimen, one tablet has all four drugs to facilitate adherence to treatment, but in the case of hepatotoxicity, there is no way to identify which drug is responsible[58]. In general, co-infection with HIV and TB seems to be one of the situations that draw the most attention to the monitoring of hepatotoxicity, since both treatments are complex and contain drugs with potential for hepatotoxicity. Both protocols emphasize the need for caution in the administration of the two concomitant therapies. Few serious outcomes were found in this review, perhaps because in most cases the suspension or change of the drug was clinically sufficient for regression of the injury. The structuring of specialized centers, the

development of clinical protocols and efficient pharmaceutical assistance seems to have been essential for the monitoring, knowledge, and management of adverse drug reactions in these patient groups.

Some studies compared different treatment regimens or combinations compared to monotherapy with drugs of known hepatotoxic potential, in order to establish a safety relation in its use. In one of the Brazilian studies of patients with rheumatoid arthritis, the use of methotrexate (MTX) or MTX associated with leflunomide had no significant difference in DILI[59]. An Argentine study in rheumatoid and psoriatic arthritis found a higher incidence of DILI in NSAIDs, whereas MTX was responsible for steatosis, but without the need to interrupt treatment[60]. Although MTX is a drug known to be hepatotoxic, it has been shown to be safe in association with leflunomide. However, monitoring of hepatic enzymes and liver function seems to be important in patients treated with other hepatotoxic drugs. In patients with Graves' disease treated in groups with propylthiouracil or methimazole at high or low doses, there was no difference in hepatotoxicity between the groups[61]. However, several cases have been reported, with the most serious cases being children and adolescents who show a frequency of acute liver failure of 1:2000 children[62]. In both studies, the safety profile for hepatotoxicity was evaluated, however, in the treatment of chronic diseases, safety should also be evaluated in the long term, in this case only cohorts with long follow-up, and pharmacovigilance studies can establish a long-term safety profile.

Amoxicillin with clavulanate leads the cases of DILI in the United States, Spain, France, and Iceland[4,5,8,42]. Drugs such as antimicrobials, non-steroidal anti-inflammatory, and other chronic medications have demonstrated a high DILI index in the world, but its prevalence of toxicity in the Brazilian population is not known[9]. However, in a case series study, anti-infective were the main hepatotoxic drugs, followed by chemotherapies[26]. Santos[63] described that patients with metastases in colorectal cancer, who underwent hepatectomy and underwent chemotherapy, had a 2.2-fold increased risk of hepatic steatosis. The most commonly reported antineoplastic drugs are immunobiological drugs, such as imatinib, and hormone antagonists, such as cyproterone and tamoxifen, but irinotecan also appears in the list of most commonly reported. However, it is hard to define the causality of antineoplastic agents when there is hepatic metastases[9].

In HIV-positive patients, HCV coinfection increased the risk of liver damage but did not justify the suspension of ARVs, as well as the use or not of protease inhibitors, which had no significant difference between monoinfected and coinfected[47,48,55,63]. In a study that evaluated the population using TBS, independent risk factors for the development of DILI were considered: age above 60 years, the first 15 d of treatment, extra pulmonary TB, HCV/HBV coinfection, CD4 count < 200 μL cells, being indigenous[28,64,65]. In a study with transplant patients, doses of rifampicin above 600 mg and lung transplantation were found to be risk factors for DILI, just as kidney transplantation seemed to act as a protective factor[46]. Two studies have demonstrated the safety of alternative TB regimens after the previous hepatotoxicity; the association of streptomycin, ofloxacin, and ethambutol for three months followed by another nine months with ofloxacin and ethambutol, and the association of streptomycin, ethambutol, and isoniazid for three months followed by ethambutol and isoniazid three months and isoniazid three months[66,67].

Some lines of Brazilian research have evaluated the genetic profile associated with the development of DILI with tuberculostatics. The *CYP2B6* gene had the 516 TT polymorphism associated with DILI[68]. Genotypes of *CYP2E1* and *CYP3A4* were not associated with hepatotoxicity; when different acetylators of NAT2 were analyzed, slow acetylators had an increased risk of DILI[41,52,64]. Another study defined the genetic profile of NAT2 and CYP2E1 as predictors of the development of adverse reactions with isoniazid[53,65]. In two studies, glutathione S transferase genotypes were not associated with the development of DILI[25,64]. Thus, it can be seen that the development of DILI has been investigated at the molecular genetics level, and Brazil has conducted important studies on the knowledge of the variants in its population.

The causality algorithms for the identification of adverse reactions are tools that help in the detection and classification of the suspicious factor probability. Only four studies reported using an algorithm. The Naranjo algorithm was one of the precursors, but its general character does not allow contemplating the specificity of DILI[69]. The RUCAM was the first and most widely used algorithm specific for DILI. Subsequently, others emerged, such as Maria and Vitorino, Drug-induced Liver Injury Network and Digestive Disease Week Japan Scale[8,51,70,71]. Algorithms are great tools for prospective data analysis. However, its validity for retrospective studies is questionable because registry biases may compromise the validity of the result[7]. The fact that there is low frequency use of these tools makes it possible to launch some

hypotheses. Are researcher's unfamiliarity regarding algorithms? Or do they think that it is hard applying them? This gap found in Brazilian studies cannot be easily answered. The use of algorithms in clinical practice is often unfeasible since they require considerable time for their application in addition to an excess of information or exams sometimes unavailable or considered unnecessary. However, in the field of research it would be very important that the algorithms were widely used tools to determine the causality of the liver injury. In addition to greater reliability of the results, would improve data quality, which would make possible to classify the liver injury and improve the knowledge of the outcomes.

Twenty-two different strategies in the definition of liver injury were found, and also made it difficult to compare the findings. HIV Research Groups consider the guideline of the AIDS Clinical Trials Group to grade the hepatic lesion according to the transaminase value range[56]. Studies with TB often follow the standards of the II Brazilian Consensus on Tuberculosis[72]. The RUCAM algorithm performs the best definition, which is the most internationally accepted standard in the determination of liver damage by drugs or plants[7].

However, in Brazil the divergences of the guidelines promoted by the public policies hinder the formation of a national database on hepatotoxicity. The concept of hepatic injury adopted is decisive in the study findings, as indicated in a study comparing three different DILI criteria in HIV patients; in these patients, DILI may be undetectable or may affect up to 77% depending on the criteria adopted[73]. This study reinforces the need for standardization of the definition of drug-induced liver injury in Brazil, also in national guideline with tools like RUCAM. The follow-up of patients undergoing treatment for chronic diseases should include the identification of adverse drug reactions and the reporting of adverse drug reactions when suspected. Monitoring of ADRs is essential to establish the safety profile of medicines during their marketing. Encouraging the use of this resource will be important to improve not only the criteria but also the definition of causality in cases of DILI[74-79].

This review had as a limitation the impossibility of inferring a frequency of DILI in Brazilian studies through meta-analysis since few of the studies found were performed aiming to determine liver injury as well as the high heterogeneity found. In this sense, all studies with hepatotoxicity data were included. The studies included with few or incomplete data could result in low quality of evidence, but due to the scarcity of Brazilian studies, we decided to maintain them. The quality of the studies included in the review was not evaluated. Due to the impossibility of performing a meta-analysis, this study aimed to have an exploratory and baseline character for future studies in the area. Retrospective studies are biased by the lack of available information, and some studies have not used criteria for the identification of drug-induced liver injury. Despite these limitations, the studies included in this review have contributed to learn more about achievements and challenges in Brazilian DILI's researches. The DILI's evidence in Brazil has been strongly influenced by public health policy. However, this relationship between health policies and evidence must be reversed with the evidence guiding public health policies.

CONCLUSION

The drugs associated with liver injury reported in the Brazilian studies were Isoniazid, Rifampicin and Pyrazinamide, Nevirapine, in addition to methotrexate, propylthiouracil, azathioprine; the Brazilian studies published on DILI investigate specific populations with chronic use of drugs, mainly tuberculostatic and antiretrovirals. These patients are included in priority health policies of care, which favors the detection of DILI and the proper management of the patient, reducing the frequency of more severe outcomes. The diversity of methods and criteria for the definition of hepatotoxicity did not allow obtaining frequency estimates. The standardization of criteria for identification of drug-induced liver injury and greater effort in pharmacovigilance could contribute to the knowledge on the injury as well as on the safety profile of drugs marketed in Brazil. This research is expected to broaden the debate to establish a solid pharmacovigilance policy and the creation of a wide national DILI monitoring network and his integration with other DILI networks. Finally, bringing together experiences and cases bringing doctors, pharmacists, industry and patients closer together.

ARTICLE HIGHLIGHTS

Research background

Drug-induced liver injury (DILI) is the main cause of safety-related drug marketing withdrawals and could increase costs and morbidity in the health system. DILI identification is a challenge due to the diversity of drugs with hepatotoxic potential, the lack of symptoms specificity, and the absence of specific biomarkers in the clinical practice.

Research motivation

Identify and summarize Brazilian studies reporting the drug-induced liver injury.

Research objectives

The aim of this study was to know the profile of DILI in Brazil. A systematic review of Brazilian DILI studies was carried out until June 2020. It was found 32 studies, being 10 retrospective cohorts, 12 prospective cohorts, 5 cross-sectional, 3 case-control, one case series and one randomized clinical trial. Tuberculosis, human immunodeficiency virus and hepatitis C virus patients were the mainly group investigated the hepatotoxicity rate ranged from one to 57%, led by isoniazid, rifampicin, and pyrazinamide. Few studies reported algorithm to assess causality Drug interruption and moderate outcomes are report in the most of studies. Severe outcomes, such as chronic liver damage and liver transplantation were reported in some studies.

Research methods

It was found 32 studies, being 10 retrospective cohorts, 12 prospective cohorts, 5 cross-sectional, 3 case-control, one case series and one randomized clinical trial. In most studies were investigated tuberculosis patients followed by other infectious conditions like human immunodeficiency virus (HIV) and hepatitis C virus. The hepatotoxicity ranged from one to 57%, led by isoniazid, rifampicin, and pyrazinamide. Few studies reported algorithm to assess causality. In most studies, there were moderate outcomes and it was necessary drug interruption. However, few severe outcomes, such as chronic liver damage and liver transplantation were reported.

Research results

DILI could be caused both by non-prescription drugs and by those used for chronic diseases. The diagnosis and notification of the DILI cases are of great importance for the early detection and reduction of damages to the patients.

Research conclusions

Twenty-two different criteria for hepatotoxicity were found. Standardization of parameter of drug-induced liver injury and greater effort in pharmacovigilance could contribute to learn more about DILI's epidemiology in Brazil.

Research perspectives

This research is expected to broaden the debate to establish a solid pharmacovigilance policy and the creation of a wide national DILI monitoring network and his integration with other DILI networks. Finally, bringing together experiences and cases bringing doctors, pharmacists, industry and patients closer together.

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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.

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REVIEW

Advances in treatment and prevention of hepatitis B

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Abstract

Chronic hepatitis B (CHB) continues to contribute to worldwide morbidity and mortality significantly. Scientists, clinicians, pharmaceutical companies, and health organizations have dedicated substantial Intellectual and monetary resources to finding a cure, increasing immunization rates, and reducing the global burden of CHB. National and international health-related organizations including the center for disease control, the national institute of health, the American Association for the study of liver disease (AASLD), The European association for the study of the Liver (EASL), The Asia Pacific association for the study of the Liver (APASL) and the world health organization release periodic recommendations for disease prevention and treatment. Our review of the most recent guidelines by EASL, AASLD, APASL, and Taiwan Association for the Study of the Liver revealed that an overwhelming majority of cited studies were published before 2018. We reviewed Hepatitis B-related literature published 2018 onwards to identify recent developments and current barriers that will likely direct future efforts towards eradicating hepatitis B. The breakthrough in our understanding of the hepatitis B virus life cycle and resulting drug development is encouraging with significant room for further progress. Data from high-risk populations, most vulnerable to the devastating effects of hepatitis B infection and reactivation remain sparse. Utilization of systems approach, optimization of experimental models, identification and validation of next-generation biomarkers, and precise modulation of the human immune response will be critical for future innovation. Within the foreseeable future, new treatments will likely complement conventional therapies rather than replace them. Most Importantly, pragmatic management of CHB related population health challenges must be prioritized to

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produce real-world results.

Key Words: Chronic hepatitis B; Hepatitis B virus; Hepatitis B prevention; Hepatitis B treatment; Hepatitis B vaccination; Hepatitis B reactivation

Core Tip: Given the hepatitis B viral life cycle's unique characteristics, a true cure is lacking. Most recent guidelines from multiple societies including the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, Asia Pacific Association for the Study of the Liver, and Taiwan Association for the Study of the Liver, primarily include data published before 2018. A significant amount of hepatitis B relevant literature has been published since 2018. Our manuscript aims to review the recent literature for new developments and to identify the global strategies and knowledge gaps that will soon shape the scientific endeavor in this field.

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INTRODUCTION

Hepatitis B virus (HBV) has infected humans for at least the past 40000 years[1] and is the 10th leading global cause of death[2]. HBV is the only DNA-based hepatotropic virus that exerts many adverse effects on the infected cells leading to necroinflammation, fibrosis, and carcinogenesis[3]. The world health organization (WHO), in 2015 has estimated 257 million people infected with chronic hepatitis B (CHB), while 887000 died from complications of hepatitis B[4]. Worldwide approximately only 10% of the patients with CHB are aware of the infection. A better understanding of hepatitis B biology, laboratory tests, and the immunological response has helped us develop vaccines and nucleoside/nucleotide analogs (NAs) to reduce new infection rates and achieve virologic suppression[5]. An overwhelming majority of studies cited in the most recent guidelines from various societies were published before 2018[6-10]. Our manuscript aims to review the recent literature for new developments and to identify the global strategies and knowledge gaps that will soon shape the scientific endeavor in this field.

METHODS

Literature search: We conducted online electronic searches (published human clinical trials in English) of the National Library of Medicine (Bethesda, MD, United States) MEDLINE database, Cochrane Library, and manual searches of selected specialty journals to identify any pertinent literature. We searched three MEDLINE databases (Ovid, PubMed, and EMBASE) using the following keywords hepatitis B, prevention of hepatitis B, hepatitis B and co-infection, management of hepatitis, hepatitis B and transplantation, hepatitis B mortality, hepatitis B vaccination, hepatitis B reactivation, systematic review for hepatitis B, meta-analysis and hepatitis B. The references of articles were reviewed for additional articles.

Inclusion criteria: Articles describing original research and high-quality review articles published within the last three years were selected. The search was focused on hepatitis B articles published in 2018 or later.

Exclusion criteria: Articles that did not contribute significantly to research and scientific knowledge after 2018 were excluded.

ADVANCES IN TREATMENT AND PREVENTION OF HEPATITIS B

Serological markers for hepatitis B infection

The serologic patterns of chronic HBV infection are varied and complex. Antigens and antibodies associated with HBV infection include hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs), hepatitis B core antigen (HBcAg) and antibody to HBcAg (anti-HBc), and hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe). Testing also can be performed to assess the presence and concentration of circulating HBV DNA. At least one serologic marker is present during each of the different phases of HBV infection. Serologic assays are commercially available for all markers except HBcAg, because no free HBcAg circulates in blood[11] (Table 1).

There is overwhelming evidence that antiviral therapy reduces mortality, and risk of hepatocellular carcinoma (HCC) and improves intermediate prognosis, and overall health outcomes. As such, the most recent document from the United States Preventive Service Task Force recommends screening for hepatitis B in adolescents and adults at increased risk of HBV, with HBsAg tests approved by the United States Food and Drug Administration, followed by a confirmatory test for initially reactive results[12]. A positive HBsAg result indicates chronic or acute infection. Screening recommendations for special populations include initial testing with anti-Hbs and or anti-Hbc in addition to HbsAg[10]. Serologic panels performed concurrently with or after HBsAg screening allow for diagnosis and to determine further management[12].

Serological markers are critical for monitoring treatment response and predicting complications. The primary endpoint for treatment is durable HBsAg loss (functional cure) based on assays with a lower detection limit (LLOD-0.05 IU/mL) with or without HBsAg seroconversion and undetectable serum HBV DNA after completing a course of treatment[13].

Zhang *et al*[14] published in 2018, results from a multicenter trial, assessing kinetics of HBsAg in 1795 HBV patients[14]. The HBsAg titers were significantly higher (P < 0.0001) in patients with HBeAg positive HBV than HBeAg negative HBV patients. They demonstrated that in patients with positive HBeAg, the HBsAg titers were inversely proportional to fibrosis, while alanine aminotransaminase (ALT) and necroinflammatory activity were directly correlated with HBsAg titers in HBeAg negative HBV patients[14].

Biomarkers for HBV functional cure include HBsAg clearance profile (CPs, defined by loss of binding at both loops 1 and 2 epitopes of the 'a' determinant)[15]. A 48th week and 192nd week HBsAg CPs analysis of genotype A CHB patients on either tenofovir or adefovir for at least four years prior revealed its positive association with HBsAg loss (SL), seroconversion, and response to treatment[15].

For most patients with CHB who do not achieve a functional cure, long-term NA is likely needed. Despite long-term therapy, liver-related complications can still occur even with sustained viral suppression. To this end, newer virological markers were developed to predict the risk of liver-related complications in these patients who often have undetectable serum HBV DNA, and the likelihood of achieving a functional cure, which is defined as off-therapy virological suppression[16].

The covalently closed circular DNA (cccDNA) protein is a template used for transcription and subsequent translation of viral proteins. The persistence of cccDNA within the nucleus of infected hepatocytes despite treatment and viral suppression is the underlying mechanism for infection reactivation after treatment cessation[17]. Of the various viral proteins synthesized, the hepatitis b core-related antigen (HBcrAg) is a combination of three related viral proteins (HBcAg, HBeAg, and a truncated 22kDa precore protein)[18,19]. HBcrAg has a superior correlation to the decline in HBV DNA levels with antiviral therapies, and with intrahepatic HBV cccDNA levels[20-23]. It is also helpful in predicting HBV reactivation in immunosuppressed individuals and the development of HCC[24-28]. Another relatively novel biomarker, HBV RNA is a pregenomic RNA containing virion similar to HBcrAg[16]. Treatment naive patients with CHB have lower serum levels (lower by 1-2 logs) of HBV RNA when compared to HBV DNA serum levels[29,30]. However, in patients receiving NA's, the HBV RNA levels are significantly higher than HBV DNA and hence it is a predictor of response. HBV RNA has a strong linear correlation with both HBV DNA and HBsAg titers[31, 32]. Both, HBcrAg and HBV RNA, can predict long-term off-therapy HBV virological control in patients treated with NA's[29,33]. A recent prospective trial by Chang *et al* [34] confirmed HBcrAg levels to reflect on-treatment hepatic fibrosis progression, and hence its role in monitoring hepatic histological changes[34]. Liao *et al*[35] demonstrated the utility of monitoring of HBV RNA and HBcrAg levels for NA-treated patients with undetectable HBV DNA and undetectable HBV RNA occurring before HBcrAg undetectability[35].

Table 1 Studies addressing hepatitis B testing and diagnosis

Ref.	Study type	Findings
Gao *et al*[32], 2017	Prospective trial	Higher HBV RNA levels, in NA-treated patients are a predictor of response
		HBV RNA has a strong linear correlation with HBV DNA and HBsAg titer
		HBcrAg and HBV RNA can predict long-term off-therapy HBV virological control in NA-treated patients
Zhang *et al* [14], 2018	Randomized, controlled, double-blind clinical trial	HBcrAg titers were significantly higher ($P < 0.0001$) in patients with HBeAg positive HBV. HBsAg titers were directly proportional to necro-inflammatory activity, and inversely proportional to fibrosis
Walsh *et al* [15], 2019	Prospective trial	HBsAg clearance profile has positive association with HBsAg loss, seroconversion, and response to treatment in patients treated chronically with Adefovir or Tenofovir
Chang *et al* [34], 2019	Prospective trial	HBcrAg levels reflect liver parenchymal fibrosis progression, and have utility in monitoring hepatic histological changes
Liao *et al*[35], 2019	Prospective trial	Demonstrated utility of monitoring HBV RNA and HBcrAg levels for NA-treated patients with undetectable HBV DNA
Multiple authors	Prior Studies	HBcrAg has a superior correlation to the decline in HBV DNA levels with anti-viral therapies, and with intrahepatic HBV cccDNA levels[20-23]
		HBcrAg can predict HBV reactivation in immunosuppressed individuals and the development of Hepatocellular Carcinoma[24-28]
		HBV RNA is a pregenomic RNA containing virion that has a similar profile to HBcrAg[16]. Treatment naïve patients with CHB have lower (1-2 logs lower) serum levels of HBV RNA compared to HBV DNA [29,30]

HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase; NA: Nucleos(t)ide analogs; HBV: Hepatitis B virus; HBcrAg: Hepatitis b core-related antigen; cccDNA: Covalently closed circular DNA; CHB: Chronic Hepatitis B.

Multiple challenges must be met before these biomarkers can be fully utilized in clinical practice. The specific methods and technical details of serum RNA detection vary widely between different studies and standardization of such is urgently needed [16]. To exclude interference from viral DNA, methods for measuring pgRNA usually require a selective DNA degradation step, which is complicated and time-consuming and also compromises the accuracy of detection[36]. Further research is needed to determine specific cutoff values of HBcrAg to determine clinical outcomes and determine the role of HBV RNA in occult hepatitis B infection, HbsAg seroclearance, HBV reactivation, and development of HCC[16]. Additionally, the biomarkers will need to be validated in different racial and ethnic populations. Studies correlating novel biomarkers with hepatic fibrosis and cccDNA require serial liver biopsies, resulting in reduced sample sizes. In a recent trial, Brakenhoff *et al*[37] showed that HBV RNA decline without concomitant viral antigen decrease is associated with a low probability of sustained response and hepatitis B surface antigen loss. This study highlighted the need for future trials that consider the kinetics of combined biomarkers to assess antiviral efficacy[37].

HEPATITIS B VACCINATION

Current recommendations advocate pre-exposure universal vaccination for newborns and non-immune individuals who are at a high risk of exposure or have a poor disease outcome [patients with hepatitis C virus infection, human immunodeficiency virus (HIV), men who have sex with men, intravenous drug users, health care workers, and household contacts of patients with a positive hepatitis surface antigen][38,39]. Until 2017, most available HBV vaccination schedules required three doses of the vaccine to be administered at specific intervals and had > 90% protective response[40].

On November 9, 2017, Heplisav-B (HepB-CpG), a single-antigen HepB vaccine with a novel immunostimulatory sequence adjuvant, was approved by the Food and Drug Administration for the prevention of HBV in persons aged ≥ 18 years[41]. The vaccine is administered in two doses, one month apart. On February 21, 2018, the Advisory Committee on Immunization Practices (ACIP)* recommended HepB-CpG for use in persons aged ≥ 18 years[42].

Unfortunately, 5%-10% of patients lack an immunological response and remain unprotected despite vaccination[43]. A hepatitis B "non-responder" refers to a person

who does not develop Hepatitis B surface antibodies after completing two whole series of hepatitis B vaccine and for whom an acute or CHB infection has been ruled out[44]. Non-response is associated with different HLA-DR alleles and impaired Th cell response, among other factors such as route of injection, age, gender, body mass, and other factors[45]. For non-responders to the initial vaccination series, a second series of the original vaccination schedule is recommended[46]. Persons with Hepatitis B surface antibody (anti-HBs) < 10 mIU/mL following receipt of 2 doses of HepB-CpG should be revaccinated with a second complete HepB vaccine series followed by anti-HBs testing 1–2 mo after the final dose. Alternatively, revaccination may consist of administration of an additional single HepB vaccine dose followed by anti-HBs testing 1–2 mo later (and, if anti-HBs remains < 10 mIU/mL, completion of the second HepB vaccine series followed again by anti-HBs testing 1–2 mo after the final dose)[47]. Post-exposure prophylaxis should be considered for individuals following a needlestick injury or potentially infectious exposure to body fluids with blood or semen)[47].

Recent studies evaluating the efficacy of alternate revaccination regimens in non-responders are promising and could shape future recommendations. Raven *et al*[48] studied 480 immunocompetent, non-responders in a multicenter, open-labeled, randomized, controlled superiority trial comparing the effectiveness of revaccination with initial regimen (control arm: With HBVaxPro 10 µg or Energix B 20 µg) *vs* three alternate regimens (Twinrix 20 µg or Fendrix 20 µg, or HBVaxPro 40 µg). Revaccinating with Fendrix 20 µg (83%) or HBVaxPro 40 (98%) resulted in significantly higher proportions of responders compared to controls (67%). Authors argued that the indication for these vaccines should be expanded to enable revaccination of non-responders[48]. In 2018, Koc *et al*[49] attempted to enhance the immune response of the HBVaxPro©-10-µg vaccine by adding a cytokine-based adjuvant. This new adjuvant AI20, containing 20-µg recombinant human Interleukin (IL)-2 attached to 20-µg aluminum hydroxide, was added to HBVaxPro©-10-µg (HBAI20). In an open-label trial, HBAI20 elicited protective anti-HBs titers in 90% of previous non-responders[49].

Additionally, researchers have turned to "Systems vaccinology" to precisely understand vaccine mechanisms and potential determinants of immunological non-response[50,51]. Technological advances with DNA microarrays and high throughput DNA sequencing, mass spectrometry powered proteomics, bioinformatics, and computational methods enable data integration that serves as the basis of systems vaccinology[52].

Qiu *et al*[53] performed transcriptome and cytokine analysis of seven responders and seven non-responders pre-and post-vaccination with a three-dose boost regimen. Compared with responders, nine coding genes (*BPI*, *DEFA1B*, *DEFA4*, *CEACAM8*, *MMP8*, *FOLR3*, *LTF*, *TCN1* and, *TKTL1*) were significantly upregulated in non-responders, which could probably be the characteristic genes in hepatitis B vaccine non-responsiveness. This probability was further strengthened by gene ontology analysis results showing that most of these differentially expressed genes were related to immune response. Cytokine analysis demonstrated that IL-27 and CXCL12 concentrations in responders were significantly higher than non-responders. In multiplex cytokine assay, IL-27 and CXCL12 may probably act as the characteristic cytokine marker for responders[53]. Da Silva *et al*[54] demonstrated a reduced baseline CXCR3+CCR6- CXCR5+ memory T cells, contributing to impaired seroconversion with vaccination in patients with chronic kidney disease (CKD)[54]. The authors further suggested an augmented 40-µg HBV dose schedule for CKD (comparable to hemodialysis patients) rather than the 20-µg dose suggested by the center for disease control (CDC)[55-57].

Booster doses are not indicated in immunocompetent individuals if the primary vaccination series is complete, as long-term follow-up studies show that immune memory persists despite declining hepatitis B surface antibody (anti-HBs) levels[58].

In a recent prospective trial published in 2019, 101 adults vaccinated with recombinant hepatitis B vaccine 20-30 years prior, were challenged with a dose of HBsAg vaccine. 100% of patients developed an anamnestic response by day 30 with a significant increase in HBsAg-specific memory B and $CD4^+$ T cells expressing at least two activation markers. These results align with current knowledge and suggest sustained immune memory and long-term protection 20-30 years after a complete primary HBsAg vaccination course during adulthood[59].

Specific immunocompromised populations present an exception to this rule. One such population is patients undergoing bone marrow transplant. In this respect, the American Association for the study of liver disease (AASLD) guidelines are informed by the "Recommendation of the ACIP" document published in January 2018[47]. The document suggests that the humoral response to the hepatitis B vaccine is reduced in

children and adults who are immunocompromised (*e.g.*, hematopoietic stem cell transplant recipients, patients undergoing chemotherapy, and HIV-infected persons)[60,61]. Modified dosing regimens, including a doubling of the standard antigen dose or administration of additional doses, might increase response rates. However, data on response to these alternative vaccination schedules is limited[62].

Chawansuntati *et al*[63] showed a reduced tumor necrosis factor (TNF)-α and IL-2 Level from CD4+ T cells in HIV-infected patients receiving standard HBV vaccinations and suggested an increased dose or frequency to counter this problem[63].

In 2018, Palazzo *et al*[64] published the results of a prospective study assessing the safety and efficacy of revaccination in 122 multiple myeloma patients on maintenance dose Lenalidomide post autologous hematopoietic stem cell transplant. The efficacy of revaccination was determined by comparing pre-and post-vaccination antibody titers. Their data suggested absolute safety and 40% efficacy in those receiving the Hepatitis B vaccine (Twinrix, GlaxoSmithKline, London)[64].

Surprisingly, the development of HBV reactivation following hematopoietic stem cell transplant (HSCT) can occur despite successful revaccination and maintenance of serum anti-HBs at more than protective levels. Nishikawa *et al*[65] in 2020, published their results from a prospective trial studying vaccination to prevent HBV reactivation after hematopoietic stem cell transplantation[65]. The authors showed that of the 27 patients vaccinated 12 mo after HSCT and monitored for two years, six showed HBV reactivation, with a 2-year cumulative reactivation incidence of 22.2%. Factors associated with HBV reactivation included the discontinuation of immunosuppressants (P = 0.0379) and baseline titers of anti-HBs (P = 0.004)[65]. Nucleic acid-based vaccine for HBV prevention is a novel approach but yet to show effectiveness in generating a sustained immune response in clinical trials[66] (Table 2).

HEPATITIS B TREATMENT

Per the 2018 updates to the AASLD guidelines, patients with CHB (Persistence of HBsAg > six months) should be considered for treatment if the ALT > 2 ULN and patients are HBeAg positive with HBV DNA > 20000 or HBeAg Negative with HBV DNA > 2000. Approved therapies are limited to single-drug regimens, including Nucleoside/Nucleotide reverse transcriptase inhibitors and pegylated Interferon (PEG-IFN). Approved regimens are divided into preferred [PEG-IFN, Entecavir (ETV), tenofovir fumarate, and tenofovir alafenamide (TAF)] and Non-Preferred (Lamivudine, Adefovir, Telbuvidine)[10].

Multiple recently published studies support the recommendations in demonstrating the safety and efficacy of IFN and Tenofovir over the non-preferred drugs.

Chuang *et al*[67] demonstrated sustained HBeAg seroconversion rates of 67.1%, five years after completion of the NEPTUNE trial, with a PEG-IFN dose of 180 μg/wk for 48 wk suggesting that the licensed regimen (180 μg × 48 wk) is more efficacious for HBeAg-positive patients than a lower dose and/or shorter treatment duration[67]. A 96-week HBV viral suppression for patients treated with both TAF, a prodrug of tenofovir disoproxil fumarate (TDF), and TDF, were comparable at 73% *vs* 75% and 90% and 91%, for HBeAg positive and HBeAg negative patients respectively[68]. A prospective randomized controlled trial (RCT) by Yim *et al*[69] studying partial responders to ETV (defined by detectable HBV DNA > 60 IU/mL), continuing ETV *vs* switching to TDF, revealed a statistically significant 12-mo HBV virological response (P = 0.022) in the subgroup that was switched to TDF[69]. In another prospective trial, stable switching to TDF monotherapy yielded non-inferior results at 96 wk compared to Lamivudine + Adefovir combination therapy in patients with Lamivudine resistant CHB and non-detectable HBV DNA[70]. Marcellin *et al*[71] published a 10-year efficacy (HBV suppression in 100% of HBeAg-negative and 98% in HBeAg positive patients) and safety data (few renal or bone-related adverse events, with no resistance) with tenofovir fumarate treatment for CHB virus infection in 585 patients (203 completed the 10-year study)[71]. A large, multicenter RCT, published in January 2019, including 320 treatment Naïve HBeAg positive patients showed that after long term treatment (144 wk), both tenofovir fumarate and ETV suppressed HBV DNA similarly (ETV *vs* TDF; -6.6485 *vs* -6.692 log 10 IU/mL, P = 0.807) and had similar serologic, biochemical, and side-effect profiles[72]. Recent encouraging data from a 104-wk prospective study on treatment of naïve HBeAg positive patients treated with telbivudine-based therapy shows a reduction in liver stiffness (monitored by Fibroscan©), from 8.6 at baseline to 6.1 at week 24, and 5.3 at week 104[73].

Table 2 Studies addressing hepatitis B vaccination strategies

Ref.	Study type	Main findings
Koc *et al*[49], 2018	Prospective open label trial	HBAI20 (HBVaxPro©-10-μg vaccine combined with an adjuvant AI20, a recombinant human IL-2) exhibited protective anti-HBs titers in 90% of previous non-responders likely due to an enhanced immune response
Qiu *et al*[53], 2018	Prospective trial	Genome wide comparative analysis revealed significant transcriptome and cytokine changes in HBV vaccine non-responders
Da Silva *et al*[54], 2018	Randomized prospective trial	Impaired seroconversion for HBV vaccination in CKD patients was linked to reduced baseline CXCR3 + CCR6- CXCR5+ memory T cells levels
Van Damme *et al* [59], 2019	Prospective trial	Immune challenge, in previously vaccinated adults (HBsAg vaccine 2-3 decades prior) showed a 100% anamnestic response by day 30 with significant increase in HBsAg-specific memory B and $CD4^+$ T cells
Raven *et al*[48], 2020	Open-labeled, randomized, controlled superiority trial	In Immunocompetent non-responders, revaccination with Fendrix 20 μg or HBVaxPro 40 μg resulted in significantly higher response rates compared to HBVaxPro 10 μg, Energix B 20 μg, or Twinrix 20 μg
Chawansuntati *et al* [63], 2018	Prospective trial	HBV patients with HIV co-infection have reduced levels of TNF-α and IL-2 levels, and may require an increased HBV vaccine dose to counter this problem
Palazzo *et al*[64], 2018	Prospective trial	Revaccination with the Hepatitis B vaccine (Twinrix, GlaxoSmithKline, London), in HBV patients on maintenance Lenalidomide post autologous hematopoietic stem cell transplant was absolutely safe with 40% efficacy
Nishikawa *et al* [65], 2020	Prospective trial	For HBV vaccinated, HSCT recipients, 2-year and 3-year cumulative HBV reactivation rates were 22.2% and 28.9% respectively. Discontinuation of immunosuppressants (P = 0.0379) and baseline titers of anti-Hbs (P = 0.004) were related to HBV reactivation

IL-2: Interleukin 2; anti-HBs: Anti Hepatitis B surface antibody; HBsAg: Hepatitis B surface antigen; HIV: Human Immunodeficiency virus; HBV: Hepatitis B virus; TNF: Tumor necrosis factor; HSCT: Hematopoietic stem cell transplant; CKD: Chronic kidney disease.

Despite the efficacy and safety of current regimens in achieving viral suppression, reactivation is, unfortunately, the norm after treatment cessation due to the persistence of cccDNA[74]. Recent studies further highlight this serious shortcoming.

The Toronto STOP study evaluated 67 HBV patients who achieved HBeAg seroconversion and undetectable HBV DNA after treatment with a NA. Patients were then randomly selected to discontinue. Sustained virological remission was maintained in only 29% of patients who stopped the treatment *vs* 82% of patients who continued NA [75]. Buti *et al*[76] studied the safety and efficacy of discontinuing HBV treated (with TDF) patients after eight years of therapy. At 24 wk following discontinuation of NA, almost a third of patients had grade 3 hepatotoxicity (indicated by aspartate aminotransferase/ALT of > 5 - < 10 ULN, and total bilirubin of > 3 - < 10 ULN)[76].

In another follow-up study of a phase 2 trial at two centers, Immune-tolerant patients with CHB received TDF and/or Emtricitabine for four years and were followed for another four years after cessation. The authors recorded a 100% virological relapse at week 4 (HBV DNA > 2000) and a 50% clinical relapse (HBV DNA > 2000 and ALT > 2 ULN) at 15 ± 11 wk[77].

Given the limitations noted by these studies, researchers have resorted to utilizing combination regimens with IFN and NA in hopes of improving seroconversion rates while others have attempted to determine predictors of response to develop a more targeted approach.

Liem *et al*[78], while looking for the optimal candidates that could benefit from a combination of PEG-IFN with nucleos(t)ide, prospectively evaluated HBeAg positive HBV patients treated with ETV. Randomized addition of PEG-IFN to ETV therapy was associated with a higher 48-week response rate (response defined as HBeAg loss), with a significant P = 0.03, compared to ETV monotherapy[78]. The HERMES Study Group published their results from a prospective RCT in 2019 showing that the addition of PEG-IFN alfa-2a (for 48 wk) to ongoing NA therapy significantly decreased HBsAg levels (defined by greater than 50% decline) in HBeAg-negative patients with genotype D infection[79].

In a recent prospective trial CHB patients who seroconverted on ETV, were switched to weekly PEG-IFN alfa-2a. The authors recorded an 88% sustained response in patients with a baseline HBsAg < 1500 IU/mL, while 50% of patients with a baseline HBsAg < 500 developing HBsAg loss[80]. The same group also validated data from 647 patients with HBeAg positive CHB on PEG-IFN alfa-2a to develop a pre-treatment scoring system using baseline factors like age, sex, alanine aminotransferase ratio, HBsAg level, and HBV DNA level to predict response to therapy[81].

A recently published large meta-analysis with 24 studies and 6674 subjects confirmed the importance of longer treatment duration and addition of IFN for HBsAg lowering and highlighted the potential value of immune-based therapies[82].

Recent identification of novel targets within the hepatitis B viral life cycle has led to the development of multiple therapeutic agents with varying mechanisms[83]. These include either direct inhibition of viral replication by targeting fundamental steps such as entry, cccDNA formation/stability, viral transcription, capsid assembly, and secretion or manipulating the host immune system for augmentation of innate and/or adaptive immunity[17]. The viral life cycle, resulting viral products, and their role in the pathogenesis of CHB is a rather broad and complex topic in and of itself. We found a recent article by Tsukuda *et al*[84] titled 'Hepatitis B viral biology and life cycle' to be an excellent resource for further information on this topic[84].

The discovery of the sodium taurocholate co-transport polypeptide (NTCP) (gene: *SLC10A1*) receptor as a gateway for HBV entry into hepatocytes was made approximately a decade ago[85]. The discovery has been a significant source of optimism, and NTCP has served as a target for developing viral entry inhibitors, including myrcludex and cyclosporine[86,87]. Additionally, NTCP complemented stable cell lines, cell cultures, and infection model systems have allowed standardized research to understand better the HBV life cycle and development of therapeutic options[88-91]. By allowing the study of authentic infection in cell lines, these model systems have helped achieve a better understanding of the formation and degradation of cccDNA, a key target to achieve the ultimate goal of HBV cure[92,93]. National institute of health (NIH)-funded trials to target viral proteins required for viral entry into uninfected hepatocytes, viral replication targeting adaptive immunity (anti-programmed cell death 1/programmed death-ligand 1 antibodies, chimeric antigen receptor T cells), and silencing of cccDNA are underway[94]. A preclinical trial of cccDNA endonucleases (CRISPR/Cas9) showed a reduction in cccDNA, other viral gene expression parameters as well as replication *in vitro*[95]. Multiple recent trials have evaluated the safety and efficacy of Core Protein (Capsid) Assembly Modulators in patients suffering from CHB. In a phase 1 study of HBeAg-positive CHB patients without cirrhosis, NVR 3-778 was well tolerated and demonstrated antiviral activity. The agent reduced serum levels of HBV DNA and HBV RNA, to the greatest extent combined with PEG-IFN. The observed reductions in HBV RNA confirmed the novel mechanism of NVR 3-778 [96]. A phase I, randomized placebo-controlled trial published in Lancet in 2020, showed acceptable safety, pharmacokinetics, and antiviral effects on an investigational HBV core protein inhibitor ABI-H0731[97]. Another phase I trial, by Zhao *et al*[98], evaluated the safety, tolerability, and pharmacokinetics of GLS4 (a novel HBV capsid assembly inhibitor), with or without ritonavir (used to enhance plasma levels of GLS4) and was found to have acceptable tolerability and sustained higher than proposed effective plasma trough concentration, when used in combination[98]. A phase I double-blind, RCT of 30 healthy adults, by Vandenbossche *et al*[99], looked into the safety, tolerability, and pharmacokinetics of JNJ-56136379 (a novel HBV capsid assembly modulator), showed it to be well-tolerated, with a more than three times the 90% effective plasma concentration required to inhibit viral replication[99].

HBV regulatory protein X (HBX) was recently found to promote transcription from cccDNA through an interaction with a host protein DDB1[100]. Sekiba *et al*[101] applied a newly constructed split luciferase assay system to comprehensive compound screening to identify candidate compounds that targeted the HBX-DDB1 interaction and showed that nitazoxanide (NTZ), efficiently inhibits the HBX-DDB1 protein interaction. NTZ significantly suppressed viral transcription and viral protein production in human primary hepatocytes naturally infected with HBV[101]. Antisense oligonucleotides are small single-stranded nucleic acid sequences that bind selectively to their target RNAs and cause degradation[102]. GSK3389404 is a liver-targeted antisense oligonucleotide that inhibits the synthesis of HBsAg and all other HBV proteins. A recent randomized double-blind controlled phase 1 trial showed acceptable safety and pharmacokinetic profile, supporting further clinical investigation in patients with CHB[103].

The human immune system controls and clears adulthood-acquired hepatitis B in over 95% of patients[94]. A large body of data links suppressed T and B cell responses to persistent hepatitis B and liver injury[104-106]. Moreover, data from trials involving B and T cell responses strongly suggest that augmentation of immunity can clear the infection[107]. Therefore, boosting the magnitude and quality of the virus-specific immune response is a rational strategy for therapy[108]. Various toll-like receptor (TLR) agonists have shown promising antiviral effects in small prospective trials. GS-9620, a TLR-7, when administered for 12 wk, though did not significantly affect serum HBsAg levels. However, it did increase T-cell and NK-cell responses[109-111]. Han *et*

al[112] demonstrated HBeAg positive CHB patients to have a lower baseline galactosylation level, and hence being suitable candidates for the use of HBsAg-hepatitis B immune globulin (HBIG) immune complex, administered as a therapeutic vaccine, to achieve HBeAg seroconversion. The marked-up regulation of IL-2 and galactosylation levels confirmed this to be an immune response[112].

The goal of therapeutic vaccination is to stimulate or boost the host immune response to restore immune control, leading to sustained suppression of HBV replication and ultimately HBsAg loss[13]. A recently published meta-analysis of 15 studies reviewed the evidence for therapeutic vaccines' efficacy and safety in CHB patients[113]. The authors concluded by saying that therapeutic vaccines do not appear to be efficacious for the treatment of CHB but were limited by few RCTs, suboptimal therapeutic vaccines, and patient selection.

An open-label phase III trial comparing a therapeutic vaccine (NASVAC, containing 100 μg of each HBs and HBc antigens, administered in 2 cycles of 5 doses) *vs* PEG-IFN alfa 2b (180 μg every week for 28 wk in naïve CHB patients showed significantly better controlled HBV DNA, 24 wk post-treatment ($P < 0.05$) and a lower rate of progression to cirrhosis in the NASVAC group[114]. HBsAg-based recombinant vaccines, administered every eight weeks for 48 wk, with a total of 7 doses, have been shown to reduce HBsAg levels ($P = 0.0005$) and achieve HBsAg seroconversion in 10.52% of the patients with low HBsAg titers[115]. A multicenter prospective phase 2 RCT by Boni *et al*[116] demonstrated improved HBV specific T cell responses, including IFN-γ, TNF-α, and IL-2, with a combined GS-4774 (yeast-based engineered vaccine) and tenofovir *vs* tenofovir alone[116].

The HBV Endeavor prospective trial by Wu *et al*[117] looked into switching HBV patients with confirmed viral suppression and HBsAg loss from nucleos(t)ide analogs to immunomodulators (IL-2) and therapeutic vaccines with IFN to enhance HBsAg loss to achieve HBV virological cure. HBsAg loss was documented to be 9.38%, 3.03%, and 3.7% in the IFN/vaccine/IL-2 group, IFN group, and the ETV group, respectively. The higher titers of CD16-NK cells and lower titers of regulatory T cells corresponded to higher response rates of HBsAg loss[117] (Table 3).

HEPATITIS B SPECIAL POPULATIONS

Mother to child transmission of hepatitis B

Antiviral therapy has been studied as an intervention to reduce perinatal HBV transmission amongst pregnant women with high HBV viral DNA levels[9,118,119]. All newborns born to HBV infected mothers should receive HBIG and HBV vaccine within 12 h of delivery followed by completion of 2 or 3 vaccine series[47]. AASLD suggests antiviral therapy starting at 28-32 wk to reduce perinatal HBV transmission when maternal HBV DNA is > 200000 IU/mL[9]. Tenofovir is recommended as the preferred agent due to lack of resistance and availability of safety data and the therapy is discontinued at some point between birth and three months postpartum[9].

Cressey *et al*[120] assessed for the first time tenofovir exposure during pregnancy and postpartum in HBV-infected HIV-uninfected women receiving TDF to prevent mother-to-child transmission of HBV. They concluded that the modest reduction in tenofovir exposures observed during pregnancy does not warrant a dose adjustment [120].

At least two recent studies have demonstrated the safety and efficacy of the addition of TDF to standard newborn immune prophylaxis in reducing maternal to child transmission (MTCT) in pregnant women, with very high viral loads[121,122]. Alternatively, in a multicenter, double-blind clinical trial performed in Thailand, authors demonstrated that in a setting in which the rate of mother-to-child HBV transmission was low with the administration of hepatitis B immune globulin and hepatitis B vaccine in infants born to HBeAg-positive mothers, the additional maternal use of TDF did not result in a significantly lower rate of transmission[123].

These studies reiterate the safety, efficacy, and practicality of Tenofovir in pregnant women at high risk for MTCT of hepatitis B. In their July 2020 guidelines on antiviral prophylaxis in pregnancy, WHO recommends that pregnant women testing positive for HBV infection (HBsAg positive) with HBV DNA ≥ 5.3 log10 IU/mL (≥ 200000 IU/mL) receive tenofovir prophylaxis from the 28th week of pregnancy until at least birth, to prevent mother-to-child transmission of HBV. This is in addition to three-dose hepatitis B vaccination in all infants, including timely birth dose[124].

In immune-tolerant (HBeAg positive) CHB patients awaiting assisted reproduction, an RCT conducted by Wu *et al*[125] showed greater viral clearance (90% *vs* 67.2%, $P =$

Table 3 Studies addressing hepatitis B treatment

Ref.	Study type	Findings
Conventional treatment agents		
Chuang *et al*[67], 2018	Prospective study	PEG Interferon at a dose of 180 μg/wk for a duration of 48 wk resulted in better sustained HBeAg seroconversion rates, than in patients with a lower dose and/or shorter treatment duration
Agarwal *et al*[68], 2018	Randomized controlled trial	96-wk HBV suppression rates were comparable in patients treated with TAF and TDF, for HBeAg positive (73% *vs* 75%) and HBeAg negative (90% *vs* 91%) patients
Yim *et al*[69], 2018	Prospective randomized controlled trial	HBV patients who were partial responders to ETV, fared better (12-mo HBV response, $P = 0.022$), when switched to TDF versus continuing ETV
Lee *et al*[70], 2018	Prospective trial	In Lamivudine resistant HBV patients with non-detectable HBV DNA, while on Lamivudine + Adefovir combination therapy, switching to TDF monotherapy yielded non-inferior results at 96-wk
Marcellin *et al*[71], 2019	Prospective trial	A 10-yr TDF efficacy study showed HBV viral suppression in 100% of HBeAg-negative and 98% in HBeAg positive patients), with few renal or bone-related adverse events, and no resistance to TDF
Cai *et al*[72], 2019	Multicenter randomized controlled trial	HBV treatment naïve HBeAg positive patients treated with ETV or TDF, showed similar HBV DNA suppression (-6.6485 *vs* -6.692 log 10 IU/mL, $P = 0.807$) at 144 wk as well as similar serologic, biochemical, and side-effect profiles
Liang *et al*[73], 2018	Prospective trial	HBV treatment naïve HBeAg positive patients treated with Telbivudine-based therapy showed a reduction in liver stiffness, monitored by Fibroscan©), from 8.6 at baseline to 6.1 at week 24, and 5.3 at week 104
Liem *et al*[75], 2019	Randomized controlled trial	In HBV patients who received NA, and achieved HBeAg seroconversion with undetectable HBV DNA, maintenance of remission was seen in 82% of those who continued NA *vs* 29% of those who discontinued NA
Buti *et al*[76], 2019	Prospective trial	HBV patients treated with TDF, and then discontinued: At 24 wk following discontinuation of NA, almost a third of patients had grade 3 hepatotoxicity (indicated by AST/ALT of > 5 - < 10 ULN, and total bilirubin of > 3 - < 10 ULN)
Wong *et al*[77], 2018	Phase II prospective trial	HBV immune-tolerant patients who received TDF and/or Emtricitabine for 4 yr and were followed for another 4 yr after cessation, showed 100% virological relapse at week 4 (HBV DNA > 2000) and a 50% clinical relapse (HBV DNA > 2000 and ALT > 2 ULN) at 15 ± 11 wk
Liem *et al*[78], 2019	Randomized prospective trial	Randomized addition of PEG-IFN to ETV therapy, in HBeAg positive HBV patients was associated with a significantly higher 48-wk response rate (HBeAg loss), compared to ETV monotherapy ($P = 0.03$)
Lampertico *et al*[79], 2019	Prospective randomized controlled trial	Genotype D, HBeAg-negative HBV patients, on NA therapy showed a significant 50% decrease in HBsAg levels, with the addition of PEG-IFN alfa-2a for 48 wk
Chan *et al*[80], 2019	Prospective trial	In CHB patients, switched to weekly PEG-IFN alfa-2a after seroconversion on entecavir, those with lower HBsAg titers, showed a greater sustained response (88% at HBsAg < 1500 IU/ml and 50% at HBsAg < 500 IU/mL)
Chen *et al*[82], 2020	Meta-analysis	Confirmed the importance of longer treatment duration and addition of IFN for HBsAg lowering and highlighted the potential value of immune-based therapies
New direct antiviral agents		
Ramanan *et al*[95], 2015	Pre-clinical prospective study	Use of ccc DNA endonucleases (CRISPR/Cas9) resulted in a reduction in both ccc DNA and other parameters of viral gene expression and replication *in vitro*
Yuen *et al*[96], 2019	Phase 1 prospective trial	Non-cirrhotic HBeAg-positive CHB patients, tolerated NVR 3-778 (a capsid assembly protein modulator), and showed reduced serum levels of HBV DNA and HBV RNA, to the greatest extent in combination with PEG-IFN
Yuen *et al*[97], 2020	Phase I, randomized placebo-controlled trial	Demonstrated acceptable safety, pharmacokinetics, and antiviral effects on an investigational HBV core protein inhibitor ABI-H0731
Zhao *et al*[98], 2019	Phase I, randomized controlled trial	Demonstrated acceptable safety and pharmacokinetics of GLS4 (a novel HBV capsid assembly inhibitor), with or without ritonavir (used to enhance plasma levels of GLS4)
Vandenbossche *et al*[99], 2019	Phase I double-blind, randomized	Demonstrated acceptable safety and pharmacokinetics of JNJ-56136379 (a

	controlled trial	novel HBV capsid assembly modulator) with more than three times the 90% effective plasma concentration required to inhibit viral replication
Han *et al*[103], 2019	Phase I double-blind, randomized controlled trial	Demonstrated acceptable safety and pharmacokinetics of GSK3389404 (a liver-targeted antisense oligonucleotide that inhibits the synthesis of hepatitis B surface antigen and all other hepatitis B virus proteins)
New immune based therapies		
Boni *et al*[109], 2018	Phase I prospective trial	Administration of a 12-wk course of GS-9620 (TLR7 agonist) was safe but did not significantly affect serum HBsAg levels. However, it did increase T-cell and NK-cell responses
Janssen *et al*[110], 2018	Phase II prospective trial	Administration of a 12-wk course of GS-9620 (TLR7 agonist) was safe, demonstrated dose dependent increase in interferon-simulated gene m RNA expression, without IFN-α expression or reduction in HBsAg levels
Agarwal *et al*[111], 2018	Randomized controlled prospective trial	Addition of Vesatolimod (TLR7 agonist) to Tenofovir in treatment naïve viremic Hepatitis B patients was found to be safe. This intervention led to dose dependent pharmacodynamic induction of ISGs, without significant improvement in HBsAg decline
Han *et al*[112], 2019	Prospective trial	During YIC treatment, 26 patients with lower IgG galactosylation level at baseline showed (cellular immune response mediated), sustained increase of serum galactosylated IgG and responded to YIC treatment by HBeAg seroconversion
Al Mahtab *et al*[114], 2018	Open-label phase III trial	Treatment naïve CHB patients showed significantly better controlled HBV DNA, 24 wk post-treatment ($P < 0.05$) and a lower rate of progression to cirrhosis in the NASVAC group (therapeutic vaccine, containing 100 μg of each HBs and HBc antigens, administered in 2 cycles of 5 doses), versus PEG-IFN alfa 2b (weekly 180 μg)
Lai *et al*[115], 2018	Randomized controlled prospective trial	In low-level HBsAg CHB patients, serial HBsAg-based vaccinations were safe, resulting in significant HBsAg decline. HLA gene expression and genotypes played a role in vaccine responsiveness
Boni *et al*[116], 2019	Multicenter phase II prospective randomized controlled trial	Demonstrated improved HBV specific T cell responses, including IFN-γ, TNF-α, and IL-2, with a combined GS-4774 (yeast-based engineered vaccine) and tenofovir versus tenofovir alone
Wu *et al*[117], 2019	Prospective controlled trial(The HBV Endeavor prospective trial)	HBV patients with confirmed viral suppression and HBsAg loss while on ETV, when switched to immunomodulators (IL-2) and therapeutic vaccines with IFN, showed HBsAg loss in 9.38%, 3.03%, and 3.7% in the IFN/vaccine/IL-2 group, IFN group, and the ETV group, respectively. Higher titer of CD16-NK cells and lower titers of regulatory T cells corresponded to higher response rates of HBsAg loss
Kalkeri *et al*[142], 2020	Prospective trial	A repurposed compound SRI-32007 demonstrated anti-HBV activity *via* inhibition of HBV core promoter activity, and might be used in studying therapeutics to manage HBV
Hepatitis B in pregnancy		
Cressey *et al*[120], 2018	Phase III randomized prospective trial	Demonstrated a geometric mean tenofovir AUC (0-24) to be 20% (95%CI: 19%-21%) lower during pregnancy than postpartum, in HBV patients with HIV, should not warrant a dose adjustment (to compensate for the modest reduction in HBV transmission)
Lin *et al*[121], 2018	Randomized double-blind prospective trial	Initiation of TDF at 24th week of gestation and then 4 weeks after delivery reduced the MTCT from 13.5% (control group) to 0% cervical transmission, in pregnant HBsAg and HBeAg positive patients with high viral loads HBV DNA titer ≥ 2×10^6 IU/mL
Wang *et al*[122], 2019	Prospective trial	Initiation of TDF at 24th week of gestation revealed a 0.7% MTCT in the ITT group, and 0% in the *per* protocol group, in pregnant HBsAg and HBeAg positive patients with high viral loads HBV DNA titer > 6 $\log_{10}$ IU/mL
Jourdain *et al*[123], 2018	Multicenter, double-blind clinical trial	Initiation of TDF at 28th week of gestation till 2 mo postpartum mildly reduced the MTCT from 2% (control group) to 0% cervical transmission, in pregnant HBsAg and HBeAg positive patients with an ALT of < 60. The authors showed that addition of TDF only mildly reduced the MTCT to infants at age 6 mo
Wu *et al*[125], 2019	Randomized control trial	Immune-tolerant CHB patients awaiting assisted reproduction showed greater viral clearance (90% *vs* 67.2%, $P = 0.002$ at week 12, and 96.6% compared to 85.2 % at week 48 respectively) when on a combination of TDF and telbivudine, compared to TDF alone. No difference was noted in the HBeAg seroconversion rates for the two groups (8.3% *vs* 3.3%; $P = 0.233$)
Hepatitis B reactivation		

Huang *et al*[127], 2013	Randomized double blind prospective trial	Prophylaxis with ETV significantly reduced HBV reverse seroconversion when compared with placebo in resolved hepatitis B patients receiving Rituximab for lymphoma (4.3% *vs* 25.9% at 18 mo; $P = 0.019$)
Kusumoto *et al*[130], 2019	Prospective trial	Resolved HBV patients with NHL, who received obinutuzumab or rituximab, and followed for HBV reactivation, revealed a strong correlation ($P < 0.0001$) of HBV reactivation with detectable baseline HBV DNA. Also, Prophylactic NA reduced risk of HBV reactivation ($P = 0.0018$)
Liu *et al*[131], 2019	Double bling randomized control trial	Resolved HBV patients with lymphoma who received chemotherapy, had similar reactivation rates with or without ETV prophylaxis (0% *vs* 3.2%; $P = 0.246$). Authors suggested that prophylactic use of entecavir was not a cost-effective strategy, especially for those with a baseline positive anti-HBs
Hammond *et al*[132], 2018	Retrospective study	The incidence of HBV reactivation, in patients on Ibrutinib, was 9.5% (2 out of the 21 patients with known past HBV infection)
Wang *et al*[135], 2018	Prospective trial	HBV DNA negative patients with HCC who underwent TACE were at risk of HBV reactivation. HBV reactivation rates were significantly lower in those receiving ETV compared with controls (5.9% vs 23.4%; $P < 0.05$)
Zhang *et al*[136], 2019	Meta-analysis	HBV DNA negative patients with HCC who underwent TACE were at risk of HBV reactivation ($P < 0.01$) and hepatitis ($P < 0.01$). Use of prophylactic anti-viral therapy significantly reduced the risk of HBV reactivation ($P < 0.01$) and hepatitis ($P = 0.02$)
Jun *et al*[137], 2018	Multi-center retrospective study	12.7% of HBV DNA negative patients with HCC who underwent RT had HBV reactivation. Use of prophylactic anti-viral therapy significantly reduced the risk of HBV reactivation ($P < 0.001$), when compared to the control group. Combined RT and TACE had significant risk for HBV reactivation ($P = 0.008$)
Liu *et al*[138], 2020	Retrospective study	CHB patients with SARS-CoV-2 infection had a 15% risk of HBV reactivation

CHB: Chronic hepatitis B; HBV: Hepatitis B virus; HBeAg: Hepatitis B e-antigen; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate; ETV: Entecavir; NA: Nucleos(t)ide analog; TLR7: Toll like receptor 7; YIC: Hepatitis B surface antigen-hepatitis B immunoglobulin immune complex; AST: Aspartate aminotransferase; ALT: Alanine aminotransaminase; PEG-IFN: Pegylated interferon; cccDNA: Covalently closed circular DNA; CRISPR: Clustered regularly, interspaced short palindromic repeats; Cas9: CRISPR associated protein 9; NK: Natural killer; IFN: Interferon; TNF: Tumor necrosis factor; IL-2: Interleukin 2; CD: Cluster of differentiation; HBIG: Hepatitis B immune globulin; AUC: Area under the ROC curve; ROC: Receiver operating characteristic; CI: Confidence interval; ITT: Intention to treat; MTCT: Maternal to child transmission; NHL: Non-Hodgkin's lymphoma; TACE: Trans-arterial chemoembolization; RT: Radio-therapy; HCC: Hepatocellular carcinoma; GGT: Gamma-glutamyl transferase; ISGs: Interferon stimulated gene transcripts; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

0.002 at week 12, and 96.6% compared to 85.2% at week 48 respectively) in patients on a combination of TDF and telbivudine, compared to TDF alone. However, there was no difference in the HBeAg seroconversion rates for the two groups (8.3% *vs* 3.3% $P = 0.233$)[125] (Table 3).

Anticancer therapy

Previous studies showed that HBV reactivation from anticancer therapies occurred in 41% to 53% of HBsAg-positive, anti-HBc–positive patients, and 8% to 18% of HBsAg-negative, anti-HBc–positive patients[126,127]. Those receiving B cell depleting therapies such as Rituximab are considered to be at a higher risk of reacti-vation[128,129]. The AASLD recommends screening patients requiring chemotherapy with both HBsAg and anti-HBc and prophylaxis with NAs before treatment initiation with B cell depleting therapies such as rituximab[10]. The role of baseline anti-HBs testing in this cohort is still not clear. Additionally, the data on hepatitis B reactivation during treatment with some of the newer immunochemotherapy agents such as obinutuzumab and Ibrutinib is sparse.

In a recent study, 326 patients with prior HBV receiving Obinutuzumab or Rituximab for B-Cell Non-Hodgkin's lymphoma (NHL) either received prophylactic NAs or underwent HBV DNA guided preemptive NA therapy. Multivariate regression analysis identified that seronegativity for anti-HBs and detectable HBV DNA levels at baseline (not the drug choice) were associated with increased risk of HBV reactivation[130]. While the reactivation rate was lower for patients receiving prophylactic antivirals, none of the patients in either group developed HBV-related hepatitis[130]. Results suggest that while prophylactic therapy can prevent reactivation and may be suitable for selected high-risk patients, HBV DNA-guided preemptive therapy can successfully prevent HBV hepatitis during anti-CD20 immunochemotherapy in B-cell NHL. Liu *et al*[131] conducted an RCT on lymphoma

patients on chemotherapy with past HBV infection (HBsAg negative, Anti HBV core total antibody positive, and negative HBV DNA), and the study concluded that the prophylactic use of ETV was not a cost-effective strategy, especially for those with a positive anti-HBs. The HBV reactivation was 3.2% compared to 0% (P = 0.246), in controls *vs* those of prophylactic ETV[131]. In a recent retrospective review, the authors identified two patients suffering from chronic lymphocytic leukemia who experienced hepatitis B reactivation after treatment with Ibrutinib. The incidence of hepatitis b reactivation, in patients on Ibrutinib, at the Dana-Farber/Harvard Cancer Institute was 9.5% (2 out of the 21 patients with known past HBV infection)[132].

These studies highlight the risk of hepatitis B reactivation with novel agents such as obinutuzumab and ibrutinib, the utility of baseline anti-HBs testing for risk stratification, and argue in favor of close surveillance with preemptive treatment being a safe and cost-effective strategy in these patients.

CHB patients receiving transarterial chemoembolization (TACE) for HCC are at a modestly increased risk for hepatitis B reactivation[133,134]. There is a lack of systemic data assessing antivirals' role in this subgroup of patients, and the most recent AASLD guidelines do not address this issue directly as such data from high-quality prospective trials and meta-analysis are needed to advance our knowledge of this field. In a recent prospective trial including 98 CHB patients with HCC requiring TACE, prophylactic antivirals were associated with a significant reduction in the incidence of hepatitis b reactivation (5.9% *vs* 23.4% $P < 0.05$)[135]. Zhang *et al*[136] recently performed a meta-analysis to investigate the reactivation of HBV following TACE in primary HCC patients (HBV-DNA negative) and evaluate TACE's effects combined with antiviral therapy. TACE significantly increased the risk of HBV reactivation (OR: 3.70; 95%CI: 1.45-9.42; $P < 0.01$) and subsequent hepatitis (OR: 4.30; 95%CI: 2.28-8.13; $P < 0.01$) in HCC patients. Preventive antiviral therapy reduced the rate of HBV reactivation (OR: 0.08; 95%CI: 0.02-0.32; $P < 0.01$) and hepatitis (OR: 0.22; 95%CI: 0.06-0.80; $P = 0.02$) in those undergoing TACE[136]. A recent multicenter retrospective study evaluated 133 patients receiving radiotherapy +/- TACE for the treatment of HCC, and the effect of antiviral therapy on HBV reactivation in quiescent HBsAg positive patients after radiotherapy for HCC was found to be 33.3% in the non-antiviral group, compared to 7.5% in the antiviral group, with a $P < 0.001$[137].

CORONAVIRUS DISEASE 2019

Another interesting HBV reactivation phenomenon was described by Liu *et al*[138] in patients who are not necessarily immune-compromised but just infected with coronavirus disease 2019 (COVD-19). Liver dysfunction is apparent in COVID-19 patients with/without chronic HBV. COVID-19 patients co-infected with chronic HBV were found to be at risk of hepatitis B reactivation, making it necessary to monitor the liver function of COVID-19 patients concurrently with HBV-DNA levels during the whole disease course[138].

FUTURE DIRECTIONS

In November 2019, the NIH hepatitis B cure strategic plan working group released a visionary statement to end the hepatitis B endemic by improved screening, strategies for vaccinations, developing better hepatitis B treatment, and follow-up care. This guidance serves as a foundation for future concerted international efforts and would further help develop novel biomarkers to diagnose disease progression, in addition to novel therapeutics[139]. Due to the need for lifelong treatment, adverse effects, poor tolerability, and persistent risk of complications, including HCC, render the current treatments dissatisfactory.

The discovery of NTCP as an HBV receptor on human hepatocytes was the first of many critical discoveries that have revolutionized HBV research. Over the past decade, the discovery has translated into a significantly improved understanding of HBV pathogenesis and led to the development of novel animal models, cell lines, biomarkers, and therapeutic agents. Our armamentarium of potential HBV drugs has undergone a rapid expansion. Direct antivirals currently being studied include HBV entry inhibitors, capsid assembly modulators, cccDNA destabilizers and endonucleases, HBX inhibitors, Inhibitors of gene expression, HBsAg release inhibitors[13]. These agents are likely going to complement existing treatments rather than replacing them. Given the safety profile of NAs, novel agents will likely be compared and

combined with NAs in upcoming trials. The initial cure for HBV will most likely require a combination of agents that modulate viral and host factors at various levels. Given the efficacy of T cells for viral control in acute hepatitis, they have been studied extensively. Novel agents act either through innate and intrinsic cell responses (Toll like receptor agonists, RIG-1) or by targeting adaptive immune responses (checkpoint inhibitors, therapeutic vaccines, genetically engineered T cells/antibodies).

Loss of T cell response to HBV or T cell exhaustion is multifactorial in nature and a major hurdle to the development of immunomodulatory therapeutic agents. These concepts have been incorporated into therapeutic strategies that involve potent adjuvants, monoclonal antibodies, or pattern recognition receptor agonists that alter the liver environment. On the other hand, our understanding of HBV-specific B cells is limited to antibody production, and further studies are required to understand better their cytokine profiles and their role as antigen-presenting cells[108].

Another major limitation to preclinical testing of novel agents is the lack of optimal animal models. Because of the strict species specificity of HBV infection, animal models for studying the host response to the virus and disease pathogenesis have been limited and suboptimal[140]. Chimpanzees are the only nonhuman immune-competent animals that are naturally susceptible to HBV infection. However, given the discontinuation of chimpanzees' use due to bioethical considerations, the only other option is Tupaia (a tree shrew), woodchuck, or mice, all of which have significant drawbacks[141]. Future efforts to develop antiviral agents against viral genome reservoir or cccDNA or promote the patient's antivirus response must include the development of infection models that are durable, stable, and more reflective of the natural HBV life cycle within the human host.

To this end, drug repurposing may offer reduced effort, time, and cost related to new drugs' the testing and marketing of new drugs. Drug repurposing involves the investigation of existing drugs with demonstrated safety profiles for new therapeutic purposes. Thousands of compounds can be screened for the desired effect using high throughput screening. A recent study demonstrated anti-HBV activity of a repurposed compound SRI-32007 through inhibition of HBV core promoter activity[142]. Drug repurposing may allow for more systematic and substantially less expensive methods to discover new treatments for diseases compared to traditional drug development.

To promote and facilitate the planning and execution of new trials in the field of CHB with the ambition of developing a 'cure', the European Association for the Study of the Liver and the AASLD jointly organized an HBV Treatment Endpoint Conference [13]. The conference provided a strategy for conducting efficient phase II/III trials while maintaining excellent safety profiles. It was agreed upon that the primary endpoint of phase III trials should be HBsAg loss and undetectable HBV DNA 6 mo after completion of treatment. HBsAg loss in ≥ 30% of patients after 1 year of therapy is the desired rate of response in these phase III trials.

A comprehensive collaboration within the scientific community is required to standardize definitions, methods, and endpoints to achieve a complete understanding of viral biology and develop novel therapies in a time and cost-effective manner. That will be, however, just the beginning of the global battle against HBV. The WHO has identified significant barriers that hinder efforts to prevent and treat CHB in the most vulnerable populations. Structural barriers include inadequate leadership, commitment, coverage of prevention programs, data, and a lack of public health approach to hepatitis. Personal barriers include lack of education/insight, widespread stigma, and discrimination, lack of affordability, and healthcare access. With these challenges in mind, the WHO has developed a core strategy to eliminate viral hepatitis as a public health threat by 2030, to reduce new infections by 90% and mortality by 65%[94].

The cornerstone of this global strategy is going to be a pragmatic and efficient vaccination program. Hepatitis B vaccine is one of the most effective vaccines, with seroconversion rates above 90% when administered properly. Additional studies are needed to identify the host genetic factors and immune mechanisms that lead to a non-response in immunocompetent patients. The vaccination response of the immunocompromised host needs to be better studied, and practical strategies including immune priming need to be developed to achieve higher seroconversion rates. Vaccines biology can potentially help define, at baseline, predictive signatures for subjects generating protective responses following HBV vaccination leading to more personalized vaccination[143]. These findings need further testing to validate the concept of baseline predictors and the feasibility and utility of targeted modulation of the immune baseline before vaccinations[143]. Elimination of HBV infection as a public health threat requires a reduction in the prevalence of HBsAg to below 0.1% in children five years of age. It can be achieved through universal immunization of newborns against hepatitis B and other interventions to prevent mother-to-child transmission of HBV

[124]. Significant challenges include low availability of HBIG due to the lack of resources required for storage and transportation and prohibitive cost. Despite the efficacy of vaccination in reducing MTCT, the birth dose vaccine coverage, especially in the African region, remains low[124]. Lack of infrastructure leads to reduced ability to test for HBV DNA and limits antiviral availability in high-risk populations. The immunocompromised patients also remain at a high risk of reactivation despite an initial vaccination response and positive antibody titers. Researchers have relied on Genome-wide association studies genome-wide association studies (GWAS) to identify the risk loci that predispose to the persistence of HBV infection, non-response to hepatitis B vaccine, and liver disease progression in chronic HBV infections[144]. Additional GWAS and fine-mapping studies, implemented with more refined case-control designs, larger samples, and in other ethnic populations, would further improve our understanding of HBV pathophysiology[144].

CONCLUSION

The breakthrough in our understanding of the HBV life cycle has resulted in a plethora of novel direct acting antivirals and immune based therapies being investigated. In the foreseeable future however, novel agents are likely to complement PEG-IFN and NAs than replace them. Recent studies utilizing combination regimens (PEG-IFN plus NA) and a longer duration of treatments with PEG-IFN have shown improved outcomes. Additionally, trials assessing alternate vaccination regimens for primary non-responders, and perinatal NAs for prevention of MTCT in high-risk individuals have shown promise and may alter future guidelines. Studies on novel biomarkers are fraught with technical difficulties, lack of standardization, and small sample size. Despite remarkable efficacy, the hepatitis B vaccine remains poorly utilized in many regions of the world due to a lack of infrastructure and implementation. Data from high-risk populations, most vulnerable to the devastating effects of hepatitis B infection and reactivation remain sparse. Utilization of systems approach, optimization of experimental models, identification and validation of next-generation biomarkers, and precise modulation of the human immune response will be critical for future innovation. Last but not the least, pragmatic management of MTCT and population health-related challenges must be prioritized to produce real-world results.

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ORIGINAL ARTICLE

Prospective Study

Castor oil as booster for colon capsule endoscopy preparation reduction: A prospective pilot study and patient questionnaire

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Abstract

BACKGROUND

Preparation for colon capsule endoscopy (CCE) requires a large liquid laxative volume for capsule excretion, which compromises the procedure's tolerability.

AIM

To assess the safety and utility of castor oil-boosted bowel preparation.

METHODS

This prospective cohort study including 20 patients (age range, 16-80 years; six men and 14 women) suspected of having colorectal disease was conducted at Kindai University Hospital from September 2017 to August 2019. All patients underwent CCE because of the following inclusion criteria: previous incomplete colonoscopy in other facility (n = 20), history of abdominal surgery (n = 7), or organ abnormalities such as multiple diverticulum (n = 4) and adhesion after surgery (n = 6). The exclusion criteria were as follows: Dysphagia, history of allergic reactions to the drugs used in this study (magnesium citrate, polyethylene glycol, metoclopramide, and castor oil), possibility of pregnancy, possibility of bowel obstruction or stenosis based on symptoms, or scheduled magnetic resonance imaging within 2 wk after CCE. The primary outcome was the capsule excretion rate within the battery life, as evaluated by the total large bowel observation rate, large bowel transit time, and bowel creasing level using a five-grade scale in different colorectal segments. The secondary outcomes were

Hospital (29-087) and the procedures were in accordance with the Declaration of Helsinki.

Clinical trial registration statement: The clinical trial is registered with University Hospital Medical Information Network, using identifier UMIN000028694. Details can be found at https://upload.umin.ac.jp/cgi-openbin/ctr_e/ctr_view.cgi?recptno=R000032809.

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrollment.

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complications, colorectal lesion detection rates, and patients' tolerability.

RESULTS

The castor oil-based regimen was implemented in 17 patients. Three patients cancelled CCE because they could tolerate castor oil, but not liquid laxatives. The capsule excretion rate within the battery life was 88% (15/17). The mean large bowel transit time was 236 min. Approximately 70% of patients had satisfactory colon cleansing levels. CCE detected colon polyps (14/17, 82%) and colonic diverticulum (4/12, 33%). The sensitivity, specificity, and diagnostic accuracy rates for detecting colorectal polyps (size ≥ 6 mm) were 76.9%, 75.0%, and 76.4%, respectively. The sensitivity, specificity, and diagnostic accuracy rates for detection of diverticulum were 100% each. Twelve patients (71%) rated CCE as more than "good", confirming the new regimen's tolerability. No serious adverse events occurred during this study.

CONCLUSION

The castor oil-based regimen could reduce bowel preparation dose and improve CCE tolerability.

Key Words: Bowel preparation regimen; Castor oil; Colon capsule endoscopy; Colonoscopy; Colorectal diseases; Prospective study

Core Tip: Castor oil, a vegetable oil collected from castor oil plant seeds, is hydrolyzed into glycerin and retinoic acid in the small intestine, stimulating bowel movement in the small intestine. Among patients treated with castor oil as a booster, the rate of capsule excretion within battery life was 88%, whereas 70% of them had a more than "good" bowel cleansing level. The questionnaire of tolerability compared with previous colonoscopy showed that 71% of patients were satisfied with the new colon capsule endoscopy procedure. Sensitivity, specificity, and diagnostic accuracy of detecting colorectal polyps (size ≥ 6 mm) were 76.9%, 75.0%, and 76.4%, respectively.

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INTRODUCTION

Colonoscopy is a well-established examination for detecting various types of colorectal diseases, including inflammatory bowel disease and colorectal tumors[1-3]. In addition to disease detection, colonoscopy plays an indispensable role in colorectal cancer (CRC) prevention through detection and removal of precancerous adenomatous polyps and early CRC. Although colonoscopy is usually performed under conscious sedation, a significant number of patients undergoing colonoscopy complain of pain and discomfort even under sedation. Thus, pain associated with colonoscopy is a major obstacle that prevents patients from undergoing this procedure for colorectal disease detection.

Such painful nature of colonoscopy is considered to result in a lower examination attendance rate than that of other types of cancer screening methods[4,5]. Colon capsule endoscopy (CCE), a recently developed technique for the detection of colorectal diseases, was approved for reimbursement under the national health insurance system of Japan in 2014. CCE is recognized as a noninvasive imaging modality that can be performed in patients complaining of colonoscopy-associated pain and discomfort. In fact, the usefulness of CCE as an alternative screening method for CRC prevention has been reported by several groups[6-8]. However, a major

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weakness of CCE lies on the fact that bowel preparations for CCE require a larger volume of laxative than that used in conventional colonoscopy because of the need for completion of capsule excretion[9-13]. For smooth capsule excretion, > 4.5 L of polyethylene glycol (PEG) is usually required for CCE[9-13]. Thus, patients need to take more than twice the volume of PEG for the observation of the entire colon by CCE than that used for conventional colonoscopy. Such a high liquid laxative volume may reduce patients' tolerability and compliance.

Therefore, the development of a new bowel preparation method with comparable liquid volume to colonoscopy is necessary to increase patient tolerability of CCE. One way to achieve clean preparation and volume reduction of liquid laxative is to use a booster to accelerate capsule excretion though the colon. Castor oil, a type of vegetable oil collected from the castor oil plant seeds, is hydrolyzed into glycerin and retinoic acid by lipase in the small intestine, which stimulates the bowel movement in the small intestine[14-16]. Castor oil is widely used as a laxative in traditional medicine in western countries[14-16]. Indeed, several regimens consisting of PEG and castor oil, the latter of which functions as a booster, were proposed for the reduction of laxative liquid volumes. Such a booster effect by castor oil has the potential to accelerate capsule excretion through the colon and reduce the volume of the liquid laxative. Thus, the use of castor oil as a booster may help us develop tolerable bowel preparation methods for patients receiving CCE.

In this study, we aimed to determine the feasibility of a new bowel preparation regimen consisting of a low volume of PEG (2 L) combined with castor oil as a booster and provide evidence that it can achieve both effective capsule excretion and sufficient colon cleansing in CCE.

MATERIALS AND METHODS

Patient selection

In total, 20 patients who were suspected of having colorectal diseases were enrolled in this study. This prospective pilot cohort study was performed at Kindai University Hospital from September 2017 to August 2019. This study was approved by the Institutional Review Board of Kindai University Hospital (29-087) and the procedures were in accordance with the Declaration of Helsinki. All study participants, or their legal guardian, provided written consent prior to study enrollment. The clinical trial is registered with University Hospital Medical Information Network, using identifier UMIN000028694. Details can be found at https://upload.umin.ac.jp/cgi-openbin/ctr_e/ctr_view.cgi?recptno=R000032809.

Patient eligibility

Patients aged between 16 and 80 years suspected of having colorectal disease were included. All 20 patients (age range, 16-80 years; sex, six men and 14 women) underwent CCE because of previous incomplete colonoscopy in other facilities (n = 20), history of abdominal surgery (n = 7), or organ abnormalities, such as multiple diverticulum (n = 4) and adhesion after surgery (n = 6).

The exclusion criteria for this study were dysphagia, history of allergic reactions to the drugs used in this study (magnesium citrate, PEG, metoclopramide, and castor oil), possibility of pregnancy, possibility of bowel obstruction or stenosis based on symptoms, or scheduled magnetic resonance imaging within 2 wk after CCE.

Study outcomes

The primary outcome was the capsule excretion rate within battery life as evaluated by total large bowel observation rate, large bowel transit time, and bowel cleansing level using a five-point scale (excellent, good, fair, poor, and inadequate), as described in the Aronchick Global Assessment Scale[17] (Figure 1). The degree of colon cleansing level was rated in different segments of the colorectum (cecum, ascending colon, transverse colon, descending-sigmoid colon, and rectum).

The secondary outcomes were complications, diagnostic accuracy of colorectal lesion, and patients' tolerability evaluated using the CCE questionnaire. The diagnosis of colorectal disease obtained by CCE was verified by subsequent colonoscopy in our university hospital (Kindai University Hospital), which is a high-volume center and, thus, it is fully equipped with endoscopy devices and many experienced colonoscopists. Therefore, our facility can perform total colonoscopy even in patients who have undergone incomplete colonoscopy at other facilities.

Patient-reported outcome

To assess patient-reported outcome, the patients were asked to complete a questionnaire regarding the tolerability of CCE. The questionnaire included CCE bowel preparation, taste of castor oil as a booster, total period of CCE procedure, and overall evaluation of CCE examination. The satisfaction level was rated on a five-point scale (excellent, very good, good, fair, and poor) in each point.

CCE procedure

CCE was performed using PillCam COLON Capsule (Medtronic, Minneapolis, MN, USA). The details of our modified CCE regimen using castor oil, as a booster, are shown in Table 1.

Our regimen used 50 g of magnesium citrate (Magcorol P; Horii Pharmaceutical Industry, Ltd, Osaka, Japan) dissolved in 180 mL of water on the day before examination. On the examination day, patients took 1 L of PEG solution plus ascorbic acid (MoviPrep; EA Pharma Co., Ltd, Tokyo, Japan) together with 500 mL of water at 6:00 AM. Patients visited the hospital at 9:00 AM and took the capsule 30 min later. Then, metoclopramide (10 mg) intravenously administered. Patients went home after the capsule reached the duodenum. When they got home, they took 20 mL of castor oil (Himashi Oil; Yoshida Pharmaceutical, Tokyo, Japan) as a booster, together with 500 mL Moviprep and 250 mL water. After 1 h, they took 500 mL of Moviprep and 250 of mL water. When the capsule was not excreted at 2 h after receiving the castor oil, they took additional Magcorol P (50 g) dissolved in 180 mL water together with 20 mL of castor oil. Our regimen required 2 L of PEG, which is approximately 50% of the volume of the bowel preparation without castor oil.

Assessment of colon cleansing levels

The degree of the colon cleansing level was rated in different segments of the colorectum (cecum, ascending colon, transverse colon, descending-sigmoid colon, and rectum), as described in the Aronchick Global Assessment Scale[17], and the overall cleansing level in the entire colon was determined.

Statistical analysis

The sensitivity, specificity, positive predictive value, negative predictive value, accuracy of adenoma detection ≥ 6 mm, accuracy of adenoma detection ≤ 5 mm, and diverticula detection were calculated for each classification category. The statistical methods of this study were reviewed by biomedical statistician Satoru Hagiwara from Kindai University Hospital.

RESULTS

Patient characteristics

Seventeen patients (85%) successfully followed our modified CCE regimen using castor oil. Three patients cancelled CCE because they could tolerate only castor oil, but not liquid laxatives. Seven patients experienced incomplete colonoscopy because of an abdominal surgery history (Table 2). The reasons for taking CCE were abdominal pain, diarrhea or constipation, elevation of tumor markers, anemia, bloody stool, and follow-up examination results after colon polypectomy or after colon cancer operation.

Effects of castor oil on CCE

As shown in Table 3, the capsule excretion rate within the battery life was 88% (15/17) among patients treated with castor oil as a booster. Two patients did not expel the capsule within the battery life duration. Thus, the combination of PEG with castor oil for bowel preparation promoted capsule excretion in CCE.

The median time of large bowel transition was 236 min. The overall cleansing level of the colon was "excellent", "good", "fair", and "poor" in seven, five, four, and one cases, respectively. No cases were judged as having "inadequate" cleansing (Tables 3 and 4). Thus, > 70% (12/17) of patients treated with PEG in combination with castor oil as a booster exhibited enough level of colon cleansing for the detection of colorectal diseases by CCE. More detailed information regarding the colon cleansing levels at five different sites is shown in Figure 2.

The percentage of those who had a more than "good" bowel cleansing level was 70% (12/17). The percentages of patients exhibiting a cleansing level of "excellent" or "very good" were higher in the proximal than in the descending-sigmoid colon. Thus,

Table 1 Modified colon capsule endoscopy regimen using castor oil as booster

Modified colon capsule endoscopy regimen		
Day before endoscopy	21:00	Magnesium citrate P 50 g + water 180 mL
Day of endoscopy	06:00	PEG 1000 mL + water 500 mL
	09:00	Patient comes to the hospital
	09:30	Capsule ingestion, intravenous metoclopramide 10 mg
	10:00	Patient goes home after the capsule reaches the duodenum
	When patient reaches home	Castor oil 20 mL, PEG 500 mL + water 250 mL
	1 h later	PEG 500 mL + water 250 mL
	2 h later	Magnesium citrate 50 g + water 180 mL
	2 h later	Castor oil 20 mL

PEG: Polyethylene glycol.

Table 2 Patient characteristics (*n* = 17)

Characteristics	
Age (yr)	
mean ± SD	59.5 ± 16.8
Range	37-80
Sex, *n* (%)	
Male	3 (18)
Female	14 (82)
History of abdominal surgery, *n* (%)	7 (41)
Reason for colon capsule endoscopy, *n* (%)	
Abdominal pain	5 (29)
Constipation	5 (29)
Elevation of tumor marker	2 (12)
Follow-up examination after polypectomy	2 (12)
Anemia	1 (6)
Bloody stool	1 (6)
Follow-up after colon cancer surgery	1 (6)

Three patients were unable to take castor oil.

the distal sites of the colon tended to show poor cleansing compared with the proximal sites. Such lower cleansing levels at the descending-sigmoid colon can be partially explained by the presence of diverticulum at this site. In fact, the diverticulum was detected in four (80%) out of five patients with a "fair" cleansing level at the descending-sigmoid colon. Although floating of oil originating from the castor oil degradation was sometimes observed, the presence of oil in the colonic lumen did not affect the detection of colorectal disease.

Detection rates of colorectal diseases

CCE detected colon polyps (14/17, 82%) and colonic diverticulum (4/12, 33%). No patient had CRCs or inflammatory bowel disease (Table 3). These colorectal diseases diagnosed by CCE were verified by subsequent colonoscopy.

The sensitivity, specificity, and diagnostic accuracy rates in adenoma detection of ≥ 6 mm were 76.9%, 75.0%, and 76.4%, respectively (Table 4). Most cases of inconsistent

Table 3 Results of colon capsule endoscopy (*n* = 17)

Variables	*n* (%) or mean (range)
Capsule excretion rate within battery life	15 (88)
Large bowel transit time (min)	236 (16-725)
Cases within 60 min	5 (29)
Cleansing level (overall)	12 (70)
Excellent	6
Good	6
Fair	5
Poor	0
Polyp detection rate	14 (82)

Table 4 Colon capsule endoscopy detection

	Disorder	No disorder
Detection of adenoma ≥ 6 mm		
Positive test result	True positive: 10	False positive: 1
Negative test result	False negative: 3	True negative: 3
Sensitivity, 76.9%; Specificity, 75.0%; Diagnostic accuracy, 76.5%		
Detection of adenoma ≤ 5 mm		
Positive test result	True positive: 2	False positive: 1
Negative test result	False negative: 3	True negative: 3
Sensitivity, 50.0%; Specificity, 66.7%; Diagnostic accuracy, 55.6%		
Detection of diverticulums		
Positive test result	True positive: 4	False positive: 0
Negative test result	False negative: 0	True negative: 13
Sensitivity, 100%; Specificity, 100%; Diagnostic accuracy, 100%		

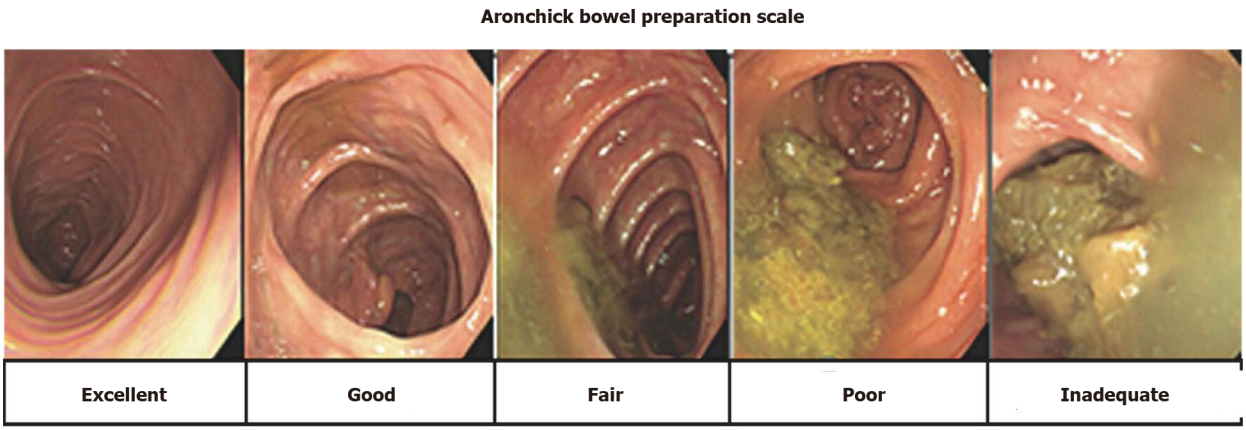

Figure 1 Aronchick Global Assessment Scale[17].

diagnosis between CCE and colonoscopy were those bearing colon polyps ≤ 5 mm because the diagnostic accuracy for small polyps ≤ 5 mm was low. Indeed, the sensitivity, specificity, and diagnostic accuracy rates in detecting adenoma ≤ 5 mm were 50.0%, 66.7%, and 55.6%, respectively (Table 4). Regarding the detection of diverticulum, the sensitivity, specificity, and diagnostic accuracy rates were all 100%

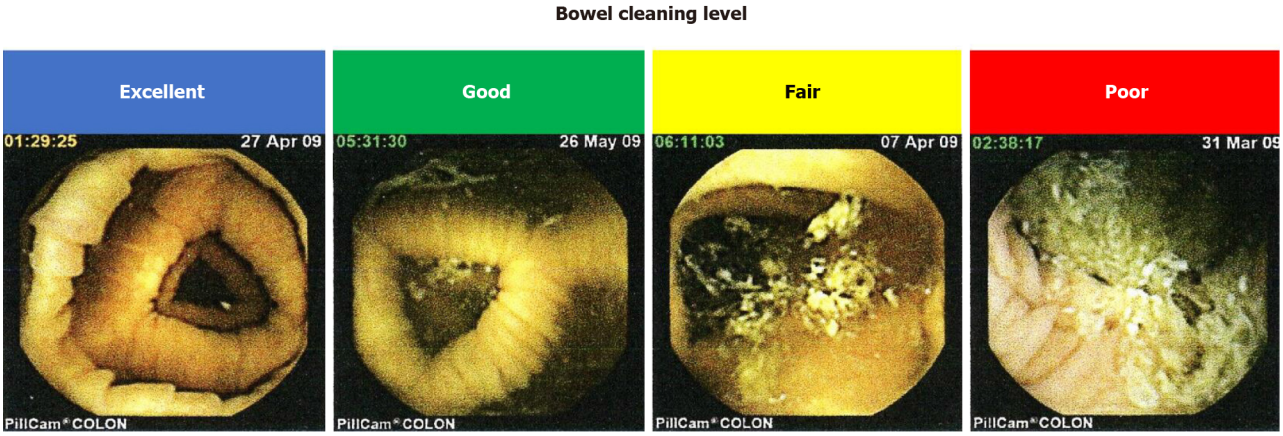

Figure 2 Degree of the colon cleansing level in different segments of the colorectum (cecum, ascending colon, transverse colon, descending-sigmoid colon, and rectum).

(Table 4).

Assessment of tolerability using the questionnaire

All participants completed the questionnaire regarding the tolerability of the bowel preparation method using castor oil as a booster for CCE. The results of the questionnaire evaluating the tolerability of our new CCE procedure from four different aspects are shown in Figure 3. Concerning total preparation of CCE, castor oil as a booster, total procedure time, and overall evaluation of CCE, 41% (7/17), 53% (9/17), 59% (10/17), and 71% (12/17) of the participants, respectively, graded each component of our new procedure as more than "good".

Complications

None of the patients experienced adverse events associated with the use of castor oil as a booster, such as bleeding, perforation, abdominal pain, vomiting, aspiration pneumonia, or allergic reaction.

DISCUSSION

In this study, we assessed the safety and utility of castor oil-boosted bowel preparation for CCE and found that this method can achieve capsule excretion and colon cleansing in CCE. This new bowel preparation method enabled us to reduce the volume of liquid laxatives to 3.5 L after using castor oil as a booster, as evidenced by the fact that 17 patients (85%) successfully completed CCE using our castor oil-boosted bowel preparation without causing severe adverse events. As aforementioned, conventional laxative regimen for CCE requires large amounts of liquid laxatives (4.5-6.0 L) to obtain a sufficient capsule excretion rate (70%-95%)[9,11,12,18,19]. Nakaji *et al*[20] showed that in their historical control group, in which patients did not receive castor oil (total liquid laxatives, 4.1 L; n = 82), the capsule excretion rate (total large intestine observation) was 83%, the average colon transit time was 259 min, the bowel cleaning level (excellent/good) was 82% and the colorectal polyp detection rate was 49%. Interestingly, no adverse events were observed.

Our castor oil-boosted regimen achieved a significant reduction in the liquid laxative volume and a high capsule excretion rate (15/17, 88%). Such a reduction in liquid laxative volume achieved tolerability of CCE, as > 70% of patients were satisfied with the CCE in the overall assessment in the questionnaire scores. In addition to tolerability, the colon cleansing levels by castor oil-based bowel preparation methods were comparable to those of conventional preparation methods. Collectively, these data suggested that the castor oil-boosted bowel preparation method is useful and safe for CCE.

Although the castor oil-boosted colon preparation regimen used in this study was tolerable in most patients undergoing CCE, there is still room for improvement in our regimen. In the questionnaire, half (54%) of the patients pointed out the unique taste and sticky texture of castor oil. Therefore, it is desirable to encapsulate or add flavor to the oil to resolve this issue. Nevertheless, > 70% of the patients rated the castor oil-

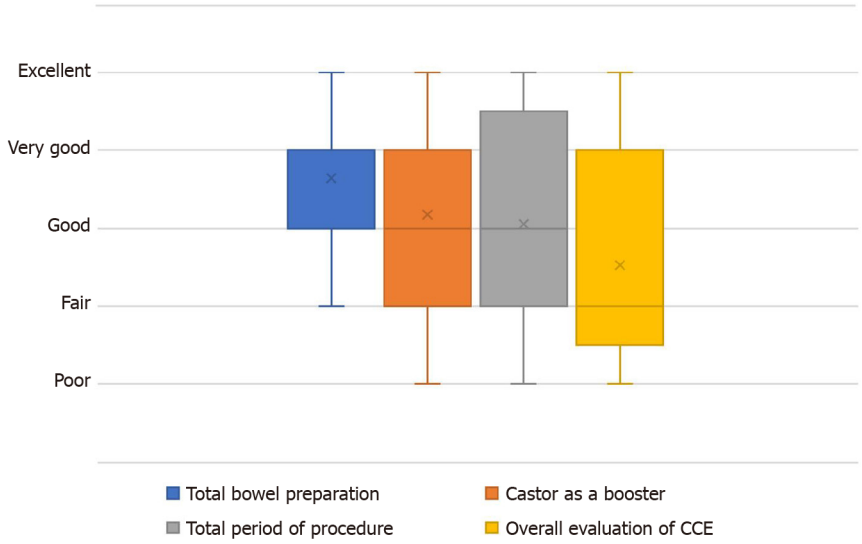

Figure 3 Results of the questionnaire. CCE: Colon capsule endoscopy.

boosted CCE in the present form as "good" or "better". Moreover, 76% of the patients indicated that they are willing to undergo CCE in the next examination.

Aside from castor oil, other boosters are used for the reduction of liquid laxative volume. Togashi *et al*[21] used gastrografin and reported a high capsule excretion rate within battery life (97%). However, gastrografin cannot be taken by individuals allergic to iodine. Thus, it is not widely used as a booster for CCE.

In line with our data, Ohmiya *et al*[22] recently reported the safety and feasibility of castor oil-boosted bowel preparation methods for CCE in a multicenter retrospective study. In their study, the capsule excretion rate within its battery life with castor oil was 97%, which is comparable to that of gastrografin-boosted preparation. Given the possibility of allergic reactions to gastrografin, castor oil appears to be superior as a booster despite the almost equal capsule excretion rates and the comparable volumes of liquid laxatives.

In our study, the mean large bowel transit time was 236 min (range, 16–725 min), which was longer than that reported by Ohmiya *et al*[22]. The longer colon transit time in our regimen as compared with that reported in the previous study[22] may be explained by the presence or absence of sodium picosulfate, sennoside, or mosapride. They administered sodium picosulfate or sennoside the day before CCE and mosapride on the day of CCE. In contrast, the patients enrolled in this study did not take any of these drugs. Therefore, additional laxatives and mosapride may further enhance the efficacy of castor oil-boosted bowel preparation for CCE. Whether the addition of sodium picosulfate, sennoside, or mosapride is absolutely required for CCE with castor oil-boosted awaits the performance of further prospective studies. Interestingly, a significant number of patients (5/17, 29%) exhibited very fast colon transit times (within 60 min) in our regimen, and the findings were consistent in 80% of them. In contrast, four cases were found in the group with a very slow transit time of ≥ 300 min, and the findings were consistent in 75% of them. However, we did not obtain significantly different results because of the limited data.

Concerning the colorectal cleansing levels, > 70% (12/17) of the patients who used our castor oil-boosted regimen achieved more than "good" bowel preparation. These data regarding the cleansing level were comparable to those of previous reports[10,13,23-25]. Therefore, the addition of sodium picosulfate, sennoside, or mosapride to our regimen can affect the colon transit time rather than the cleansing level. Despite a relatively small number of cases and poor detection rates of adenomas ≤ 5 mm and no sampling the tissue for capsule endoscopy as inherent limitation, we evaluated the diagnostic performance of colorectal polyps. The sensitivity, specificity, and diagnostic accuracy rates in detecting colorectal polyps with a maximum size ≥ 6 mm were approximately 75%. Comparable to our present data, the sensitivity and specificity rates of second-generation CCE with at least one polyp with a size ≥ 6 and ≤ 5 mm were reported to range between 84% and 94% and between 64% and 94%, respectively [7,24-27].

CONCLUSION

Reduction of liquid laxative volume and sufficient capsule rate can be achieved using our castor oil-boosted bowel preparation method for CCE. This study provides evidence regarding the safety and feasibility of this new bowel preparation method despite its limitation in the study design (*i.e.*, the small cohort size in a single university hospital). Nevertheless, it should be emphasized that the castor oil-boosted bowel preparation may help us perform tolerable and safe CCE, and this needs to be confirmed in future prospective multicenter studies.

ARTICLE HIGHLIGHTS

Research background

Colon capsule endoscopy (CCE) is a usefulness imaging modality because it can be performed non-invasively. However, there is one major limitation of CCE, as bowel preparations for CCE require a larger volume of laxative than that used in conventional colonoscopy because of the need for capsule excretion completion. Therefore, the development of a new bowel preparation method with comparable liquid volume to colonoscopy is necessary to increase patients' CCE tolerability.

Research motivation

Castor oil could have the potential to accelerate the capsule excretion through the colon and reduce the volume of the liquid laxative.

Research objectives

In this study, we attempted to clarify the effectiveness and tolerability of our modified regimen, which uses castor oil as a booster.

Research methods

Twenty patients suspected of colorectal diseases were enrolled in this prospective cohort study. We used modified CCE regimen using castor oil as a booster. The capsule excretion rate within the battery life, bowel cleansing level in different segments of the colorectum, and detection rates of colorectal lesions were evaluated. In this study, we asked the patients to complete a questionnaire to assess the CCE tolerability.

Research results

Seventeen patients (85%) successfully followed our castor oil–based regimen, whereas three patients (15%) were unable to ingest castor oil because of its taste and failed to expel the capsule within the duration of battery life. The mean large bowel transit time was 236 min. The percentage of patients with satisfactory colon cleansing levels was 70%. The sensitivity, specificity, and diagnostic accuracy rates in detecting colorectal polyps with a size ≥ 6 mm were 76.9%, 75.0%, and 76.4%, respectively. Twelve patients (71%) evaluated the CCE procedure as more than "good" in the questionnaire, thus confirming the tolerability of our new regimen.

Research conclusions

This study shows the safety and utility of modified bowel preparation for CCE, which uses castor oil, and found that that it can achieve capsule excretion, colon cleansing, high tolerability of CCE preparation, and reduction of liquid laxative volume.

Research perspectives

A prospective multicenter trial is required to assess the safety and utility of castor oil–boosted bowel preparation for CCE.

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EVIDENCE REVIEW

Influence of nutritional status in the postoperative period of patients with inflammatory bowel disease

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Abstract

Inflammatory bowel diseases (IBDs) are a group of chronic inflammatory diseases that affect the gastrointestinal tract, including Crohn's disease (CD) and ulcerative colitis. Surgery is a treatment option, and more than half of the patients with CD will undergo surgical interventions over the course of the disease. Postoperative complications are common in IBD patients, the most frequent being intra-abdominal sepsis, infection of the surgical site, and adynamic ileum, and nutritional status is a factor that can influence postoperative outcome. Recent studies have shown that malnutrition, obesity, sarcopenia, and myosteatosis are predictors of surgical complications. However, most were retrospective studies with small patient samples and heterogeneity of clinical and nutritional assessment methods, which limit the extrapolation of data. Therefore, knowing the pathophysiological mechanisms of IBD and identifying the best parameters for assessing nutritional status are essential for prompt implementation of adequate nutritional interventions.

Key Words: Inflammatory bowel diseases; Crohn disease; Ulcerative colitis; Nutritional status; Postoperative complications; Surgery

Core Tip: Nutritional status influences the postsurgical results of patients with inflammatory bowel diseases (IBDs). Despite the limitations of previously published studies, malnutrition, obesity, sarcopenia, and myosteatosis were identified as negative predictive factors for postoperative complications in people diagnosed with IBDs.

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INTRODUCTION

Inflammatory bowel diseases (IBDs) are a group of chronic inflammatory diseases that affect the gastrointestinal tract, and the most common are Crohn's disease (CD) and ulcerative colitis (UC)[1]. Although the incidence of IBD in most Western countries is stable, the prevalence exceeds 0.3% in some regions, which results in a high disease burden[2]. In addition to drug therapy, surgical interventions are needed by most patients with CD[3]. In IBD, surgery is indicated for clinical intractability, complications, and neoplasms, and is considered an option in CD patients with isolated ileal disease[4]. Postoperative complications are frequent in IBD, especially intra-abdominal sepsis, surgical site infection (SSI), and adynamic ileum[5-9]. Increased understanding of the effects of nutritional status on surgical outcomes and the patient characteristics that are predictive of surgery-associated complications are essential for prompt implementation of adequate nutritional interventions[10]. The purpose of this review was to gather scientific evidence on the influence of nutritional status in the postoperative period of people with IBD.

IBDs

Although the details are not completely clear, it is assumed that the pathogenesis of IBD involves genetic, environmental, and immunological factors[1]. The clinical course of the disease is highly variable but is most often characterized by periods of activity and remission[11]. The last 100 years have seen an increase and stabilization in the occurrence of IBD in Western countries, while in some countries in Africa, Asia, and South America, the incidence continues to increase and still lacks stability. This trend has been attributed mainly to Westernization and recent industrialization in those regions. Given the reality and economic impact of IBD, healthcare systems and professionals must be prepared to implement prevention policies, conduct scientific research, and provide adequate attention to the IBD population[12,13]. Currently, the therapeutic objectives of IBD include symptomatic treatment, induction of clinical remission, and other goals, such as the prevention of complications, healing of the mucosa, improvement of quality of life, and remission without the need of steroids[14,15]. In addition to medications (*e.g.*, aminosalicylates, corticosteroids, immunomodulators, and immunobiologicals) and enteral nutritional therapy exclusively for the pediatric population, surgical procedures can also be used to treat IBD patients[16,17].

SURGICAL TREATMENT

Elective surgery may be indicated for UC and CD patients[18]. IBD patients presenting with toxic colitis, bleeding, perforations, obstructions, and abscesses usually require emergency surgical interventions[19]. Chronic intestinal inflammation and prolonged treatment with immunosuppressive drugs increase the risk of the development of gastrointestinal neoplasms in IBD patients[20]. The presence of IBD in patients with colorectal cancer increases the risk of prolonged hospitalization following surgery, hospital readmission within 30 d of discharge, open surgery, total colectomy, total proctocolectomy, deep vein thrombosis, and postoperative infection[21].

Most people diagnosed with CD will need surgery, and approximately half will have a recurrence after intestinal resection. The presence of disease in any region of the small intestine, perianal fistula, and an age between 45 and 59 years increase the relative risk of surgery[3]. The main objectives of surgical treatment are symptom control, maintenance of intestinal function, and anatomical preservation of organs[18]. Studies have shown that the percentage of postoperative complications varies from 9% to 33%, with intra-abdominal sepsis following an anastomotic leak, intra-abdominal collection, or a parietal abscess; SSI, and adynamic ileum (*i.e.* the absence of bowel

muscle contraction movements)[22,23].

Patients with CD undergoing ileal resection often experience malabsorption of bile acids. Bile acids are essential for the digestion of fats, and their active reabsorption occurs in the distal ileum. The absence of this portion of the intestine compromises the digestion of lipids in the diet, promoting steatorrhea, fecal excretion of fats. In addition, ileal resection and the consequent accumulation of bile acids in the lumen can increase intestinal permeability and motility, impair the integrity of the mucosa, promote bacterial overgrowth, and favor the formation of kidney and gallstones. The selenium homotaurocholic acid test is the gold standard method for detecting the condition, and the first line of treatment is the use of intraluminal bile acid ligands such as cholestyramine[24-27]. Surgery is performed less often in patients with UC and may be indicated in cases of neoplasia, dysplasia, and refractory disease. The most common interventions include total proctocolectomy with permanent terminal ileostomy and the making of an ileal pouch with anastomosis to the anal canal. Among the main risk factors for both early colectomy and late colectomy are male sex and hospitalization at diagnosis[18,28]. The occurrence of postoperative complications in UC varied from 9% to 65% (early) and from 17% to 55% (late), and was higher than the occurrence of complications in CD. Adynamic ileum, infection, and pouchitis were the most common complications observed in the UC population[29,30]. Compared with open surgery, laparoscopy is a minimally invasive technique with better 30 d postoperative outcomes, especially in relation to the need for a pulmonary ventilator after 48 h, organ space infection, superficial and deep SSI, urinary tract infection, and renal failure[31]. It should be noted that regardless of the type of surgery, the surgeon's primary goal is to ensure performance of a long-lasting, reproducible, and safe procedure[32].

Although the literature is controversial, a systematic review and meta-analysis found that the use of corticosteroids and anti-tumor necrosis factor increased the risk of intra-abdominal infections in the postoperative period[33]. In addition, in the era of biological products, it has been observed that after non-elective surgery, mortality has remained high in UC and has slightly decreased in CD. A population-based study found that mortality was primarily associated with comorbidities and age[34,35].

NUTRITIONAL STATUS AND POSTOPERATIVE COMPLICATIONS

Surgery is an invasive procedure that results in tissue damage, the breaking of a physical barrier, and possible exposure to microorganisms that result in inflammation and metabolic stress. Inflammation involves innate and adaptive immune responses and pro- and anti-inflammatory mediators. The severity of the inflammatory response depends, among other factors, on age and the type and location of the surgery, the medications used, and preoperative health status[36].

Malnutrition

In patients with IBD, malnutrition often prolongs the inflammatory response and slows recovery from illness and surgery, hinders wound healing, and is related to increased hospital stay and healthcare costs[37-39]. Various factors contribute to the deterioration of nutritional status in this population, such as reduced food intake, increased intestinal losses, malabsorption of nutrients, increased nutritional needs associated with systemic inflammation, and iatrogenic factors (*e.g.*, surgery and medications)[40,41]. As malnutrition is a modifiable risk factor for adverse outcomes of surgery, prompt identification enables early nutritional interventions[10], several studies have investigated methods of preoperative nutritional assessment[42-45].

Body mass index (BMI) is a practical, widely used predictor of surgical complications. A low BMI seems to increase the risk of postoperative infectious complications and intra-abdominal sepsis in patients with CD, and is better predictor than serum albumin concentration[46,47]. However, recent studies have identified preoperative hypoalbuminemia is a risk factor for complications in both CD and UC, and that the incidence of undesirable outcomes was increased in eutrophic patients with hypoalbuminemia[45,48]. It is noteworthy that the studies were retrospective and had small patient samples, therefore, the results should be interpreted with caution[46,47]. In fact, serum albumin may not be a good marker of the nutritional status of patients with IBD, especially in the active phase[49].

Both albumin and C-reactive protein (CRP) are acute-phase proteins, and their concentrations change with the inflammation that occurs after surgical trauma[50]. The CRP/albumin ratio (CAR) is considered as a novel prognostic index based on inflam-

mation. A study including IBD patients undergoing elective colorectal surgery found that postoperative CAR predicted surgical complications, more accurately than CRP alone. Patients with a CAR ≥ 2.2 had increased risks of complications, prolonged hospital stays, and SSIs, which indicated that value was of possible use as a cutoff for the early detection of undesirable results[51]. The CAR was also able to predict postsurgical survival in people with colorectal cancer[52].

Considering the limitations of nutritional status markers, the preoperative assessment must be complete, including the assessment of nutritional risk scores and information about food consumption and weight loss[53]. The guidelines of the European Society for Clinical Nutrition and Metabolism on nutrition in surgery define severe nutritional risk as the presence of least one of the following: Weight loss > 10%-15% in 6 mo; a BMI < 18.5 kg/m^2; Subjective Global Assessment grade C or Nutritional Risk Screening > 5; or a preoperative serum albumin < 30 g/L without evidence of hepatic or renal dysfunction[38].

Obesity

The prevalence of overweight and obesity has increased in both the general population and in people with IBD[54-56]. Obesity is an inflammatory state, and the metabolic activity of adipose tissue includes the secretion of pro- and anti-inflammatory cytokines that can promote immune-mediated diseases such as IBD[57]. Data on the influence of obesity on IBD are controversial. Some studies show an association with unfavorable outcomes of the disease, such as the need for surgery and hospitalization, reduced drug efficacy, and complications[57-59]. Others have not demonstrated such associations[60-63] and consider obesity to be a marker of less severe disease[62].

It has been suggested that obesity has a negative influence on postoperative results [57]. Despite having less disease severity at the time of surgery, obesity increased the risk of SSI in CD patients after ileocolic resection, as well as the risk of requiring laparoscopic modification of conventional surgery, which may lead to worse outcomes in the future[31,64]. A recent meta-analysis concluded that obesity was associated with general postsurgical complications, high SSI rates, greater blood loss, and longer hospital stays in patients with IBD[65]. A point to be highlighted is that SSI is related to the size of the surgical extraction site, which tends to be larger in obese patients[64]. Because SSI is likely to prolong hospitalization and has been shown to increase readmission rates after colectomy, preoperative weight loss has been suggested in order to minimize it[66,67].

Few studies have investigated the effect of weight loss on the outcomes following surgery for IBD[57]. Bariatric surgery is one of the ways of treating obesity[68], but its use in IBD is limited because of the complexity of those diseases and the scarcity of studies to support the decision-making of health professionals[69]. Reviews of the impact of bariatric surgery on the clinical course of IBD found that it is relatively safe and reduces the risk of complications[69,70]; however, more robust original articles evaluating surgical outcomes must be added to the literature to increase the reliability of those findings. It should be noted that malnutrition is common in patients with IBD and that people with high BMIs may also have nutritional deficiencies[37,71,72]. Therefore, it is essential to carry out a thorough nutritional assessment of possible candidates for bariatric surgery[69].

Most studies use BMI to determine obesity. However, the index has limitations, such as the inability to distinguish body composition and fat distribution. Although interest in the role of visceral fat in IBD patients has increased recently, few clinical trials have been conducted. The available results include associations between body fat measurements (mesenteric fat index, morphometric analysis, visceral fat area) and inflammation and postsurgical complications that were not observed when BMI was chosen as a variable[73-75].

Sarcopenia

In IBD patients, malnutrition and excess weight can coexist with sarcopenia, which is a skeletal muscle syndrome characterized by progressive and generalized reduction in the quantity and quality (*i.e.* strength or physical performance) of muscle mass[76]. The etiology of sarcopenia is multifactorial, involving aging, physical inactivity, presence of other diseases (*e.g.*, inflammatory, malignant and endocrine), organ failure, and inadequate intake or use of nutrients (*e.g.*, anorexia, malabsorption, limited access to healthy foods and drug interactions). In the last 10 years, several studies conducted in different populations reported that muscle strength has a prominent role[77,78].

In a meta-analysis, sarcopenia was found to be an independent risk factor for the need of surgery and the occurrence of postoperative complications, with no difference between UC and CD. However, the data should not be extrapolated, as all the studies

evaluated sarcopenia only by body composition and the muscle mass; type of surgery and postsurgical outcome data were heterogeneous[79]. In a study that evaluated only people with CD, Galata *et al*[80] observed that the skeletal muscle mass index was the only risk factor for abscesses and anastomotic leaks. Patients with sarcopenia had lower serum albumin levels and BMIs and higher CRP levels, which can be useful indicators for nutritional screening of the syndrome[79].

Although it is more common in malnourished people, sarcopenia can affect those who are overweight. A study carried out in 90 IBD patients with sarcopenia defined as a low skeletal muscle mass in a computed tomography cross-section at the L3 vertebral level, found that a BMI ≥ 25 kg/m² predicted the need for surgery. However, the sample number was limited (n = 3) and there was no information on the surgical results[81].

Myosteatosis

Myosteatosis is a negative prognostic factor in cancer and has been associated with worse overall survival in a variety of cancers[82,83]. The pathophysiology of myosteatosis is not well understood, but it is believed that there is a relationship between aging and excess weight that results in ectopic fat deposition in skeletal muscle[84]. O'Brien *et al*[85] found that the hospital stays were longer and readmissions 30 d after bowel resection were more frequent in IBD patients with myosteatosis. There are few recent studies of the effects of the change in body composition that occurs in myosteatosis. Better knowledge of the pathogenesis and validation of diagnostic criteria for myosteatosis are essential for conducting reliable studies to elucidate the impact of this condition on postoperative evolution and to accurately assess preoperative nutritional status[83].

Nutritional support

Insufficient food intake increases the risk of postoperative complications of abdominal surgery. The optimization of nutritional status in the preoperative period contributes to better surgical results in CD patients[86,87]. Given the importance of perioperative nutritional support, new IBD guidelines recommend early initiation of nutritional therapy in patients with malnutrition and/or unsatisfactory food consumption. The recommendation stems from a prediction of the inability to eat for more than 7 d in the perioperative period and impossibility of maintaining an oral intake above 60%-75% of nutritional needs for more than 10 d[27].

The choice of the type of nutritional therapy will depend on the clinical condition and nutritional status of the patient. Whenever possible, one should choose enteral nutrition (EN) over parenteral nutrition (PN). However, if EN does not supply more than 60% of the energy needs, then EN should be supplemented by PN, especially in the perioperative period. Exclusive PN is indicated in patients with diarrhea and severe vomiting, absence of access, bowel obstruction, severe shock, intestinal ischemia, high output fistula, and severe intestinal bleeding[27,53].

Most of the guidelines contained in the Enhanced Recovery After Surgery protocols can be applied to IBD patients undergoing surgical interventions. From a metabolic and nutritional perspective, some precautions must be taken in order to speed up postoperative recovery and reduce hospital stay. They include avoiding long periods of fasting before surgery, promoting metabolic and blood glucose control, reducing factors that intensify catabolism or impair the function of the gastrointestinal tract, re-establishing oral feeding as soon as possible, and promoting early mobilization in order to favor protein synthesis[27,38,53].

CONCLUSION

Surgical intervention during the course of IBD is a common practice, and postsurgical complications such as intra-abdominal sepsis, SSI, and adynamic ileum are prevalent. Nutritional status that involves malnutrition, obesity, sarcopenia, and myosteatosis is predictive of the worst outcomes of surgery by increasing the risk infectious and noninfectious complications. Further studies are needed to understand the pathophysiological mechanisms, standardize diagnostic criteria and determine the best preoperative nutritional assessments. This knowledge is essential to establish measures to prevent postsurgical complication in IBD patients.

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LETTER TO THE EDITOR

Overview on drug-induced liver injury in Brazil

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Abstract

Drug-induced liver injury (DILI) is an uncommon event in clinical practice, which makes knowing its true incidence difficult. Prospective, retrospective and registry-based studies are the most important methods to obtain epidemiological data on DILI. Latin America (LA) has a historical lack of prospective studies on this topic. New definitions and the creation of hepatotoxicity registries have significantly improved the epidemiological understanding of hepatic drug reactions in several regions of the world. The Latin American DILI network, referred to as LATINDILI, has been created in 2011, and recently published its own DILI recommendations describing the most relevant issues on the management of hepatotoxicity in general, and those based on findings from our own LA experience in particular. Although most of the registries do not carry out population-based studies, they may provide important data related to the prevalence of DILI. The joint work among researchers and the corresponding health and regulatory authorities should be stimulated due to the high impact that hepatotoxicity represents for public health.

Key Words: Hepatotoxicity; Drug-induced liver injury; Drug-induced liver injury registries; Herbs; Hepatitis

Core Tip: Liver damage induced by drugs and herbs was historically underreported in Latin America until the advent of a Latin American Registry of Hepatotoxicity (LATINDILI), which progressively improved knowledge about the most frequently involved drugs inducing liver injury in this region. This article letter emphasizes on the value of being able to centralize cases linked to hepatotoxicity in a Latin American drug-induced liver injury network, and discuss the present and future advantages of this

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valuable tool, which should work along with regulatory entities to achieve a high impact on public health policy.

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TO THE EDITOR

I have read with great interest the systematic review by Becker *et al*[1], analyzing Drug-induced liver injury (DILI) publications in Brazil. The authors carried out a thorough search on the main bibliographic sources over a long period of time, including several decades.

Our group published more than a decade ago a review on DILI articles reported from Latin America (LA) up to 2010[2]. Only well documented case reports and series with a small number of patients could be identified. We found the same difficulties to Becker *et al*[1], since the definitions used for DILI were heterogeneous at that moment, and we did not find any prospective or retrospective studies carried out with a careful and detailed design that would had involved a large number of patients[2].

Many papers published before 2011 do not meet the criteria for DILI proposed by an expert meeting led by Aithal *et al*[3], which defined hepatotoxicity as (1) An ALT elevation ≥ 5 upper limit of normal (ULN), (2) An ALP elevation ≥ 2 ULN, or (3) An ALT elevation ≥ 3 ULN with a simultaneous elevation of total bilirubin concentration ≥ 2 ULN[3].

Of note, liver enzymes elevation below this cutoff are nowadays interpreted as adaptive phenomena. This is a very frequent asymptomatic biochemical issue observed at the beginning of drug intake, and it should not be initially interpreted as hepatotoxicity, because these biochemical parameters usually return to normal values despite continued drug consumption[4].

All DILI articles coming from LA should mention our LATINDILI registry, because, for the first time, we have a very well-structured hepatotoxicity network capable of recruiting patients associated with liver damage induced by drugs, thus being able to study the epidemiological behavior of medicaments and herbs used more often in our region[2]. This ambitious research project became a registry in 2011, and has already recruited more than 400 patients, with 8% of them corresponding to herbal-induced liver toxicity (HILI). Unfortunately, our registry was not mentioned by Becker *et al*[1]. However, its recognition would have help them to establish better reference points for comparisons within the region and guidance on DILI distinction based on our operational criterion[2].

LATINDILI is a collaborative and interdisciplinary network aimed to (1) Establish the characteristics of DILI expression, search for risk factors, and evaluate the outcome; (2) Improve the instruments for causality assessment; (3) Increase knowledge on etiopathogenic mechanisms and identification of susceptible subjects; and (4) Help to develop diagnostic and predictive biomarkers in DILI[2].

Interestingly, the authors also stated that their research is expected to broaden the debate to establish a solid pharmacovigilance policy and the creation of a wide national DILI monitoring network and his integration with other DILI networks[1]. This is a very important point linked to one of the main objectives of DILI registries, which highlight the importance of working in close connection with regulatory and health authorities to strengthen both pharmacovigilance and the reporting cases of drug-induced liver reactions[5].

In addition, one of the most relevant objectives from our registry is to make physicians fully aware that hepatotoxicity is a distinct disease in which we have to improve its early diagnosis and management, and to be able to report these cases to the LATINDILI registry. If this feedback works in a regular and organized manner, it will allow clinicians to design and facilitate the carry out of multicenter clinical trials to assess the effect of new therapeutic agents with potential to induce idiosyncratic DILI [6].

Finally, LA already has its recommendation position paper for DILI management, which include our own data, and reinforces points exclusively inherent to LA, such as the differential diagnoses that should be made regarding the presence of tropical diseases, which can be mistakenly interpreted as DILI.

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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.

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ORIGINAL ARTICLE

Prospective Study

Addition of castor oil as a booster in colon capsule regimens significantly improves completion rates and polyp detection

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Institutional review board statement: This study was approved and registered on the November 15, 2019, as a service evaluation project by the process improvement department which is part of the quality safety and risk management directorate of Tallaght University Hospital, Tallaght, Dublin 24, Ireland.

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Abstract

BACKGROUND

Incomplete excretion rates are problematic for colon capsule endoscopy (CCE). Widely available booster regimens are suboptimal. Recently published data on one day preparation CCE protocol using castor oil appeared effective.

AIM

To assess the impact of adding castor oil to a standard split-dose (2-d) preparation in an unselected Western patient cohort.

METHODS

All patients aged 18 or more referred to our unit for a CCE over a 5-mo period were prospectively recruited. Controls were retrospectively identified from our CCE database. All patients received split bowel preparation with Moviprep® [polyethylene glycol (PEG)-3350, sodium sulphate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid for oral solution; Norgine B. V, United States], a PEG-based solution used predominantly in our colonoscopy practice. Control booster regimen included Moviprep® with 750 mL of water (booster 1) on reaching the small bowel. A further dose of Moviprep® with 250 mL of water was given 3 h later and a bisacodyl suppository (Dulcolax®) 10 mg after 8 h, if the capsule was not excreted. In addition to our standard booster regimen, cases received an additional 15 mL of castor oil given at the time of booster 1. A nested case control design with 2:1 ratio (control:case) was employed. Basic demographics, completion rates, image quality, colonic transit time, diagnostic yield and polyp detection were compared between groups, using a student *t* or chi-square tests as appropriate.

form is not applicable as this study has been registered as a service evaluation project by the process improvement department which is part of the quality safety and risk management directorate in our hospital.

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RESULTS

One hundred and eighty-six CCEs [mean age 60 years (18-97), 56% females, n = 104], including 62 cases have been analysed. Indication breakdown included 96 polyp surveillance (51.6%), 42 lower gastrointestinal symptoms (22.6%), 28 due to incomplete colonoscopy (15%), 18 anaemia (9.7%) and 2 inflammatory bowel disease surveillance (1.1%). Overall, CCE completion was 77% (144/186), image quality was adequate/diagnostic in 91% (170/186), mean colonic transit time was 3.5 h (0.25-13), and the polyp detection rate was 57% (106/186). Completion rates were significantly higher with castor oil, 87% cases (54/62) *vs* 73% controls (90/124), P = 0.01. The number needed to treat with castor oil to result in an additional complete CCE study was 7, absolute risk reduction = 14.52%, 95% confidence interval (CI): 3.06- 25.97. This effect of castor oil on excretion rates was more significant in the over 60 s, P < 0.03, and in females, P < 0.025. Similarly, polyp detection rates were higher in cases 82% (51/62) *vs* controls 44% (55/124), P = 0.0001, odds ratio 5.8, 95%CI: 2.77-12.21. Colonic transit times were similar, 3.2 h and 3.8 h, respectively. Image quality was similar, reported as adequate/diagnostic in 90% (56/62) *vs* 92% (114/124).

CONCLUSION

In our capsule endoscopy centre, castor oil addition as a CCE booster significantly improved completion rates and polyp detection in an unselected Western cohort.

Key Words: Castor oil; Colon capsule endoscopy; Bowel preparation; Completion rates; Excretion rates

Core Tip: This is the largest prospective study to date, assessing the impact of castor oil and its novel use as a colon capsule endoscopy (CCE) booster in an unselected cohort. Our study shows that adding castor oil to a simple split-dose CCE bowel preparation regime has a significant impact on capsule excretion rates and polyp detection.

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INTRODUCTION

Colon capsule endoscopy (CCE), as a diagnostic tool, has emerged as a viable alternative to colonoscopy. Patient preference, incomplete colonoscopy and contraindications to colonoscopy represent the majority of current CCE indications. There is growing international data to validate its use in colonic polyp screening where it has been shown to outperform colonoscopy in polyp detection[1], and in colonic polyp surveillance where it has been shown to reduce colonoscopy burden in patients with normal CCE[2]. Given its ability to assess the small bowel, CCE also offers a unique non-invasive option for inflammatory bowel disease (IBD) surveillance[3,4].

Allowing for variation between sites, CCE bowel preparation regimens are predominantly polyethylene glycol (PEG) based[5]. Patients are initially given PEG to cleanse the colon and this is followed by boosters to ensure CCE excretion. A complete study requires continuous image capture from the caecum to the haemorrhoidal plexus within the battery life of the capsule. Unfortunately, incomplete CCE remains problematic with significant variation in reported excretion rates ranging from as low as 70% to as high as 88%[6]. A further potential drawback of CCE is inadequate bowel cleansing. A recent meta-analysis reported median rates of adequate cleansing of 78% and 81% with CCE-1 and CCE-2, respectively[7]. This can be explained by its inability to insufflate the colon, aspirate liquids, control its transit speed, and clean the mucosal

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surface[6]. Despite its technical limitations, CCE appears to have similar bowel preparation rates to colonoscopy[8].

Multiple booster and cleansing agents have been proposed in the literature in an attempt to improve CCE excretion and bowel preparation rates. Among these, a novel use of castor oil as an additional booster agent in CCE practice has been studied. Castor oil is a pale-yellow vegetable oil pressed from castor beans, produced by the Ricinus plant found mainly in tropical regions. Aside from its other medicinal uses, which include skin care, castor oil has been used as a laxative in traditional medicine for hundreds of years[9].

More recently, the use of castor oil in CCE has been described in several studies. In 2016, the addition of castor oil to CCE boosters has been trialled in a small number of dialysis patients with the aim of reducing liquid loading and resulted in 100% excretion rates (20/20)[6]. A further study looked at the addition of castor oil to a one day bowel preparation protocol developed by a Japanese study group for an Ulcerative Colitis cohort, which yielded excretion rates of 93.9% (31/33)[10]. Finally, a multicentre retrospective study in Japan selecting 319 patients receiving a one-day PEG-based CCE regimen in a mixed cohort of faecal immunochemical test positive, screening and lower gastrointestinal (GI) symptom patients, assessed excretion rates with and without castor oil. Of 152 patients receiving castor oil as a CCE booster, 97% excreted the capsule within the life of its battery compared to 81% (136/167) without castor oil[6]. Given this promising data, we aimed to prospectively assess the effectiveness of adding castor oil as an additional booster to our CCE protocol in an unselected patient cohort. Historically our CCE bowel preparation has been based on a 2 Litre split-dose PEG solution (Moviprep®, Norgine, Denmark) followed by boosters made of the same solution, which has been shown to be effective in the available literature[11].

MATERIALS AND METHODS

Study design and population

This was a prospective open-label single-centre pilot study assessing the impact of castor oil on CCE performance. This study was approved as a service evaluation project by the process improvement department which is part of the quality safety and risk management directorate in our hospital. All patients referred routinely for CCE over a 5-mo period (November 2019 to March 2020) received an additional 15 mL of castor oil in conjunction to our standard booster regime. All patients were 18 years or older and had no contraindications to CCE or bowel preparation regimens. All patients with a history of IBD, chronic nonsteroidal anti-inflammatory drug use, previous bowel surgery or any other risk for capsule retention, completed a capsule patency test prior to CCE. The outcome of this pilot was then compared to a control (non-castor oil) cohort identified retrospectively from our CCE database.

Procedure details

CCE was carried out using the PillCam™ COLON2 (Medtronic, Minneapolis, MN, United States). Figure 1 outlines the bowel preparation protocol used for each CCE procedure.

Two days prior to attending the capsule department for a CCE, all patients received four 12 mg Senna tablets. This was followed by a two-litre split-dose bowel preparation with Moviprep® (PEG-3350, sodium sulphate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid for oral solution; Norgine B. V, United States), a PEG-based solution used predominantly in our colonoscopy practice. The patients were instructed to ingest the 1st litre on the evening before, and the 2nd litre on the morning of the procedure. In the event of delayed gastric emptying, recorded as presence of capsule in the stomach 30 min post ingestion, all patients without contraindications received intravenous prokinetics; 10mg of metoclopramide followed by 250 mg erythromycin, if unsuccessful.

Control booster regimen included Moviprep® with 750 mL of water (booster 1) on reaching the small bowel. A further dose of Moviprep® with 250 mL of water was given 3 h later and a bisacodyl suppository (Dulcolax®) 10 mg after 8 h, if the capsule was not excreted. Cases followed the same regimen with the addition of 15 mL of castor oil given with booster 1. The studies were all read by trained CCE readers, unblinded to bowel preparation, and the final reports were reviewed and signed off at our local departmental capsule review board.

Time	Procedure/patient instructions	Regimen/ medication	Dose/volume
Day -7	Stop iron tablets	Senna tablets	4 x 12 mg
Day -2: 19:00			
Day -1	Liquid diet (*e.g.*, black tea, black coffee, clear broth, soft drinks, jelly, ice cream, *etc*.)		
	Drink at least 10 glasses of water throughout the day		
	Clear fluids only from midnight		
Day -1: 19:00		Sachet A&B Moviprep® + water	1 L
Day of procedure			
07:00	Essential medications may be taken with sips of water	Sachet A&B Moviprep® + water	1 L
Time of appointment	Capsule swallowed		
+ 30 min	Video checked for capsule passage into small bowel	**Optional** IV Metoclopramide	10 mg
		IV Erythromycin	250 mg
	Administer prokinetics if delayed gastric emptying		
Confirmation of capsule in small bowel	Booster 1	Moviprep® A&B + Water	750 mL
	(Only cases) Patient can now drink fluids freely	**Castor oil**	**+15 mL**
+ 3 hr	Booster 2	Moviprep® A&B + Water	250 mL
	Patient can now have a light meal and take remaining medications		
+ 5 hr	Patient notes capsule excretion	**Optional** Dulcolax® suppository	10 mg
	Administer rectal suppository if capsule not visualised		

Figure 1 Bowel preparation procedure.

Data analysis

A nested case control design was employed with a 2:1 ratio (2 controls:1 case) whereby controls were taken from our capsule database in chronological order without any selection bias.

We recorded patient demographics including age, gender and indication for CCE. CCE excretion/completion was defined as uninterrupted image capture from the caecum to the dentate line within its battery life. In the event of failed capsule excretion, CCE was considered complete if images of the haemorrhoidal plexus were recorded.

Colonic image quality was based on the reader's overall impression of the bowel preparation and recorded as either "adequate" or "inadequate" at the time of reporting. All CCE procedures were read by trained capsule endoscopists and reports

reviewed at weekly capsule review meetings with at least one CCE expert reader present. The cleansing level was evaluated based on a previously validated scale and classified as poor (large amount of faecal residue), fair (enough residue to preclude a completely reliable examination), good (small amount of residue, not enough to interfere with examination) and excellent (no more than small amounts of adherent faeces) for each colonic segment. Examinations scored as 'poor' or 'fair' in any segment were considered 'inadequate', whereas those scored as 'good' or 'excellent' in all segments were considered 'adequate'[12,13].

Colonic transit time was automatically generated by the PILLCAM™ SOFTWARE V9 and recorded directly from the CCE report. Findings were recorded and clinically significant findings included: Colonic polyps, cancers, inflammation and bleeding. Extra colonic findings were also documented where present. A CCE positivity rate was calculated by including studies with significant colonic findings as outline above. Adverse events and complications were documented.

Results were compared between the two groups of patients. Statistical analysis employed a student *t* test and chi-square tests as appropriate, utilising the GraphPad online software. A *P* value of less than 0.05 was considered statistically significant. Odds ratios (OR), number needed to treat (NNT) and absolute risk reduction were calculated as required. Per protocol analysis was undertaken including patients only who were able to swallow the capsule and took at least some of the study medication.

RESULTS

Patient demographics

A total of 186 CCEs have been analysed; 124 controls and 62 cases receiving castor oil with booster 1. In all, the mean age was 60 years of age and 56% were females (104/186). The age and gender breakdown did not statistically differ between the two populations. The following were indications for CCE in order of prevalence; 96 polyp surveillance (51.6%), 42 lower GI symptoms (22.6%), 28 due to incomplete colonoscopy (15%), 18 anaemia (9.7%) and 2 IBD surveillance (1.1%). Allowing for a slightly larger proportion of castor oil patients referred for anaemia work up; the indication breakdown did not significantly vary. Table 1 outlines the breakdown of demographics and indications between the two groups.

Assessing the effect of castor oil

Overall CCE completion was 77% (144/186). Image quality was adequate and/or diagnostic in 91% (170/186). Mean colonic transit time was 3.5 h with a range of 0.25-13. Overall CCE positivity (presence of significant colonic findings) was 59% (109/186) and the polyp detection rate was 57% (106/186). Additional pathology including colonic diverticulae, small bowel findings and gastric findings were found in 63% (78/124), 22% (27/124) and 12% (15/124) of the overall studies, respectively. There were no cases of colorectal cancer recorded in this study.

Completion rates were significantly higher with castor oil, 87% (54/62) compared with 73% controls (90/124), (P = 0.01). The NNT with castor oil to result in an additional complete CCE study was 7, absolute risk reduction = 14.52%, [95% confidence interval (CI): 3.06- 25.97]. Polyp detection rates were also higher in the castor oil group 82% (51/62) *vs* 44% (55/124), ($P \leq 0.0001$), with an OR of 5.8, (95%CI: 2.77-12.21). Similarly, overall positivity rates, which include studies with polyps, colitis and bleeding, were higher with castor oil, 84% (52/62) *vs* 46% (57/124), ($P \leq 0.0001$), OR of 6.1, (95%CI: 2.85 to 13.11).

Transit times were similar, 3.2 h and 3.8 h, with and without castor oil, respectively. Castor oil did not contribute to poorer image quality as rates were similar between the two groups; reported as adequate and/or diagnostic in 90% (56/62) *vs* 92% (114/124). Table 2 outlines comparisons between cases and controls.

Impact of gender, age and indication on CCE completion

Castor oil appears to improve completion rates. This effect is more significant in the over 60 s, ($P < 0.03$). Similarly, the effect of the addition of castor oil is more pronounced in females, ($P < 0.025$). This is shown in Table 3. The NNT with castor oil to have one more complete study was 6 for both female gender (absolute risk reduction 18.5%, 95%CI: 1.94-34.36) and older age (absolute risk reduction 18%, 95%CI: 1.65-34.46). The NNT with castor oil to have one more complete study was 5 for older females (absolute risk reduction 24.36%, 95%CI: 1.23 to 47.48).

Table 1 Basic demographics of patients and indications for colon capsule endoscopy, *n* (%)

	Total	With castor oil	Without castor oil	*P* value
	186	62	124	
Age				0.2365
Mean	60.0	62.0	59.0	
Range	18-97	22-97	18-86	
Gender				0.8357
Male	82 (44%)	28 (45.2)	54 (43.5)	
Female	104 (56%)	34 (54.8)	70 (56.5)	
Indications				
Polyp surveillance	96	30/62 (48.4)	66/124 (53.2)	0.5362
Lower gastrointestinal symptoms	42	10/62 (16.1)	32/124 (25.8)	0.1382
Incomplete colonoscopy	28	11/62 (17.7)	17/124 (13.7)	0.4712
Anaemia	18	10/62 (16.1)	8/124 (6.5)	0.0355
IBD surveillance	2	1/62 (1.6)	1/124 (0.8)	0.6174

IBD: Inflammatory bowel disease.

Table 2 Effects of castor oil on colon capsule endoscopy performance, *n* (%)

Variables	Overall	With castor oil	Without castor oil	*P* value
Capsule completion	144/186 (77)	54/62 (87)	90/124 (73)	0.0128
Image quality(adequate/diagnostic)	170/186 (91)	56/62 (90)	114/124 (92)	0.3558
Colonic transit time (hr)				
Mean:	3.5	3.2	3.8	0.1779
				95%CI: -2.90 to 0.54
Range:	0.25-13	0.25-13	0.5-13	
CCE positivity	109/186 (59)	52/62 (84)	57/124 (46)	< 0.0001
				CI: 2.85 to 13.11
				OR 6.1
Polyp detection rate	106/186 (57)	51/62 (82)	55/124 (44)	< 0.0001
				CI: 2.77 to 12.21
				OR 5.8

CCE: Colon capsule endoscopy; OR: Odds ratio; CI: Confidence interval.

The male gender appears to be a predictor of higher excretion rates (83% *vs* 73%), however this does not reach statistical significance, (P = 0.0553). Unsurprisingly, younger age is a significant predictive factor of higher excretion rates (86% *vs* 71%), (P = 0.0094).

Allowing for low incidence, castor oil did not appear to influence excretion rates in patients referred following an incomplete colonoscopy, anaemia work-up and IBD surveillance.

Adverse events

There were no reported significant adverse events with castor oil and no documented events of patients refusing castor oil. There were also no significant complications associated with CCE procedure or the remainder of bowel preparation regimens, including capsule retention, bowel obstruction, severe abdominal pain, IBD flare and

Table 3 Colon capsule endoscopy completion vs non-completion, *n* (%)

Variable	Total	With castor oil	Without castor oil	*P* value
Overall capsule completion	144/186 (77)	54/62 (87)	90/124 (73)	0.0128
Age:				
≤ 60	67/78 (86)	24/26 (92)	43/52 (83)	0.1250
> 60	77/108 (71)	30/36 (83)	47/72 (65)	0.0253
Gender:				
Male	68/82 (83)	25/28 (89)	43/54 (80)	0.1352
Female	76/104 (73)	29/34 (85)	47/70 (67)	0.0251
Indication:				
Polyp surveillance	75/96 (78)	28/30 (93)	47/66 (71)	0.0075
Lower gastrointestinal symptoms	36/42 (86)	10/10 (100)	26/32 (81)	0.0450
Incomplete colonoscopy	19/28 (68)	7/11 (63)	12/17 (7)	0.3502
Anaemia	12/18 (67)	8/10 (80)	4/8 (50)	0.0899
IBD surveillance	2/2 (100)	1/1 (100)	1/1 (100)	1.0

IBD: Inflammatory bowel disease.

anaphylaxis to medications.

DISCUSSION

With the increasing demand for solutions in tackling long colonoscopy waiting lists, CCE has become an attractive alternative. Given its potential, the importance of maximising CCE's performance has been recognised in the literature with a growing body of work looking into improving capsule excretion, image quality, detection of pathology and patient acceptance. Our study is the largest European study to date prospectively assessing the use of castor oil as an addition to a CCE booster regimen in an unselected cohort. Our data suggests small volumes of cheap and readily available castor oil (15 mL) can significantly increase excretion rates (87%) without compromising image quality or colonic transit times. This effect appears more significant in an older population and in females.

The significance of castor oil in completion rates is matched by other studies including the largest to date multicentre retrospective study from Japan, reporting rates as high as 97%[6]. Of note, the authors used a very different and complex preparation regimen comprising of 7 different agents [magnesium citrate, sodium picosulphate (MCSP), Senna, Moviprep®, Mosapride, metoclopramide, Daikenchuto®] and up to 3 L of bowel preparation in one day. This contrasts with our simple split-dose regimen requiring less bowel preparation volumes on the day of the procedure. Our protocol is based on evidence from Denmark showing no added value in adding gastrografin or magnesium citrate in a split-dose regimen[11]. This study included MCSP, a preparation highlighted in recent European guidelines for its safety concerns. Because of hyperosmolarity and magnesium content, solutions containing MCSP are contraindicated in patients with congestive heart disease, hypermagnesemia, rhabdomyolisis, GI ulcerations, and severe impairment of renal function, which can lead to magnesium accumulation[14]. This could be one of the factors contributing to a lower excretion rate in our study (87% *vs* 97%). A further factor worth noting is that male gender has been identified as a significant predictor for capsule excretion in both studies and could be responsible for higher excretion rates in the Japanese study, which reports a male majority in its castor oil group of 66% (101 *vs* 51) as opposed to a female majority in our study of 54% (29 *vs* 25). Similar findings have been reported for standard colonoscopy[15]. Our study reveals that excretion rates also vary by indication, with polyp surveillance and lower GI symptom cohorts doing better, with 93% and 100% excretion rates, respectively.

Unlike other proposed booster agents like sodium phosphate which has been associated with nephropathy and electrolyte disturbances[16], castor oil appears safe and acceptable to patients with no significant side effects reported during the study period. Indeed, unlike other proposed booster regimens, castor oil has been used for thousands of years and is only contraindicated in pregnancy as it is known to induce uterine contractions[17]. Given its lower volume, castor oil has an advantage over larger volume ascorbic acid-based, magnesium-based, sulphate-based, or gastrografin-based booster preparations[11,18,19] as this is more likely to be acceptable to patients. It is important to note, our protocol added 15 mL of castor oil to booster 1, contrasting with some other studies which have utilised higher doses of 30-60 mL with variable efficacy. The excretion rate in our study remains suboptimal, < 90%, which is the minimum standard for adequate bowel preparation in colonoscopy as recommended in recent European guidelines[14]. Whether increasing the dose of castor oil leads to further improvement in completion rates is unclear and warrants further investigation.

Oral ingestion of castor oil stimulates lipases in the small intestine to produce ricinoleic acid which in turn produces a strong laxative effect[9]. Reassuringly, this agent has not had an effect on the overall colonic transit rates as seen in our study. This finding is consistent with previous studies suggesting this effect is selective to small bowel mucosa, by activating intestinal EP3 receptors, and not the colon[17], in turn preserving the diagnostic value of CCE. It is also important to note that overall image quality appears to be unchanged despite castor oil's effect on small bowel transit which can result in the capsule reaching the colon prematurely, *i.e.*, before colonic cleansing is complete with a split dose PEG regimen.

The authors acknowledge limitations of this being a single centre study. This can, however, also be viewed as a strength as this ensured that all patients received a high quality and uniform CCE procedure in accordance with our departmental protocol. Secondly, this study incorporates a retrospective control cohort which can contribute to a selection bias. Thirdly, due to a departmental polyp surveillance initiative which overlapped with the period of this study, our patient cohort was skewed by a large proportion (52%) of CCE patients referred for polyp surveillance. This resulted in a particularly high overall polyp detection rate of 57%. Correlation with colonoscopy could be of benefit but this data was not available as most of CCE patients did not require a short-term follow up colonoscopy within the period of the study. This does not affect the validity of our data as cases and controls did not vary significantly by age, gender or CCE indication. Surprisingly, despite a smaller proportion of castor oil CCEs referred for polyp surveillance compared to the non-castor oil group (48.4% *vs* 53.2%), polyp detection rates were almost twice as high (44% *vs* 82%). One potential reason for this is the higher completion rates leading to more frequent visualisation of the entire colonic mucosa and increased detection of left sided lesions. This highlights the value of castor oil in CCE bowel preparation and its potential as an alternative tool in polyp screening or surveillance.

CONCLUSION

In our capsule endoscopy centre, the addition of a single 15 mL dose of castor oil to booster 1, as part of a simple split dose Moviprep® CCE protocol, appears safe, acceptable by patients and significantly improves completion rates and polyp detection in an unselected cohort.

ARTICLE HIGHLIGHTS

Research background

Colon capsule endoscopy (CCE) has emerged as a valuable tool in gastroenterology. There remains significant variation in bowel preparation and booster preparations between capsule endoscopy centres. Currently, there is limited data available on the use of castor oil as an additional agent in booster regimens for CCE. Our study is the largest study to date that assesses the use of castor oil in CCE procedures prospectively in a western population.

Research motivation

Our capsule endoscopy centre recognises the suboptimal completion rates of CCE, in our centre and worldwide, and investigates the addition of castor oil in improving

this. With this study, we aim to add to the limited available data on castor oil in CCE preparation regimens and highlight the need for further research.

Research objectives

Our main objective was to assess the impact of adding castor oil to a standard split-dose (2-d) preparation in an unselected Western patient cohort in our CCE practice. Our secondary objectives included studying the impact of castor oil on diagnostic yield and identifying patient factors associated with CCE completion and/or more likely to benefit from castor oil. Our study suggests that adding castor oil is significantly associated with higher capsule completion rates and in turn, higher diagnostic yield. This highlights the need for further research in this field, as completion rates is a recognised limitation of this diagnostic test.

Research methods

Our study identified a retrospective "control" arm (without castor oil) and collected data on a prospective "cases" arm (with castor oil), employing a 2:1 nested control: case design, in assessing the benefit of adding castor oil to a 2-d bowel preparation regimen in our CCE practice. We utilised student t and chi-square tests when comparing basic demographics, completion rates, image quality, colonic transit time, diagnostic yield and polyp detection between the two groups. This was a novel study methodology, with respect to castor oil use, yet to be replicated in other centres.

Research results

Our study evaluated 186 CCE procedures (62 cases and 124 controls). We found that overall CCE completion was 77% and was significantly higher in the castor oil group with 87% *vs* 73%. This effect of castor oil appears to be more effective in older populations and females. Interestingly, positivity rates and polyp detection rates also increased with the addition of castor oil, 84% *vs* 46% and 82% *vs* 44%, respectively. Reassuringly, adding castor oil did not reduce image quality or colonic transit time.

Research conclusions

What are the new theories that this study proposes? – Castor oil not only improves completion rates but also has potential to improve diagnostic yield of CCE. Castor oil appears safe and acceptable by patients and can be used in an unselected cohort with little to no adverse events. What are the new methods that this study proposed? – This study proposes the addition of low dose castor oil as a booster agent to a standard split-dose CCE bowel preparation.

Research perspectives

What is the direction of the future research? - There is a need to explore and expand on research of using castor oil in CCE in different populations, alternative doses and in combination with other bowel preparation regimens, with the aim of improving CCE performance parameters.

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