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Original Article

Significant correlation between glucose metabolism status and acute radiation enteritis resulting from concurrent chemoradiotherapy in rectal cancer

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Abstract: Objective: To explore the relationship between glucose metabolism and acute radiation enteritis from chemoradiotherapy for rectal cancer. Methods: In this retrospective study, the clinical data of 75 rectal cancer patients who received concurrent chemoradiotherapy in Binzhou Second People's Hospital from February 2019 to February 2022 were collected and analyzed. According to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research on Treatment of Cancer (EORTC) radiation response grading criteria, the patients were classified into four groups with different glucose metabolism statuses: NGR (normal glucose regulation) group, IFG (impaired fasting glucose) group, IGT (impaired glucose tolerance) group, and DM (diabetes mellitus) group. Two-factor logistic regression was used to analyze whether IFG, IGT, or DM were risk factors for acute radiation enteritis. Results: (1) The fasting plasma glucose (FPG, F=20.550, $P < 0.001$), 2-hour post-meal blood glucose (2hPG, F=14.920, $P < 0.001$), triglycerides (TG, F=3.355, $P=0.024$), high-density lipoprotein cholesterol (HDL-C) (F=4.109, $P=0.010$), low-density lipoprotein cholesterol (LDL-C, F=4.545, $P=0.006$), and systolic blood pressure (SBP, F=5.398, $P=0.002$) differed greatly among the NGR group, IFG group, IGT group, and DM group, all $P < 0.05$. (2) The incidence of acute radiation enteritis was 34.67% in the 75 patients, and in DM patients it was higher than in the NGR, IFG, or IGT patients ($\chi^2=14.702$, $P=0.002$). (3) There were significant differences in BMI (F=3.594, $P=0.044$) and DBP (F=3.954, $P=0.033$) among the asymptomatic group, mild group, and severe group ($P < 0.05$). (4) Body mass index (BMI) was positively correlated with acute radiation enteritis in IFG, IGT, and DM patients ($OR=1.361$, $P=0.020$). (5) DM was positively correlated with acute radiation enteritis ($OR=6.167$, $P=0.039$). Conclusions: DM was significantly correlated with acute radiation enteritis induced by concurrent chemoradiotherapy for rectal cancer, while IFG and IGT were not.

Keywords: Glucose metabolism status, rectal cancer concurrent chemoradiotherapy, acute, radiation enteritis, correlation

Introduction

Rectal cancer is a frequently occurring digestive system malignancy originating from the rectal mucosal epithelium, accounting for about 60%-75% of colorectal cancer, which seriously endangers public health [1]. Concurrent chemoradiotherapy is an important treatment method, referring to a combination of chemotherapy drugs and radiotherapy [2]. Neoadjuvant chemoradiotherapy is a standard treatment for rectal cancer, and it is effective in inhibiting cancer cell spread and metastasis as well as killing cancer cells [3]. Even without preoperative chemoradiotherapy, postoperative chemoradiotherapy can increase the local control and the overall survival rate [4]. However, ionizing radiation can induce inflammatory reactions in the intestinal mucosa during radiotherapy for rectal cancer, leading to acute radiation proctitis [5]. Acute radiation proctitis is one of the common adverse reactions in concurrent chemoradiotherapy for locally advanced (stage II or III) rectal cancer, with an incidence of 2%-39% [6]. Its clinical manifestations include rectal pain or bleeding, diarrhea, anes-

Table 1. Grouping criteria of blood glucose status

Group	Diagnostic criteria
NGR group	FBG < 6.1 mmol/L and 2hPG < 7.8 mmol/L
IFG group	6.1 mmol/L ≤ FBG < 7.0 mmol/L and 2hPG < 7.8 mmol/L
IGT group	FBG < 7.0 mmol/L and 7.8 mmol/L ≤ 2hPG < 11.1 mmol/L
DM group	FBG ≥ 7.0 mmol/L or 2hPG ≥ 11.1 mmol/L

Notes: FPG: fasting plasma glucose; NGR: normal glucose regulation; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; DM: diabetes mellitus.

thesia, and mucous stool. Rectal stenosis, rectovaginal fistula, and anemia may occur in severe cases. These can lead to reduced chemotherapy tolerance and even forced termination of chemoradiotherapy, thereby reducing the effect of tumor control and prognosis [7]. Therefore, the early prevention and diagnosis of radiation proctitis are of vital practical significance for rectal cancer treatment. The acute phase of radiation proctitis is contraindicated by electronic colonoscopy. In addition, the proportion and compliance of patients in the chronic phase undergoing colonoscopy are not high. At present, there is still a lack of simple, convenient, and effective methods for radiation proctitis diagnosis in clinical practice [8]. Glucose metabolism is closely related to inflammatory factors in serum [9]. Other studies have shown that the degree of abnormal glucose metabolism was positively correlated with the degree of inflammatory reaction [10]. Based on this, we aimed to discuss the correlation between glucose metabolism status and acute radiation enteritis in rectal cancer treated by concurrent chemoradiotherapy for the purpose of providing a data reference and new ideas for prevention, treatment, and diagnosis.

Materials and methods

Source of patients

In this retrospective analysis, the clinical data of 75 patients with rectal cancer who received concurrent chemoradiotherapy in Binzhou Second People's Hospital from February 2019 to February 2022 were collected and analyzed. This study complied with the ethical guidelines of the Declaration of Helsinki. The ethics committee of Binzhou Second People's Hospital had approved this study.

Inclusion criteria: (1) The patients who met the clinical diagnostic criteria for rectal cancer [11]; (2) The patients who received preoperative neoadjuvant and postoperative adjuvant chemoradiotherapy; (3) The patients with the Eastern Cooperative Oncology Group (ECOG) score of 0 to 2, and who tolerated the concomitant chemoradiotherapy; (4) The patients with tumor node metastasis (TNM) (8th edition) stage II or III. Exclusion criteria: (1) The patients who received short course of radiotherapy or radiotherapy alone; (2) The patients who had received ≥ 2 cycles of chemotherapy before chemoradiotherapy; (3) The patients with hemocytopenia before concurrent chemoradiotherapy; (4) The patients with concomitant malignant tumors other than rectal cancer; (5) The patients with other serious organ dysfunction.

Diagnostic criteria

Diagnostic criteria and grouping of glucose metabolism status: In line with diabetes diagnostic criteria [12], the patients were categorized into 4 groups according to blood glucose status, as shown in **Table 1**.

The diagnostic criteria of acute radiation enteritis caused by concurrent chemoradiotherapy for rectal cancer [13]: 1. The cumulative absorbed dose of the rectum irradiated by fractional irradiation or equivalent once irradiation ranges 45-60 Gy. 2. For pelvic organ tumors, tenesmus, draining mucus stool, and abdominal pain or other symptoms emerges in a few days after intracavitary irradiation or external irradiation or rectal local high-dose accidental irradiation, and intestinal dysfunction (constipation or diarrhoea), blood in stool, anal tingling, stool pain, or other rectal reactions lasts for weeks or even six months. 3. A fibre colonoscopy shows rectal mucosal oedema, congestion, haemorrhage, erosion, or necrosis.

According to the radiation response rating-related criteria [14], acute radiation enteritis was classified as grade 0 to 4, as shown in **Table 2**. Then the study subjects were divided into 3 groups on the basis of the grading criteria of radiation response: asymptomatic group (grade 0), mild group (grade 1), and severe group (≥ grade 2).

Table 2. Grading criteria for acute radiation enteritis

Grading	Criteria
Grade 0	No significant change.
Grade 1	Increased bowel movements or habits change, but no medication needed; Rectal paresthesia, but no pain medication needed.
Grade 2	Diarrhea, requiring anti-parasympathetic medication; Rectal or abdominal pain, requiring painkillers; Mucus outflow, but don't need toilet paper.
Grade 3	Diarrhea, requiring parenteral nutrition support; Bleeding, abdominal distension (plain X-ray film confirmed intestinal ring expansion).
Grade 4	Acute or subacute intestinal obstruction, sinus canal, perforation; Gastrointestinal bleeding, requiring blood transfusion; Abdominal pain or tenesmus, requiring bowel diversion or gastrointestinal decompression.

Concurrent chemoradiotherapy

Radiotherapy: three-dimensional conformal radiotherapy or intensity-modulated radiotherapy was selected. According to the Radiation Therapy Oncology Group (RTOG) principle, we divided the target volume and normal tissues. The clinical target volume (CTV) included perirectal and internal iliac lymph nodes, primary tumor/tumor bed, pelvic wall, mesorectal membrane, and presacral space. The prescription dose of planning target volume (PTV) was 45-50.96 Gy/25 times.

Patients with synchronous chemotherapy could choose single-drug chemotherapy or combination chemotherapy. Single-drug chemotherapy: capecitabine (2500 mg/m^2 in the morning and evening twice; after 14 days of continuous administration, the drug was stopped for 7 days, and 21 days was a course of treatment). Combined chemotherapy: mFOLFOX6 (calcium leucovorin 400 mg/m^2, oxaliplatin 85 mg/m^2, fluorouracil 400 mg/m^2 d_1, fluorouracil 2400 mg/m^2 for 46 h; 14 days was a course) or CapeOx (oxaliplatin 130 mg/m^2 d_1, capecitabine 825 mg/m^2 bid $d_{1\text{-}14}$, 21 days was a course). Drug manufacturers and approval number: Capecitabine (Jiangsu Hengrui Pharmaceutical Co., Ltd., approved by H20133365), Calcium Folinate (Shanxi Pude Pharmaceutical Co., Ltd., approved by H14022464), Oxaliplatin (Jiangsu Aosaicon Pharmaceutical Co., Ltd., approved by H20051985), Fluorouracil (Shanghai Xudong Haipu Pharmaceutical Co., Ltd., approved by H31020593).

Observational indices

The main indices observed in this study were fasting blood glucose (FBG) and 2-hour postload blood glucose (2hPG), while the secondary indices were gender, age, BMI, TNM stage, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

(1) Sample collection: before radiotherapy, 6 mL of morning fasting venous blood was drawn and centrifuged, and the upper serum was retained and stored at -80°C for testing. (2) Related index detection: FBG, 2hPG, TC, TG, LDL-C, and HDL-C were detected with Shandong Boke BK-400 automatic biochemical analyzer. According to related guidelines [15], fasting plasma glucose (FPG) ≤ 7 mmol/L and 2hPG < 10 mmol/L were taken as the normal levels.

On the grounds of the guidelines [16], TG ≥ 2.26 mmol/L was deemed to be hypertriglyceridemia, and TC ≥ 6.22 mmol/L as hypercholesterolemia. HDL-C < 1.04 mmol/L was identified as subnormal HDL-C. LDL-C ≥ 4.14 mmol/L was elevated LDL-C. Any of the above conditions was considered as dyslipidemia.

The diagnostic criteria for hypertension [17]: SBP ≥ 140 mmHg (1 mmHg =0.133 kPa), DBP ≥ 90 mmHg or taking antihypertensive drugs.

Statistical methods

SPSS 23.0 software was used for data analysis. The measured data were described as mean ± standard deviation and compared using the t-test (comparison between the two groups) or ANOVA followed with Bonferroni method (comparison among multiple groups). The enumerated data were expressed by number of cases and compared using chi-square test. Two-factor logistic regression was conducted to analyze whether IFG, IGT, or DM were

Table 3. Clinical characteristics of different glucose metabolism status in 75 rectal cancer patients

Clinical characteristic	NGR group (n=23)	IFG group (n=18)	IGT group (n=17)	DM group (n=17)	F/χ^2	*P*
Gender (male/female, cases)	13/10	11/7	9/8	9/8	0.322	0.956
Age (years)	61.22±8.12	59.22±8.01	62.65±5.87	61.35±6.25	0.674	0.571
BMI (kg/m^2)	22.12±2.99	22.85±3.13	22.52±4.40	24.24±3.23	1.322	0.274
TNM stage (stage II/stage III, cases)	11/12	9/9	11/6	9/8	1.245	0.742
FPG (mmol/L)	4.62±0.42	6.00±1.39*	7.37±1.52*,#	8.33±2.56*,#	20.550	< 0.001
2hPG (mmol/L)	4.55±0.67	7.75±4.12*	9.09±1.50*	10.35±4.10*	14.920	< 0.001
Blood lipid indices (mmol/L)						
TC	4.11±0.67	4.88±1.01	4.32±1.53	4.11±0.85	2.288	0.085
TG	1.08±0.61	1.40±1.05	1.56±1.11	2.11±1.33*	3.355	0.024
HDL-C	1.38±0.25	1.10±0.28*	1.14±0.27*	1.12±0.39*	4.109	0.010
LDL-C	2.53±0.53	3.20±0.80*	3.05±0.86*	3.28±0.72*	4.545	0.006
SBP (mmHg)	116.43±14.85	129.67±9.81*	127.65±9.11*	125.82±10.35*	5.398	0.002
DBP (mmHg)	76.09±9.43	81.89±9.63	82.35±9.51*	78.41±8.07	2.076	0.111

Notes: *denotes comparison with NGR group, #denotes comparison with IFG group, $P < 0.05$. BMI: body mass index; TNM: tumor node metastasis; FPG: fasting plasma glucose; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure.

risk factors for acute radiation enteritis. All tests were two-sided, and $P < 0.05$ was considered significant.

Results

Clinical characteristics of 75 rectal cancer patients with different glucose metabolism status

Among the 75 patients, 23 cases (30.67%) had NGR, 18 cases (24.00%) had IFG, 17 cases (22.67%) had IGT, and 17 cases (22.67%) had DM. The levels of FPG (F=20.550, $P < 0.001$), 2hPG (F=14.920, $P < 0.001$), TG (F=3.355, P=0.024), HDL-C (F=4.109, P=0.010), LDL-C (F=4.545, P=0.006), and SBP (F=5.398, P=0.002) were significantly different among the NGR group, IFG group, IGT group, and DM group. Compared to the NGR group and IFG group, FPG levels in the IGT group and DM group were higher (IGT group vs. NGR group: t=8.293, $P < 0.001$; IGT group vs. IFG group: t=2.785, P=0.009; DM group vs. NGR group: t=6.857, $P < 0.001$; DM group vs. IFG group: t=3.373, P=0.002). Compared to the NGR group, the levels of 2hPG (IFG group vs. NGR group: t=3.676, $P < 0.001$; IGT group vs. NGR group: t=12.920, $P < 0.001$; DM group vs. NGR group: t=6.694, $P < 0.001$), HDL-C (IFG group vs. NGR group: t=3.377, P=0.002; IGT group vs. NGR group: t=2.902, P=0.006; DM group vs. NGR group: t=2.568, P=0.014), LDL-C (IFG group vs. NGR group: t=3.219, P=0.003; IGT group vs. NGR group: t=2.361, P=0.023; DM group vs. NGR group: t=3.799, $P < 0.001$) and SBP (IFG group vs. NGR group: t=3.262, P=0.002; IGT group vs. NGR group: t=2.751, P=0.009; DM group vs. NGR group: t=2.233, P=0.031) in the IFG, IGT, and DM groups were significantly higher. Compared to the NGR group, the TG level in the DM group was higher (t=3.286, P=0.002), as shown in **Table 3** and Supplementary Table 1.

Comparison of the prevalence of acute radiation enteritis in patients with different clinical characteristics

Acute radiation enteritis occurred in 26 patients (34.67%). There was no significant difference in the prevalence of acute radiation enteritis among patients with different clinical characteristics such as gender, age, BMI, TC, TG, HDL-C, LDL-C, SBP, or DBP (all $P > 0.05$). However, the incidence of acute radiation enteritis in DM patients was higher than that of NGR, IFG, and IGT patients, and the difference was statistically significant (χ^2=14.702, P=0.002), as shown in **Table 4**.

Clinical characteristics of patients with acute radiation enteritis of different severities

Among 26 patients with acute radiation enteritis, 15 cases (57.69%) were asymptomatic, 7 cases (26.92%) were mild, and 4 cases

Table 4. Comparison of the prevalence of acute radiation enteritis under different clinical characteristics

Clinical characteristics	Total	Acute radiation enteritis		χ^2	*P*
		With (n=26)	Without (n=49)		
Gender				0.075	0.784
Male	42 (56.00)	14 (18.67)	28 (37.33)		
Female	33 (44.00)	12 (16.00)	21 (28.00)		
Age (year)				0.088	0.766
≥ 60	45 (60.00)	15 (20.00)	30 (40.00)		
< 60	30 (40.00)	11 (14.67)	19 (25.33)		
BMI (kg/m^2)				0.100	0.951
< 25	56 (74.67)	19 (25.33)	37 (49.33)		
25-28	13 (17.33)	5 (6.67)	8 (10.67)		
> 28	6 (8.00)	2 (2.67)	4 (5.33)		
TNM stage (cases)				0.824	0.364
Stage II	40 (53.33)	12 (16.00)	28 (37.33)		
Stage III	35 (46.67)	14 (18.67)	21 (28.00)		
TC				0.000	1.000
Normal	71 (94.67)	25 (33.33)	46 (61.33)		
Abnormal	4 (5.33)	1 (1.33)	3 (4.00)		
TG				0.000	1.000
Normal	63 (84.00)	22 (29.33)	41 (54.67)		
Abnormal	12 (16.00)	4 (5.33)	8 (10.67)		
HDL-C				1.000	0.317
Normal	57 (76.00)	18 (24.00)	39 (52.00)		
Abnormal	18 (24.00)	8 (10.67)	10 (13.33)		
LDL-C				0.269	0.604
Normal	69 (92.00)	25 (33.33)	44 (58.67)		
Abnormal	6 (8.00)	1 (1.33)	5 (6.67)		
SBP				0.004	0.951
Normal	68 (90.67)	23 (30.67)	45 (60.00)		
Abnormal	7 (9.33)	3 (4.00)	4 (5.33)		
DBP				0.001	0.981
Normal	65 (86.67)	22 (29.33)	43 (57.33)		
Abnormal	10 (13.33)	4 (5.33)	6 (8.00)		
Glucose metabolic state				14.702	0.002
NGR	23 (30.67)	10 (13.33)	13 (17.33)		
IFG	18 (24.00)	3 (4.00)	15 (20.00)		
IGT	17 (22.67)	2 (2.67)	15 (20.00)		
DM	17 (22.67)	11 (14.67)$^{*,\&}$	6 (8.00)		

Notes: *denotes comparison with IFG, $^{\&}$denotes comparison with IGT, $P < 0.05$. BMI: body mass index; TNM: tumor node metastasis; FPG: fasting plasma glucose; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; NGR: normal glucose regulation; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; DM: diabetes mellitus.

(15.38%) were severe. BMI (F=3.594, P=0.044) and DBP (F=3.954, P=0.033) showed significant differences among the asymptomatic group, mild group, and severe group ($P < 0.05$), as shown in **Table 5** and Supplementary Table 2.

Risk factors for acute radiation enteritis in IFG, IGT, and DM patients

BMI was positively correlated with acute radiation enteritis in IFG, IGT, and DM patients (*OR*=1.361, *P*=0.020), as shown in **Table 6**.

Table 5. Clinical characteristics of patients with different severity of acute radiation enteritis

Clinical characteristics	Asymptomatic group (n=15)	Mild group (n=7)	Severe group (n=4)	F/χ^2	*P*
Gender (male/female, cases)	8/7	3/4	3/1	1.103	0.576
Age (year)	61.80±8.67	62.71±7.09	60.00±7.11	0.143	0.868
BMI (kg/m^2)	22.06±2.86	23.75±3.21	27.14±5.50[&]	3.594	0.044
TNM stage (stage II/stage III, cases)	6/9	4/3	2/2	0.593	0.743
Blood lipid indices (mmol/L)					
TC	4.42±1.03	4.34±0.72	4.55±0.90	0.063	0.939
TG	1.72±0.83	1.37±0.51	1.74±0.76	0.572	0.572
HDL-C	1.17±0.41	1.30±0.32	1.30±0.21	0.398	0.676
LDL-C	2.75±0.72	2.79±0.40	3.33±0.94	1.161	0.331
SBP (mmHg)	124.40±12.61	127.86±15.24	117.75±14.31	0.708	0.503
DBP (mmHg)	73.47±10.90	82.00±6.85	87.25±9.50[&]	3.954	0.033
Glucose metabolic state				6.179	0.396
NGR	7 (26.92)	2 (7.69)	1 (3.85)		
IFG	3 (11.54)	0 (0.00)	0 (0.00)		
IGT	1 (3.85)	0 (0.00)	1 (3.85)		
DM	4 (15.38)	5 (19.23)	2 (7.69)		

Notes: [&]indicates the same index compared with the asymptomatic group, $P < 0.05$. BMI: body mass index; TNM: tumor node metastasis; SBP: systolic blood pressure; DBP: diastolic blood pressure; NGR: normal glucose regulation; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; DM: diabetes mellitus.

Table 6. Risk factors of acute radiation enteritis in IFG, IGT, and DM patients

Variable	*B*	*S.E*	*Wals*	*P*	*OR*	95% *CI*	
						Lower limit	Upper limit
Gender	-0.197	0.747	0.070	0.792	0.821	0.190	3.549
Age	0.015	0.049	0.089	0.765	1.015	0.922	1.116
BMI	0.308	0.132	5.450	0.020	1.361	1.051	1.764
TNM stage	-0.482	0.734	0.432	0.511	0.617	0.146	2.602
TC	0.281	0.309	0.831	0.362	1.325	0.724	2.425
TG	0.441	1.183	0.139	0.709	1.554	0.153	15.794
HDL-C	-0.548	0.467	1.378	0.240	0.578	0.231	1.444
LDL-C	-0.072	0.044	2.679	0.102	0.930	0.853	1.014
SBP	-0.068	0.049	1.923	0.166	0.934	0.849	1.029
DBP	0.644	0.362	3.172	0.075	1.904	0.937	3.867

Notes: BMI: body mass index; TNM: tumor node metastasis; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Logistic regression analysis of risk factors for acute radiation enteritis

Regardless of whether the variables were adjusted, DM was screened out as a risk factor for acute radiation enteritis (OR=4.500, 3.840, 7.457, 6.167; All $P < 0.05$), while IFG and IGT were not (all $P > 0.05$), as shown in **Table 7**.

Discussion

As an adverse reaction, acute radiation proctitis is not rare in concurrent chemoradiotherapy for stage II and III rectal cancer. Improper control will affect the treatment [18]. Early prevention and diagnosis of acute radiation proctitis are helpful for tumor control. At present, there is no consensus on diagnostic index for acute radiation proctitis. A correlation between abnormal glucose metabolism and inflammatory response has been demonstrated [19]. Therefore, it is worth exploring whether glucose metabolism status is related to acute radiation enteritis induced by concurrent chemoradiotherapy for rectal cancer.

The incidence of acute radiation enteritis in this study was 34.67%, which is consistent with the results of a previous study [20]. Our study analyzed the clinical characteristics of rectal can-

Table 7. Logistic regression analysis of IFG, IGT, and DM as risk factors for acute radiation enteritis

Variable	*P*	*OR*	95% *CI*	
			Lower limit	Upper limit
Model 1				
IFG	0.119	0.323	0.078	1.336
IGT	0.433	0.590	0.158	2.208
DM	0.020	4.500	1.274	15.898
Model 2				
IFG	0.144	0.329	0.074	1.465
IGT	0.536	0.635	0.151	2.673
DM	0.043	3.840	1.043	14.137
Model 3				
IFG	0.077	0.238	0.048	1.169
IGT	0.493	0.593	0.133	2.637
DM	0.017	7.457	1.436	38.726
Model 4				
IFG	0.146	0.288	0.054	1.543
IGT	0.507	0.588	0.123	2.820
DM	0.039	6.167	1.100	34.577

Notes: Model 1: Unadjusted; Model 2: Adjusted according to gender, age, BMI and TNM stage; Model 3: TC, TG, HDL-C, and LDL-C were further adjusted; Model 4: Further adjust SBP and DBP. BMI: body mass index; TNM: tumor node metastasis; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; NGR: normal glucose regulation; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; DM: diabetes mellitus.

cer patients with different glucose metabolism states and the prevalence of acute radiation enteritis under different clinical characteristics. We found statistical differences in FPG, 2hPG, TG, HDL-C, LDL-C, and SBP levels under different metabolic states such as NGR, IFG, IGT, and DM. These results indicate that the above characteristics may affect the glucose metabolism status of rectal cancer patients in some way. In addition, the prevalence of acute radiation enteritis was significantly different among patients with different glucose metabolism states. The prevalence (14.67%) in the DM group was the highest, which was significantly higher than that in the IFG and IGT groups, but not significantly different from that of the NGR group (13.33%). There were significant differences in BMI and DBP levels among the asymptomatic group, mild group, and severe group, indicating that BMI and DBP levels were related to the severity of acute radiation enteritis in our study. However, further comparison showed that the BMI and DBP levels of the severe group patients were significantly different from those of the asymptomatic group patients, but not from those of the mild group patients. These suggest that low levels of BMI and DBP have no effect on the occurrence of mild acute radiation enteritis, but when the BMI and DBP reach a certain level this will promote the occurrence of acute radiation enteritis.

We also found that BMI was positively correlated with the risk of acute radiation enteritis in IFG, IGT, and DM patients (*OR*=1.361, *P*=0.020). In addition, logistic regression analysis found that DM was a risk factor for acute radiation enteritis regardless of whether the variables were adjusted. This is consistent with the conclusions of a previous study [21]. The possible reason is that DM status may indicate abnormal intestinal microbiota in patients with rectal cancer undergoing concurrent chemoradiotherapy, and abnormal intestinal microbiota will damage the mucosal barrier and further increase the risk of intestinal mucosal inflammation, which creates favorable conditions for the occurrence of radiation enteritis [22]. The dysregulation of gut microbes contributes to many human diseases, including obesity and diabetes. The involvement of gut microbiota in the occurrence and development of type 2 diabetes mellitus (T2D) has been confirmed [23]. The ecological balance of intestinal microbiota is disturbed, such as the imbalance caused by a high-sugar and high-fat diet, which may be related to insulin resistance and the destruction of islet β-cell apoptosis, and eventually, this leads to the occurrence of T2D [24]. The involvement of intestinal microbiota in the pathogenesis of T2D may be related to low-grade chronic inflammation, the production of short-chain fatty acids, activation of the nuclear receptor signaling pathway, and other factors [25]. Studies had pointed out that intestinal microbiota regulated small intestinal radiation damage [26]. The activated TLR2, TLR4, and TLR5 receptors can protect against ionizing radiation damage through the TLR signaling pathway. The ligands of Toll-like receptors (TLRs) are mainly different bacterial components. Studies have shown that bacteria and their products could also protect intestinal epithelial cells from radiation-induced apoptosis through the AP-1 protein [27]. In addition, TLR

channels could also strengthen the integrity of epithelial barrier-tight junctions, inhibit intestinal inflammation, maintain intestinal homeostasis, and affect the proliferation and apoptosis of crypt cells [28]. Therefore, we speculate that DM may indicate abnormal intestinal microbiota and reduce the body's resistance to ionizing radiation injury, thus increasing the possibility of radiation enteritis. However, due to the lack of relevant research, this conclusion still needs more evidence.

Strengths and limitations

Using a retrospective analysis method, we investigated the relationship between glucose metabolism status and acute radiation enteritis induced by concurrent chemoradiotherapy for rectal cancer. DM is a risk factor for acute radiation enteritis, which could provide guidance and new ideas for diagnosis and prevention. However, the retrospective nature with small sample size may cause some bias in the results. Therefore, we should shift the future research direction to a prospective controlled and multicenter study to enhance the reliability of the results in this study.

Conclusions

DM is significantly correlated with acute radiation enteritis induced by concurrent chemoradiotherapy for rectal cancer, while IFG and IGT are not.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Significance of the bonferroni method for pair-to-pair comparison between groups (clinical characteristics of different glucose metabolic states)

Index	0	1	2	3
FPG				
0	-	0.056	< 0.001	< 0.001
1	-	-	0.092	0
2	-	-	-	0.557
2hPG				
0	-	0.007	< 0.001	< 0.001
1	-	-	0.863	0.075
2	-	-	-	0.912
TG				
0	-	0.974	0.982	0.020
1	-	-	0.954	0.306
2	-	-	-	0.805
HDL-C				
0	-	0.028	0.098	0.061
1	-	-	0.867	0.914
2	-	-	-	0.958
LDL-C				
0	-	0.036	0.201	0.016
1	-	-	0.952	0.867
2	-	-	-	0.918
SBP				
0	-	0.004	0.026	0.096
1	-	-	0.867	0.743
2	-	-	-	0.823

Notes: 0 represents NGR group, 1 represents IFG group, 2 represents IGT group, and 3 represents DM group. Bonferroni method was applied. TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; 2hPG: 2-hour post-load blood glucose.

Supplementary Table 2. Significance of the bonferroni method for pair-to-pair comparison among groups (clinical characteristics of patients with different severity)

Index	0	1	2
BMI			
0	-	0.012	0.037
1	-	-	0.002
DBP			
0	-	0.016	0.016
1	-	-	0.008

Notes: 0 represents the asymptomatic group, 1 represents the mild group, and 2 represents the severe group. Bonferroni method was applied. BMI: body mass index; DBP: diastolic blood pressure.