Correlation of insulin-resistance with blood fat and glucose in elder patients after surgery for hepatic carcinoma

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Abstract. The present study was designed to analyze variations in blood fat, blood glucose and insulin-resistance in elder patients following surgery for hepatic carcinoma. It also investigated the correlation of insulin with the level of serum leptin and blood fat. A total of 80 patients with primary hepatic cancer who were admitted to The First Hospital of Lanzhou University for treatment between October 2014 and June 2016 were enrolled in the study. At the 1-year follow-up, the patients were divided into two groups based on their recurrence of hepatic cancer after surgery. The levels of serum leptin were detected prior to, one month and one year after surgery; the changes in blood fat, body mass index (BMI), waistline and hipline were measured at one year after surgery; alterations in the fasting blood glucose and blood glucose were measured at 2 h after meal. The fasting insulin (FINS) level and homeostasis model assessment-insulin resistance (HOMA-IR) index were also measured. Correlations between serum leptin and total cholesterol, FINS and fasting blood glucose were analyzed. In the recurrence group, the levels of serum leptin and FINS level were significantly reduced, while waistline and hipline were increased, compared with the non-recurrence group ($P<0.05$). The BMI and fasting blood glucose in the recurrence group was significantly elevated in comparison with the non-recurrence group ($P<0.05$). The HOMA-IR index was significantly increased in the recurrence group compared with the non-recurrence group ($P<0.05$). These results indicated that following surgery for hepatic cancer, the level of serum leptin in patients with recurrence was decreased with an increase in susceptibility to abnormal metabolism of blood fat and glucose. In addition, the serum leptin was negatively correlated with the total cholesterol level and fasting blood glucose and positively correlated with the FINS level in patients. It was concluded that leptin levels decreased in patients with postoperative recurrence, as well as the accumulation of visceral adipose tissue and the development of abnormal blood glucose metabolism was observed.

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Key words: hepatic malignant tumor, postoperative recurrence, serum leptin, blood fat, blood glucose, insulin resistance

Introduction

Hepatic malignant tumor is one of the most common malignant tumors in the world. The morbidity and mortality rates of males were, respectively, the 5th and the 2nd in the world, and for females were the 9th and 6th in the world (1). Hepatic malignant tumors contain primary hepatic carcinoma and secondary hepatic carcinoma, the common clinical manifestations include liver pain, abdominal distension, anorexia, fatigue, wasting, progressive liver enlargement or upper abdominal mass, and some patients have symptoms containing low fever, jaundice, diarrhea, upper gastrointestinal bleeding, and so on (2). The etiology and exact molecular mechanism of hepatic malignant tumors are not completely clear. At present, it is considered that the pathogenesis of hepatic cancer is a complex process of multi-factor and multi-step. Epidemiological and experimental data showed that many factors, consisting of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, aflatoxin, drinking water pollution, alcohol, cirrhosis, sex hormones, nitrosamines, trace elements and so on, are related to the incidence of hepatic malignant tumors (3). Individualized comprehensive therapy according to different stages of hepatic carcinoma is the key to improving the curative effect. Therapeutic methods include surgery, hepatic artery ligation, hepatic artery chemoembolization, radiofrequency, cryotherapy, laser, microwave, chemotherapy and radiotherapy. Biological therapy and traditional Chinese medicine treatment are also useful in the treatment of hepatic malignant tumors (4).

Hepatic liver malignant tumors are the most common solid tumors, and surgical treatment has been regarded as the preferred and the most efficient method (5). Surgical resection, which can effectively prolong the survival time and improve the quality of life of patients, is still the main treatment for hepatic cancer. However, abdominal pain, jaundice, fatigue, weight loss and unexplained fever symptoms are usually observed

Table I. Basic information of patients in the recurrence group and non recurrence group.

Variables	Non-recurrence group (n=40)	Recurrence group (n=40)
Sex		
Male	30	31
Female	10	9
Average years of age	69.5±2.0	69.6±2.0
Patients complicated with HB	32	31
HB disease course (years)	5-35	5-40
Average HB disease course (years)	21.3±1.7	23.4±2.0
Patients with alcohol-intake history	35	36
Alcohol-intake history (years)	5-40	5-40
Average alcohol-intake history (years)	23.3±2.1	23.4±2.0
Staging of hepatic carcinoma		
Stage I	25	26
Stage II	15	14

HB, hepatitis B.

in patients after treatment. Both increased AFP levels and imaging examination results indicate the recurrence of hepatic cancer. In addition, more than 30% of patients show distant metastasis within 1 year after surgery. Studies have shown that there are 3 major causes of postoperative recurrence of hepatic cancer, including the existence of metastasis before surgery, preoperative assessment error leads to incomplete surgery and reduced immune function (6).

A previous study confirmed that patients after surgery of hepatic carcinoma may experience abnormal metabolism of blood fat and glucose (7). However, there remain few studies focusing on the levels of blood fat, blood glucose and insulin as well as the correlations among them. Serum leptin, a protein hormone secreted by adipocytes (8), is expressed in multiple organs and systems, and can be used in metabolic disorders, such as losing weight through regulating the metabolism of fat, carbohydrate and protein, thereby suppressing the appetite, reducing the intake of energetic substance (9) and increasing the energy efficiency (10). A study (11) has confirmed that serum leptin is significantly associated with the clinical efficacy and recurrence of hepatic carcinoma patients. To better explore the variations in metabolism of blood fat and glucose, and insulin functions of hepatic carcinoma patients with recurrence after surgery, we analyzed the alterations in these indicators and investigated the correlations of serum leptin with the blood fat, fasting blood glucose and insulin levels.

Patients and methods

Patients. We enrolled a total of 80 patients with primary hepatocellular carcinoma who were admitted to The First Hospital of Lanzhou University (Lanzhou, China) between October 2014 and June 2016 for open surgery, and these patients were diagnosed with computed tomography in upper abdomen and biopsy with samples collected from the surgery or before surgery. All participants underwent surgical treatment with an estimated survival time over 1 year. Before enrollment, participants had signed the informed consent and this study was approved by the Ethic Committee of The First Hospital of Lanzhou University. Patients complicated with severe liver or kidney dysfunction, hyperlipidemia before surgery, cachexia, mellitus diabetes, decreased insulin function or insulin-resistance and mental diseases, BMI >28 kg/m^2 before surgery, and those refusing to be enrolled in this study were excluded. After 1-year follow-up, patients were divided into two groups according to the recurrence of hepatic carcinoma after surgery, i.e., the recurrence group and non-recurrence group. The basic information of patients are shown in Table I. Differences in sex, age, ratio of patients complicated with HB, HB disease course, alcohol-intake history and duration, staging of hepatic carcinoma showed no statistical significance (P>0.05).

Methods. All enrolled participants underwent surgical treatment followed by regular outpatient follow-up by abdominal ultrasonic examination and CT examination to identify the postoperative recurrence. We also compared the levels of serum leptin before, one month and one year after surgery, changes in blood fat, body mass index (BMI), waistline and hipline in one year after surgery, alterations between the fasting blood glucose and blood glucose at 2 h after meal, and the fasting insulin (FINS) level and homeostasis model assessment insulin resistance (HOMA-IR) index. Finally, we analyzed the correlations of serum leptin with the total cholesterol, FINS and fasting blood glucose.

Evaluation methods. Serum leptin was detected by enzyme-linked immunosorbent assay (ELISA) (cat. no. E-EL-H0113c; Elabscience, Wuhan, China). The procedures included:

Table II. Comparison of the blood fat after 1-year follow-up between the two groups (mmol/l, mean ± SD).

Group	Time	TC	TG	LDL-C	HDL-C
Recurrence group	Before operation	8.1±0.05	3.6±0.11	4.7±0.08	0.9±0.01
	1 year after operation	6.2±0.03	2.4±0.02	3.5±0.03	1.1±0.01
Non-recurrence group	Before operation	8.1±0.06	3.6±0.12	4.7±0.09	0.9±0.02
	1 year after operation	5.4±0.01	1.8±0.01	2.5±0.02	1.4±0.01
t^a	-	206.804	67.882	88.828	89.443
P-value	-	<0.0001	<0.0001	<0.0001	<0.0001
t^b	-	280.733	94.541	150.919	141.421
P-value	-	<0.0001	<0.0001	<0.0001	<0.0001
t^c	-	160.000	169.707	175.412	84.853
P-value	-	<0.0001	<0.0001	<0.0001	<0.0001

[a]Comparison between before operation and 1 year after operation in recurrence group; [b]comparison between before operation and 1 year after operation in non-recurrence group; [c]comparison between non-recurrence group and recurrence group 1 year after operation. TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Dilution-loading-incubation-dosing-washing-enzyme adding-incubation-washing-color development-termination and determination (8). Normal reference range was 0.69-11.46 μg/l. As for the detection of indicators associated with blood fat, the normal reference range of total cholesterol (TC) referred to the levels of triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) detected by an automatic biochemical analyzer (Abbott AEROSET; Diamond Diagnostics Inc., Holliston, MA, USA). Specimens were collected at the enrollment and 1 year after intervention from the fasting elbow venous blood in the morning. BMI was calculated using the formula: BMI = body weight (kg)/height x height (m); waistline was measured in supine position and stable breath at 1 cm above the belly button, while the hipline was measured in the fullest part of the hips. The measurement of blood glucose, including fasting blood glucose and blood glucose at 2 h after meal, was carried out with the HITACHI 7080 Automatic Biochemical Analyzer (Beckman Coulter, Inc., Brea, CA, USA) (normal range of fasting blood glucose: 3.9~6.1 mmol/l; normal range of blood glucose at 2 h after meal: <7.8 mmol/l). The level of HOMA-IR was calculated with the formula: HOMA-IR=[fasting blood glucose (mmol/l) x FINS (mU/l)]/22.5, in which the normal range of FINS was 3.0-24.9 U/ml, and the normal ratio of HOMA-IR was 1. In addition, the assay of FINS was carried out with the Beckman Access DXI 800 spectrometer (Beckman Coulter, Inc.).

Statistical analysis. Statistical Product and Service Solutions v21.0 (IBM Corp., Armonk, NY, USA) was used for statistical processing. Measurement data were presented as mean ± standard deviation (SD), and Student's t-test was adopted for the comparison of mean between the two groups. Enumeration data were presented as %, and chi-square test was performed for the intergroup comparison of rate. Scatter diagram was prepared with the correlation analysis. Correlation analysis was performed using scatter chart Pearson's correlation analysis. P<0.05 was considered to indicate a statistically significant difference.

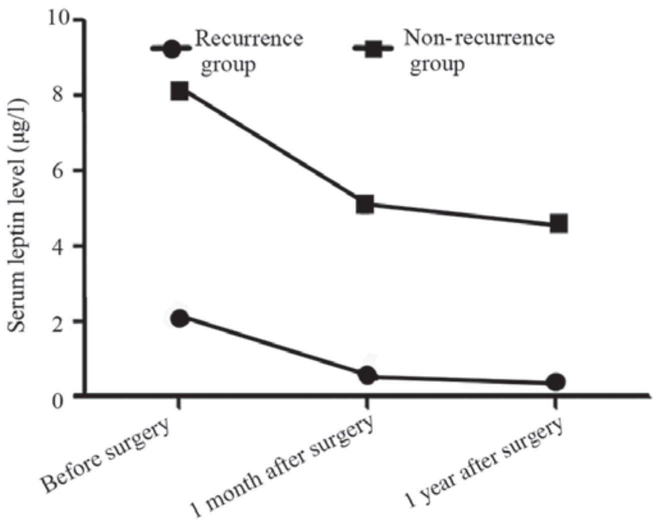

Figure 1. Comparison between the serum leptin levels prior to surgery, and 1 month and 1 year after surgery between the two groups. In the recurrence group the serum leptin levels before surgery were significantly reduced compared with those in the non-recurrence group. P<0.05.

Results

Comparison of the serum leptin levels before, 1 month and 1 year after surgery between the two groups. In the recurrence group, the serum leptin levels before, 1 month and 1 year after surgery were (2.1±0.1), (0.6±0.1) and (0.4±0.1) μg/l, significantly lower than those [(8.1±0.2), (5.1±0.2) and (4.5±0.3) μg/l] in the non-recurrence group (t=169.707, 127.279 and 82.000, P<0.05; Fig. 1).

Comparison of the blood fat at 1 year after surgery between the two groups. There was no significant difference in the levels of TC, TG, LDL-C and HDL-C between the two groups before operation (P>0.05). One year after operation, LDL-C, TC and TG in both groups was lower than that before

Table III. Comparison of the BMI, waistline and hipline between the two groups (mean ± SD).

Group	Time	BMI (kg/m^2)	Waistline (cm)	Hipline (cm)
Recurrence group	Before operation	27.9±1.1	95.2±2.4	98.1±2.0
	1 year after operation	26.5±1.2	93.5±2.1	96.1±1.6
Non-recurrence group	Before operation	28.0±1.1	95.2±2.5	98.0±2.0
	1 year after operation	23.3±1.0	89.8±1.6	93.0±1.5
t^a	-	5.439	3.371	4.939
P-value	-	<0.0001	0.001	<0.0001
t^b	-	19.995	11.506	12.649
P-value	-	<0.0001	<0.0001	<0.0001
t^c	-	12.956	8.864	8.940
P-value	-	<0.0001	<0.0001	<0.0001

[a]Comparison between before operation and 1 year after operation in recurrence group; [b]comparison between before operation and 1 year after operation in non-recurrence group; [c]comparison between non-recurrence group and recurrence group 1 year after operation. BMI, body mass index.

Table IV. Comparison of the levels of fasting blood glucose and blood glucose at 2 h after meal between two groups (mmol/l, mean ± SD).

Group	Time	Fasting blood glucose	Blood glucose at 2 h after meal
Recurrence group	Before operation	16.2±1.7	12.0±1.4
	1 year after operation	8.9±1.1	14.2±1.3
Non-recurrence group	Before operation	16.2±1.6	12.1±1.4
	1 year after operation	7.8±1.1	5.6±0.9
t^a	-	24.700	27.361
P-value	-	<0.0001	<0.0001
t^b	-	11.012	5.911
P-value	-	<0.0001	<0.0001
t^c		14.685	23.769
P-value		<0.0001	<0.0001

[a]Comparison between before operation and 1 year after operation in recurrence group; [b]comparison between before operation and 1 year after operation in non-recurrence group; [c]comparison between non-recurrence group and recurrence group 1 year after operation.

operation (P<0.05) and HDL-C was higher than that before operation (P<0.05). After 1-year follow-up, we found that the levels of TC, TG and LDL-C (the indicators of blood fat) in the recurrence group were significantly higher than those in the non-recurrence group (P<0.05), while the level of HDL-C was significantly lower than that in the non-recurrence group (P<0.05; Table II).

Comparison of the BMI, waistline and hipline between the two groups. There was no significant difference in BMI, waist circumference and hip circumference between the two groups before operation (P>0.05). One year after operation, the BMI, waist circumference and hip circumference of the two groups were lower than those before operation (P<0.05). In the recurrence group, the BMI was significantly higher than that in the non-recurrence group (P<0.05), and similar results were also found in comparison of waistline and hipline (P<0.05; Table III).

Comparison of the fasting blood glucose and blood glucose at 2 h after meal. There was no significant difference in fasting blood glucose and blood glucose at 2 h after meal between the two groups before operation (P>0.05). At one year after operation, the fasting blood glucose and blood glucose at 2 h after meal in the two groups were lower than those before operation (P<0.05). In the recurrence group, the fasting blood glucose was significantly higher than that in the non-recurrence group (P<0.05), and the blood glucose at 2 h after meal was also higher than that in the non-recurrence group (P<0.05; Table IV).

Comparison of the levels of FINS and HOMA-IR index between the two groups. There was no significant difference in the levels of FINS and HOMA-IR between the two groups before operation (P>0.05), and the levels of FINS and HOMA-IR 1 year after operation were lower than those before operation (P<0.05). In the recurrence group, the level of FINS

Table V. Comparison of the levels of FINS and HOMA-IR index between the two groups (mean ± SD).

Group	Time	FINS (mU/l)	HOMA-IR
Recurrence group	Before operation	9.3±0.2	1.7±0.03
	1 year after operation	4.5±0.1	1.5±0.02
Non-recurrence group	Before operation	9.3±0.2	1.7±0.03
	1 year after operation	8.4±0.3	0.9±0.01
t[a]	-	135.765	35.082
P-value	-	<0.0001	<0.0001
t[b]	-	15.787	160.000
P-value	-	<0.0001	<0.0001
t[c]	-	78.000	169.706
P-value	-	<0.0001	<0.0001

[a]Comparison between before operation and 1 year after operation in recurrence group; [b]comparison between before operation and 1 year after operation in non-recurrence group; [c]comparison between non-recurrence group and recurrence group 1 year after operation. FINS, fasting insulin; HOMA-IR, homeostasis model assessment-insulin resistance.

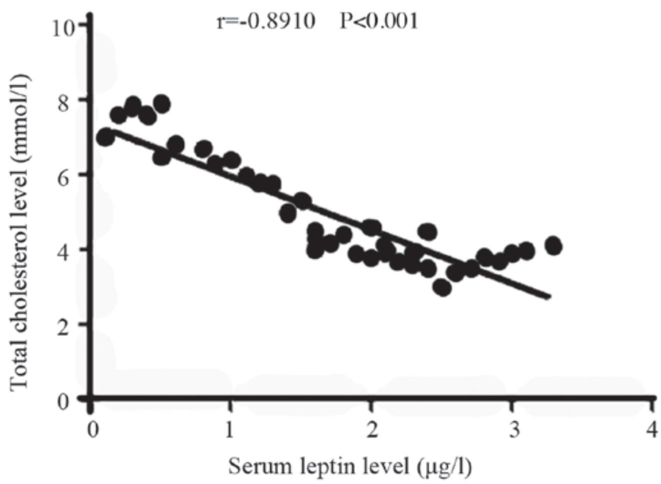

Figure 2. Correlation between the levels of serum leptin and TC in the recurrence group. In the recurrence group, the level of serum leptin is negatively correlated with that of TC (r=-0.8910, P<0.001). TC, total cholesterol.

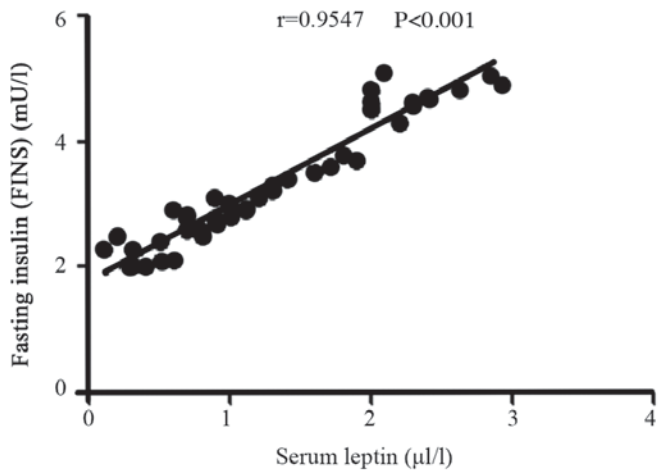

Figure 3. Correlation between the serum leptin level and FINS level in the recurrence group. In the recurrence group, the level of serum leptin is positively associated with the FINS level (r=0.9547, P<0.001). FINS, fasting insulin.

was significantly lower than that in the non-recurrence group, while the HOMA-IR index level was significantly higher than that in the non-recurrence group (P<0.05; Table V).

Correlation between the serum leptin and TC levels in the recurrence group. In the recurrence group, the level of serum leptin was negatively correlated with that of TC (r=-0.8910, P<0.001; Fig. 2).

Correlation between the serum leptin level and FINS level in the recurrence group. In the recurrence group, the level of serum leptin was positively correlated with the FINS level (r=0.9547, P<0.001; Fig. 3).

Correlation between the serum leptin level and the fasting blood glucose in the recurrence group. In the recurrence group, the level of serum leptin was negatively correlated with the fasting blood glucose level (r=-0.9562, P<0.001; Fig. 4).

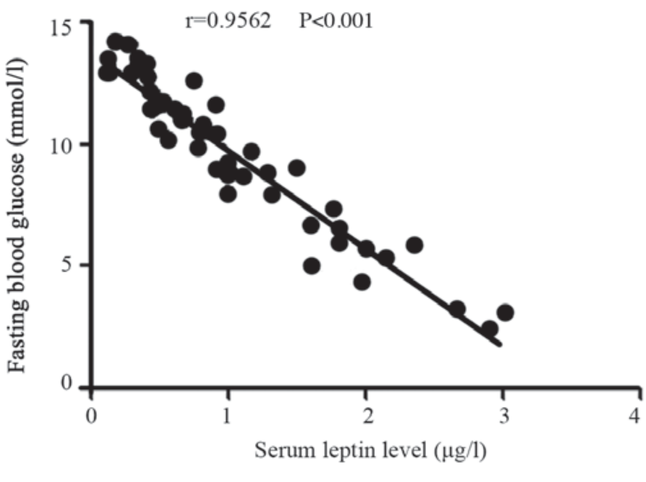

Figure 4. Correlation between the serum leptin level and the fasting blood glucose in the recurrence group. In the recurrence group, the level of serum leptin is negatively associated with the fasting blood glucose level (r=-0.9562, P<0.001).

Discussion

Liver is a major organ for energy metabolism. Once the hepatic functions are damaged, abnormalities will emerge in the metabolism of blood fat and glucose (12). However, elder patients are more susceptible to hyperlipidemia, hyperglycemia, hypertension and chronic obstructive pulmonary disease. Particularly for the elder hepatic carcinoma patients, their liver functions are significantly damaged with an obvious decline in compensation function, plus the adverse effect of surgical treatment, anesthesia and postoperative chemotherapy, severely compromising the normal functions of the liver (13). Previous studies confirmed that in over 90% of hepatic carcinoma patients, the level of serum leptin is decreased (14) with the abnormality in metabolism of blood fat and glucose (15). However, for hepatic carcinoma patients who experienced recurrence after surgery, there are few studies reporting the variations in levels of serum leptin, blood glucose and blood fat. Thus, more studies are required to attest whether the changes in these indicators are significant.

In this study, all participants were divided into the recurrence group and non-recurrence group based on the postoperative recurrence. We found that in the recurrence group, the levels of serum leptin before, one month and one year after surgery were significantly lower than those in the non-recurrence group ($P<0.05$), suggesting that in the hepatic carcinoma patients with postoperative recurrence, the serum leptin level was significantly decreased, thereby remarkably attenuating its regulatory effect on the energy metabolism. In addition, comparisons of the indicators of blood fat, BMI, waistline and hipline one year after surgery in the two groups showed that the levels of TC, TG and LDL-C in the recurrence group were significantly higher than those in the non-recurrence group, while the level of HDL-C was significantly lower than that in the non-recurrence group; besides, the BMI, waistline and hipline in the recurrence group was significantly larger than those in the non-recurrence group; these results suggested that hepatic carcinoma patients with postoperative recurrence are more susceptible to the abnormality of blood fat, thereby affecting the weight and fat distribution. Furthermore, we compared the fasting blood glucose, blood glucose at 2 h after meal, FINS and HOMA-IR index, and found that compared with the non-recurrence group, the levels of fasting blood glucose, blood glucose at 2 h after meal and HOMA-IR index were significantly higher, and the FINS level was decreased; these results revealed that in the hepatic carcinoma patients with postoperative recurrence, the abnormal regulation of blood glucose will be further exacerbated, making patients more susceptible to the simultaneous increases in fasting blood glucose and blood glucose after meal, and frequently complicated with the abnormality in functions of insulin and emergence of insulin-resistance. The analysis of correlation of serum leptin with TC, FINS and fasting blood glucose showed that in the recurrence group, the level of serum leptin was negatively correlated with TC and fasting blood glucose levels, and positively correlated with the FINS level.

In hepatic carcinoma patients, the serum leptin level is significantly correlated with the metabolism of blood fat and glucose. Adipose tissue accumulation (central-visceral-waistline and peripheral-hipline) was negatively correlated with serum leptin level, and the leptin receptor sensitivity was significantly reduced in pathological state, resulting in imbalance of the normal fat-islet axis feedback mechanism and the accumulation of fat, especially visceral fat accumulation (16,17). Decrease in serum leptin (18) will result in the decline in appetite of patients with weight loss. But sufficient nutrition is usually provided for hepatic carcinoma patients with postoperative recurrence, and massive intake of nutrients cannot timely participate in the metabolism (19,20), which will further lead to the abnormality in blood fat metabolism, the increase in BMI and accumulation of fat in abdomen and hips (21), thereby inducing an increase in blood glucose; besides, the long-term hyperglycemia can further stimulate the hepatic carcinoma cells, which can induce the accumulation of nutrients (22), thicken the basilemma in capillary, and decrease the membrane permeability (23), thus facilitating the cell proliferation (24-26), and further giving rise to the postoperative recurrence.

In conclusion, leptin levels decreased in patients with postoperative recurrence, and accumulation of visceral adipose tissue and abnormal blood glucose metabolism also occurred. Serum leptin level is negatively correlated with total cholesterol level and fasting blood glucose and positively correlated with FINS levels in patients with postoperative recurrence. However, more studies are needed to investigate whether serum leptin is the relevant factor for hepatic cancer recurrence, and to explore the prognostic value of serum leptin in hepatic cancer.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

SL drafted the manuscript. SL and LZ collected and interpreted the data. YZ and JW performed the ELISA experiments. SL and XY conceived and designed the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of The First Hospital of Lanzhou University (Lanzhou, China). Written informed consent was obtained from the patients or their guardians prior to their inclusion in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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