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ORIGINAL ARTICLE

Blood sugar level affects the recurrence of hepatocellular carcinoma after laparoscopic surgery: a retrospective study

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Summary

Purpose: *To investigate the effect of blood sugar level on the recurrence of hepatocellular carcinoma (HCC) after laparoscopic surgery.*

Methods: *The data of 177 patients with primary HCC who underwent laparoscopic radical liver resection were retrospectively analyzed. Patients were divided into the hyperglycemia group (n=56) and the control group (n=121) according to whether postoperative fasting blood sugar (FBS) was ≥6.1 mmol/L. Postoperative hospitalization and blood glucose level during follow-up were observed and recurrence and relative risk factors of HCC of patients from the two groups were analyzed. The recurrence rate of HCC after one and two years were compared between the two groups, and the influencing factors of recurrence after laparoscopic surgery were analyzed by single-factor analysis.*

Results: *The recurrence rate one year after surgery in patients with hyperglycemia and the control group were 30.4 and 16.5% respectively, and the recurrence rate two years after surgery were 64.3 and 37.2%, respectively. The recurrence rate one and two years after surgery in HCC patients from the hyperglycemia group were significantly higher than those of the control group (p<0.05). Multivariate analysis showed that FBS, Child-Pugh grade B, low differentiated carcinoma and high postoperative AFP were risk factors for recurrence of HCC after laparoscopic surgery, which affected significantly the disease-free survival (DFS) of postoperative HCC (p<0.05).*

Conclusion: *The recurrence rate of patients with elevated FBS after laparoscopic surgery of HCC was high during the 2 postoperative years, and FBS was high, while the Child-Pugh grade B, low grade of tumor differentiation, and postoperative AFP were risk factors affecting the recurrence rate. Monitoring high-risk patients should be strengthened to reduce the recurrence rate.*

Key words: *fasting blood glucose, hepatocellular carcinoma, laparoscopic surgery, recurrence*

Introduction

Primary HCC is one of the most common malignant tumors in the human digestive system, with a high mortality rate. In China, about 460,000 new cases and 420,000 deaths of HCC are registered each year [1]. The main clinical manifestations of these patients are persistent stabbing and dull pain in the liver, weight loss, fatigue, bloating, loss of appetite, anemia, abdominal distension and jaundice, while paraneoplastic syndromes are completing the clinical picture [2]. The recurrence of HCC seriously affects the patient prognosis. Recurrence after radical resection of HCC, especially early recurrence (≤ 2 years), is a difficult problem affecting the postoperative prognosis of patients [3]. The recurrence rate after radical resection or local ablation of HCC is high, reaching about 80% within 5 years [4-6]. Studying the factors associated with the recurrence of HCC may prevent the recurrence and increase the patient survival. Among them, the number and size of HCC lesions were associated with recurrence of HCC [7,8]. Hepatitis C virus (HCV) and hepatitis B virus (HBV) were

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also important factors for recurrence of HCC. It has been reported that the antiviral therapies of HCV and HBV can reduce the recurrence and prolong the survival time of HCC [9-11].

Some studies have pointed out that there was a certain correlation between HCC related hyperglycemia and NCAO5 gene defects, and hyperglycemia caused by perturbed glucose metabolism could promote the progression of HCC [12]. Diabetes was also reported as a risk factor for liver cancer, pancreatic cancer, renal cancer and colon cancer [13,14]. Studies discussing the impact of diabetes on the recurrence of HCC were rather controversial [15-18]. Therefore, in the present study FBS level and its impact on the recurrence of HCC after laparoscopic surgery were investigated.

Methods

Patients

The clinical data of 177 patients with primary HCC admitted to Yantaishan Hospital from January 2010 to January 2015 were retrospectively analyzed. Among them, 137 were males and 40 females, aged 18 to 89 years (mean 53.8 ± 8.2). Exclusion criteria: (1) patients with endocrine disorders that might affect blood glucose (except for diabetes); (2) intraoperative rupture of the tumor or extrahepatic invasion; (3) mixed type of primary HCC or tumors with no definite staging confirmed by postoperative pathological examination; (4) patients with perioperative death, early recurrence and lost to follow-up (2 months and 24 months); (5) incomplete follow-up data.

Methods

Liver function tests, FBS, AFP, abdominal ultrasound or CT, MRI, and chest X-ray. were repeated once a month in the 6 postoperative months, and then once every three months. The first postoperative recurrence was the study endpoint. The follow-up time was up to June 1, 2017. Postoperative patients were followed-up at the outpatient department every month after liver surgery. The diagnosis of HCC recurrence was based on the dynamic enhancement imaging such as enhanced CT, MRI and/or PET/CT and hepatic arteriography. Space-occupying lesions detected by ultrasound or elevated AFP levels were not considered as recurrence criteria.

Observation indicators

FBS, recurrence rate of HCC 1 and 2 years after surgery, age, gender, history of alcohol consumption, combination with cirrhosis, preoperative AFP, Child-Pugh score, surgical approaches, intraoperative blood transfusion and tumor pathology, were observed during the follow-up period.

Statistics

SPSS 19.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. All quantitative data were expressed as mean ± standard deviation. Comparison

Table 1. Patient characteristics

	Hyperglycemia group (n=56) *n (%)*	*Control group (n=121)* *n (%)*	*p value*
Age, years			0.568
<65	39 (69.6)	79 (65.3)	
>65	17 (30.4)	42 (34.7)	
Gender			0.270
Male	42 (75)	95 (78.5)	
Female	14 (25)	26 (21.5)	
History of alcohol consumption			0.631
Yes	10 (17.9)	18 (14.9)	
No	46 (82.1)	103 (85.1)	
Underlying liver diseases			0.092
Yes	50 (89.3)	116 (95.9)	
No	6 (10.4)	5 (4.1)	
Combination with cirrhosis			0.170
Yes	44 (78.6)	83 (68.6)	
No	12 (21.4)	38 (31.4)	
Child-Pugh classification			0.312
Grade A	43 (76.8)	84 (69.4)	
Grade B	13 (23.2)	37 (30.6)	
Postoperative AFP, ng/ml			0.080
<8	36 (64.3)	93 (76.9)	
>8	20 (35.7)	28 (23.1)	

between groups was done using one-way ANOVA test followed by *post hoc* test (least significant difference). Percentages (%) were used to express the enumeration data and chi-square test was used for data analysis. p values <0.05 were considered statistically significant.

Results

General data

A total of 177 patients with primary HCC were studied. There was no significant difference in gender, age, underlying diseases and Child-Pugh classification between the two groups (p>0.05). Results are shown in Table 1.

Recurrence of HCC

The overall recurrence rate of HCC at one and two postoperative years was 20.9% (37/177) and 45.8% (81/177), respectively, compared with the control groups which were 16.5% (20/121) and 37.2% (45/121), and 30.4% (17/56) and 64.3% (36/56) in the hyperglycemia group, respectively (p=0.001 and p<0.05, respectively). The results are shown in Table 2. Patients with FBS > 8.0 mmol/L had a shorter tumor recurrence time than those with FBS control 6.1-8.0 mmol/L (p=0.016). The results are shown in Figure 1.

Factors influencing of HCC recurrence

Two years after the operation, 81 (45.8%) patients recurred and 96 (54.2%) did not. There was no significant correlation between HCC recurrence and general patient characteristics such as age, gender, history of alcohol consumption, underlying liver diseases, and combination with cirrhosis (p>0.05; Table 3). FBS, Child-Pugh score, tumor pathology and postoperative AFP were closely related to the recurrence of HCC after laparoscopy (p<0.05). The results are displayed in Tables 4 and 5.

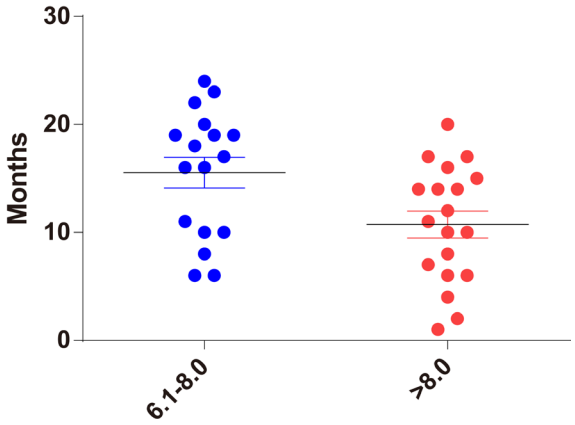

Figure 1. Comparison of blood glucose level and tumor recurrence time. The higher the blood glucose level, the earlier the tumor recurrence.

Table 2. Recurrence of HCC one and two years after surgery

	First postoperative year n (%)	*Second postoperative year n (%)*
Hyperglycemia group	17 (30.4)	36 (64.3)
Control group	20 (16.5)	45 (37.2)
p value	0.035	0.001

Table 3. HCC recurrence and general data

	Recurrence group (n=81) n (%)	*Control group (n=96) n (%)*	*p value*
Age, years			0.522
<65	52 (64.2)	66 (68.8)	
>65	29 (35.8)	30 (31.2)	
Gender			0.802
Male	62 (76.5)	75 (78.1)	
Female	19 (23.5)	21 (21.9)	
History of alcohol consumption			0.737
Yes	12 (14.8)	16 (16.7)	
No	69 (85.2)	80 (83.3)	
Underlying liver diseases			0.583
Yes	76 (93.8)	88 (91.7)	
No	5 (6.2)	8 (8.3)	
Combination with cirrhosis			0.631
Yes	60 (74.1)	68 (70.8)	
No	21 (25.9)	28 (29.2)	

Univariate analysis of the effect on DFS rate

Univariate analysis showed that fasting blood glucose, Child-Pugh score, poorly differentiated tumor and postoperative AFP were risk factors for DFS after radical resection of HCC ($p<0.05$; Figure 2).

Discussion

Diabetes has been widely accepted as a risk factor for the occurrence and prognosis of HCC, with a large number of high-quality studies confirming this point. A meta-analysis by Chen et al. [19] with 21 studies reported the same conclusion. This meta-analysis suggested that the overall relative risk of developing HCC in patients with diabetes mellitus and chronic liver disease was 1.86, 1.90, 1.69 and 1.93, respectively. Most of the current researches focused on the relationship between the diabetes mellitus and progression and prognosis of HCC. However, the specific mechanisms of diabetes mellitus in promoting HCC is still unclear [5,20]. Among them, mechanisms about gradual development of non-alcoholic fatty liver, nonalcoholic steatohepatitis and cryptogenic cirrhosis were widely studied [20]. However, there is little research on the recurrence of HCC after hyperglycemia. Now there are studies discussing the influence of diabetes on the recurrence of HCC, but controversy still exists [15-18]. In this study we aimed to investigate the relationship between recurrence of HCC and the level of blood glucose after laparoscopic surgery.

The results of this study showed that when the long-term FBS was ≥ 6.1 mmol / L, early postoperative recurrence of HCC was high and the DFS was shortened with statistically significant differences. Previous clinical studies have shown that there was no correlation between postoperative hyperglycemia and recurrence of HCC [21]. However, there are also studies reporting that there

Table 4. HCC recurrence and surgery-related factors

	Recurrence group (n=81) n (%)	*Control group (n=96) n (%)*	*p value*
Child-Pugh classification			0.025
A	70 (86.4)	92 (95.8)	
B	11 (13.6)	4 (4.2)	
Surgical approach			0.303
Lobectomy of liver	12 (14.8)	18 (18.8)	
Partial hepatectomy	69 (85.2)	78 (81.2)	
Intraoperative blood transfusion, ml			0.607
≤200	58 (71.6)	80 (83.3)	
>200	23 (28.4)	16 (16.7)	
Pathological findings			0.041
High and moderate differentiation	53 (65.4)	76 (79.2)	
Poor differentiation	28 (34.6)	20 (20.8)	

Table 5. Recurrence of HCC and laboratory indicators

	Recurrence group (n=81) n (%)	*Non-recurrence group (n=96) n (%)*	*p value*
Preoperative AFP, ng/ml			0.299
≤400	66 (81.5)	72 (75)	
>400	15 (18.5)	24 (25)	
Fasting blood sugar, mmol/L			0.001
<6.1	45 (55.6)	76 (79.2)	
≥6.1	36 (44.4)	20 (20.8)	
Postoperative AFP, ng/ml			0.016
<8	52 (64.2)	77 (80.2)	
>8	29 (35.8)	19 (19.8)	

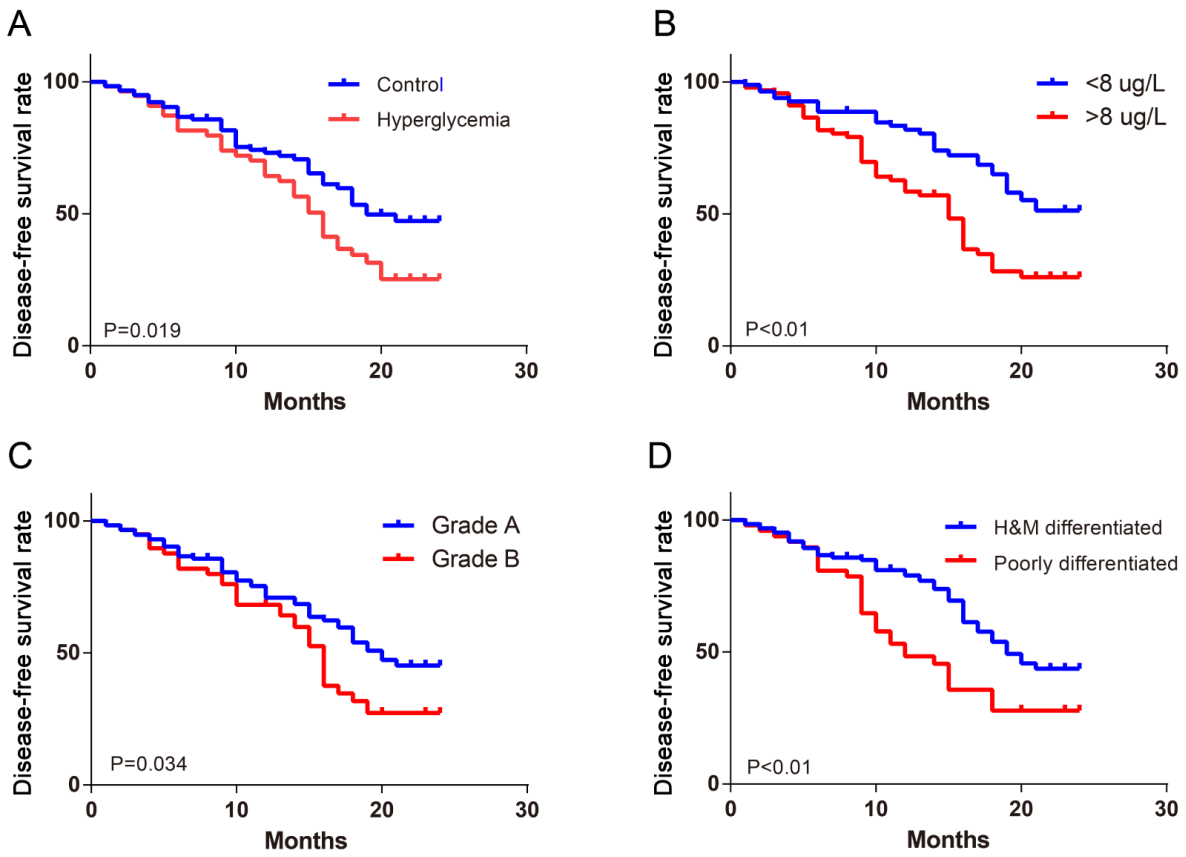

Figure 2. Influencing factors and disease-free survival at 24 months after radical resection of HCC. **A:** Disease-free survival at 24 months after radical resection of HCC in patients from the control group and hyperglycemia group. **B:** Disease-free survival of patients whose postoperative AFP level was >8.1 ng/ml and <8.1 ng/ml **C:** Disease-free survival of patients with Child-Pugh score A and B. **D:** Disease-free survival of high & medium (H&M) differentiated and poorly differentiated HCC.

was no significant difference in the recurrence rate of HCC between non-diabetic and diabetic patients with well-controlled long-term blood glucose after RFA treatment. It has been suggested that if blood glucose level was adequately controlled, diabetes itself was not an important risk factor. In contrast, hyperglycemia was an important risk factor for HCC recurrence according to the results in this study. It was also found in this study that hyperglycemia was the influencing factor of tumor recurrence time in the hyperglycemia group with statistically significant difference. Therefore, FBS level was an independent risk factor for early recurrence of HCC.

In addition to high blood sugar level, this study also found that AFP > 8.1 ng/ml at postoperative 2 months, Child-Pugh classification and tumor pathology were independent risk factors for tumor recurrence in HCC patients. Based on these four independent risk factors, we analyzed the impact on postoperative DFS rate of HCC. Hyperglycemia, AFP> 8.1 ng/ml at 2 postoperative months, Child-Pugh classification and tumor pathology were also independent risk factors influencing the postoperative DFS rate of HCC, thus affecting the prognosis of HCC.

It has been found that long-term hyperglycemia promoted the occurrence of HCC. Long-term hyperglycemia would result to capillary basement membrane thickening, decreased permeability, mitochondrial respiratory enzymes damage, enhanced anaerobic glycolysis and subsequently lead normal cells to carcinogenesis. Also, hyperglycemia, as a nutrient medium, further promoted the growth of hepatoma cells, while increased the saturation of glucose transporter of hepatoma cells and accelerated cell energy [22,23]. It was found that hyperglycemia could activate the polyol pathway to form advanced glycation end products in rats [24]. Additionally, Iwasaki et al. confirmed that high glucose alone, as well as in combination with proinflammatory cytokines, could stimulate the nuclear factor Kappa-B-mediated transcription in hepatocytes *in vitro* [25]. The abovementioned suggested that there may be some correlation between hyperglycemia and recurrence of HCC.

In summary, the 2-year postoperative recurrence rate of HCC patients with hyperglycemia

that underwent laparoscopic surgery was high, and high level of FBS, Child-Pugh grade B, low grade of tumor differentiation and high level of postoperative AFP were risk factors of postoperative recurrence which affected the postoperative DFS rate. Therefore, controlling the blood glucose level within normal range is conducive to reducing the recurrence of HCC patients after laparoscopic surgery.

Some of the limitations of this study are noteworthy. For example, this was a retrospective study, and the sample size was rather small. Prospective large-sample studies are needed to further clarify the relationship between postoperative recurrence of HCC and blood glucose level.

Conclusions

The recurrence rate of patients with elevated blood glucose after laparoscopic surgery of HCC was high within the 2 postoperative years, and high FBS, Child-Pugh grade B, low grade of tumor differentiation, and high postoperative AFP were the risk factors affecting the recurrence rate. Monitoring high-risk patients should be strengthened to reduce the recurrence rate.

Conflict of interests

The authors declare no conflict of interests.

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