Characteristics and Clinical Significance of Lipid Metabolism in Patients with Gastrointestinal Stromal Tumor

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Research

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Abstract

Objective

To investigate the characteristics and clinical significance of serum lipids in patients with gastrointestinal stromal tumor (GISTs).

Methods

The clinical and pathological data of 694 cases of GIST patients in Liyuan hospital and Union hospital from 2012 to 2016 were retrospectively analyzed. To compare the differences of blood lipid levels in patients with different risk levels.

Results

There was no significant correlation between preoperative lipid profile and some clinical features, including age, tumor frequency, CD117 or SMA positive or negative, and Ki67% < 5% or not (P 0.05). LDL-C, HDL-C and CHOL were significantly higher in women than men (P < 0.05). Compared to patients with tumor size over 5cm, TG, HDL-C and CHOL were significantly higher in those under 5cm (all P < 0.05). LDL-C, HDL-C and CHOL were higher in CD34 positive subjects than in negative ones. TG in the DOG-1 positive group was higher than that in negative one (P < 0.05). HDL-C was lower in S-100 positive subjects than in S-100 negative subjects (P < 0.05). Lipids indexes were correlated with the risk grade and tumor site of GISTs (P < 0.05). TG/HDL-C was significantly different in patients with GIST with different tumor sites, CD34 and DOG-1 positive or not (P < 0.05).

Conclusion

The clinical and pathological characteristics of the patients with GIST are closely related to the level of blood lipids. Blood lipids level can help judge benign or malignant of GIST to a certain extent.

Introduction

Gastrointestinal stromal tumors (GISTs) is a kind of gastrointestinal tumors considered to originated from Cajal cells. Although its incidence is approximately 1.28 per 0.1 million in China, GIST is the most common gastrointestinal mesenchymal tissue tumors[1, 2]. GISTs, which can occur anywhere in the gastrointestinal tract, are most commonly in the stomach, followed by the duodenum. Lipid metabolic disorders are associated with a variety of malignant tumors, such as thyroid cancer, lung cancer, liver cancer, stomach cancer, colorectal cancer, et al[3].Gastrointestinal stromal tumors do not distinguish between benign and malignant, but are classified into very low, low, medium and high malignant levels according to their clinicopathological characteristics[4]. At present, it is difficult to distinguish benign and malignant gastrointestinal stromal tumors, and EUS-FNA is the most accurate, safe and reliable examination method in clinic[5]. In this paper, 694 patients with gastrointestinal stromal tumors were retrospectively analyzed for preoperative lipid levels for the first time, so as to further clarify the relationship between lipid levels and the clinicopathological characteristics of patients with stromal tumors, which is of certain significance for the judgment of benign and malignant patients.

1 Materials And Methods

1.1 Patients

We consecutively selected 741 patients with gastrointestinal stromal tumors, who was underwent surgical resection from 2012 to 2016 in Tongji Hospital of Huazhong University of Since and Technology. All patients were diagnosed gastrointestinal stromal tumor according to Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. (2012) [6] .The risk stratifications were consistent with NIH 2008 modified and AFIP classification. Inclusion criterias: (1) clear pathological and immunohistochemical diagnosis;(2) complete clinical data;(3) no history of serious diabetes;(4) no history of serious cardiopulmonary disease. Exclusion criterias: (1) absence of pathological data;(2) other malignant tumors;(3) a history of severe diabetes;(4) a history of severe cardiopulmonary disease. According to the inclusion and exclusion criterias, a total of 694 patients with gastrointestinal stromal tumors were eligible, including 388 males and 306 females. According to the classification of NIH 2008 modified version and AFIP, there were 340 cases in the low-risk group, 70 cases in the medium-risk group and 284 cases in the high-risk group, as shown in Fig.1. The trial was conducted in accordance with the principles of the Declaration of Helsinki and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at each participating center. All information was accessed after informed consent.

1.2 specimen collection and detection

5ml fasting venous blood was collected 1-2 days after acquiring admission of all patients, and serum was centrifuged within 2h. The detection indexes were as follows: triglyceride (TG), low-density lipoprotein - cholesterol (LDL-C), high-density lipoprotein - cholesterol (HDL-C), total cholesterol (CHOL), and TG/ HDL-C. Serum TG (GPO-PAP method), HDL-C, LDL-C (direct method) and CHOL (CHOD-PAP method) were determined by different corresponding detection methods. Reference range for normal values was set by department of clinical laboratory, Tongji Hospital of Huazhong University of Since and Technology: TG 0.05 ~ 1.70 mmol/L; HDL-C 1.04 ~ 1.55 mmol/L; LDL-C < 3.37 mmol/L; CHOL 2.90 ~ 5.20 mmol/L.

1.3 statistical methods

SPASS 23.0 software was used for statistical analysis of the data, and one-way analysis of variance was used to analyze the relationship between various factors and blood lipids. The counting data were represented by (X±s), the measurement data were represented by chi-square, the single factor anova was selected for more than two measurement data, and the box graph of different risk content was calculated by Graphpad.

2 Bears Fruit

2.1 relationship between clinical characteristics and various blood lipid indexes

There was no significant relationship between preoperative blood lipid indexes and patient age or whether the tumor was multiple (all P >0.05). LDL-C, HDL-C and CHOL were significantly higher in female patients than in male patients (all P < 0.05). TG, HDL-C and CHOL were significantly higher than those with tumor size < 5cm (all P < 0.05). There were significant differences in serum lipids and TG/ HDL-C levels at different mesenchymal sites (all P < 0.05), as shown in table 1.

Table1

The relation between clinical significance and blood lipids in GISTs（X±s）

		n	TG	P	LDL-C	P	HDL-C	P	CHOL	P	TG/HDL-L	P
			(mmol/L)		(mmol/L)		(mmol/L)		(mmol/L)			
Sex	Male	388	1.28±0.79	0.223	2.39±0.73	0.000	1.08±0.30	0.000	3.97±0.89	0.000	1.33±1.06	0.526
	Female	306	1.37±1.13		2.61±0.82		1.27±0.36		4.44±1.06		1.27±1.55	
Age	<60y	312	1.27±0.79	0.188	2.49±0.79	0.928	1.17±0.35	0.920	4.17±1.01	0.848	1.25±1.07	0.276
	≥60y	382	1.36±1.07		2.48±0.77		1.16±0.33		4.18±0.99		1.35±1.46	
Tumor cites	Esophageal	10	1.24±0.79	0.08	2.19±0.53	0.000	1.18±0.49	0.000	3.75±0.79	0.000	1.29±0.97	0.002
	Stomach	383	1.35±0.99		2.60±0.78		1.22±0.33		4.35±0.99		1.24±1.14	
	Duodenum	58	1.53±1.18		2.35±0.82		1.07±0.37		4.02±0.99		1.79±1.98	
	Jejunoileum	129	1.33±1.05		2.21±0.72		1.03±0.33		3.79±0.94		1.51±1.70	
	Colorectal	28	0.99±0.34		2.67±0.97		1.28±0.27		4.38±1.03		0.84±0.49	
	External gastrointestinal tract	86	1.14±0.46		2.48±0.78		1.15±0.34		4.06±0.94		1.10±0.59	
Tumor size	<5cm	384	1.42±1.10	0.004	2.54±0.80	0.060	1.21±0.35	0.000	4.29±1.00	0.000	1.36±1.39	0.230
	≥5cm	310	1.21±0.72		2.43±0.75		1.11±0.33		4.03±0.98		1.24±1.16	
Multiple or not	Yes	113	1.29±0.57	0.736	2.51±0.68	0.770	1.14±0.31	0.475	4.19±0.87	0.896	1.24±0.71	0.557
	Not	581	1.33±1.01		2.49±0.79		1.17±0.35		4.17±1.02		1.32±1.38	

2.2 relationship between pathological features of tumor and various lipid indexes

There was no significant correlation between preoperative lipid indexes and that whether CD117 positive or not, SMA was positive or not, and ki67% was less than 5% (all P > 0.05). LDL-C, HDL-C and CHOL were significantly higher in CD34 positive subjects than in CD34 negative subjects. TG in the DOG-1 positive group was significantly higher than that in the DOG-1 negative group (P < 0.05). HDL-C was significantly lower in S-100 positive subjects than in S-100 negative subjects (P < 0.05). TG/ HDL-C was significantly lower in CD34 positive subjects than in CD34 negative subjects and in DOG-1 positive subjects than in DOG-1 negative subjects (all P < 0.05), as shown in table 2.

Table 2

The relation between pathological significance and blood lipids in GISTs（X±s）

		n	TG	P	LDL-C	P	HDL-C	P	CHOL	P	TG/HDL-L	P
			(mmol/L)		(mmol/L)		(mmol/L)		(mmol/L)			
CD117	Positive	665	1.32±0.96	0.860	2.49±0.78	0.810	1.16±0.34	0.336	4.18±0.99	0.804	1.31±1.31	0.991
	Negative	9	1.27±0.46		2.43±0.59		1.05±0.35		4.09±0.92		1.31±0.77	
CD34	Positive	574	1.31±0.91	0.555	2.54±0.78	0.000	1.19±0.34	0.000	4.24±0.99	0.000	1.26±1.14	0.010
	Negative	98	1.38±1.19		2.24±0.70		1.02±0.33		3.83±0.96		1.62±1.99	
DOG-1	Positive	663	1.31±0.85	0.000	2.49±0.78	0.758	1.17±0.34	0.125	4.18±0.99	0.985	1.29±1.22	0.001
	Negative	9	2.47±3.94		2.42±0.69		0.99±0.34		4.17±0.91		2.77±4.31	
SMA	Positive	231	1.41±1.24	0.089	2.44±0.79	0.173	1.13±0.34	0.147	4.11±1.02	0.198	1.42±1.65	0.127
	Negative	441	1.28±0.76		2.52±0.77		1.17±0.34		4.21±0.99		1.26±1.09	
S-100	Positive	16	1.32±0.71	0.978	2.46±0.93	0.862	0.98±0.33	0.031	3.96±1.18	0.372	1.66±1.34	0.28
	Negative	657	1.32±0.96		2.49±0.77		1.17±0.34		4.18±0.99		1.30±1.31	
Ki67%	<5%	395	1.34±1.08	0.583	2.47±0.74	0.409	1.18±0.34	0.081	4.18±0.92	0.886	1.32±1.46	0.875
	≥5%	269	1.30±0.75		2.53±0.82		1.13±0.34		4.17±1.09		1.30±1.06	
Rank of risk	Extremely low	117	1.34±0.83	0.012	2.62±0.80	0.033	1.27±0.36	0.000	4.44±0.95	0.000	1.24±1.21	0.169
	Low	224	1.48±1.27		2.47±0.75		1.17±0.34		4.19±0.97		1.46±1.56	
	Medium	70	1.28±0.60		2.64±0.80		1.20±0.32		4.38±1.07		1.17±0.69	
	High	283	1.20±0.75		2.41±0.79		1.11±0.33		4.01±0.99		1.24±1.21	

2.3 relationship between risk groups and various blood lipid indexes

There were significant differences in the levels of serum lipids in different risk levels of stromal tumors (all $P < 0.05$). TG, LDL-C, HDL-C and CHOL in patients with high risk stratification were significantly lower than those in patients with low risk, while TG/ HDL-C showed no significant difference in patients with different risk levels, as shown in Fig. 2.

3 Discussion

In this paper, the blood lipid levels of 694 patients with gastrointestinal stromal tumor are analyzed, and the results indicates that the blood lipid levels of patients with gastrointestinal stromal tumor was related to multiple factors, including gender, tumor site, tumor size, CD34, CD117 and S-100. The contents of TG, LDL-C, HDL-C and CHOL in patients with highly malignant gastrointestinal stromal tumors are significantly lower than those in patients with other dangerous levels of stromal tumors, which suggests that stromal tumors affect lipid metabolism to some extent, and lipid levels can predict their malignancy to a certain extent.

Currently, there are many studies on gastrointestinal stromal tumors, the pathogenesis of which is mainly tyrosine kinase receptor (KIT) and/or platelet derived growth factor receptor-alpha (PDGFRA) gene mutations. However, there exists wild-type KIT /PDGFRA in 10-15% GISTs[7], in which clinicopathological characteristics are related to a variety of factors. Lipid metabolism disturbance is proved to exist in most tumor patients, and elevated lipid levels promote multiple types of tumors[8–10]. However, some studies have shown that obesity plays a protective effect on gastrointestinal stromal tumors. In the 1920s, Warburg, a German scientist, discovered for the first time that tumor cells would give priority to anaerobic fermentation even in the case of sufficient oxygen supply, providing tumor cells with sufficient energy and the prerequisite material needed for the synthesis of biological macromolecules, which is the Warburg effect[11]. Warburg effect indicates that tumor cells not only need energy to grow, but also need to synthesize a large number of macromolecules. Aerobic glycolysis can not only improve the efficiency of tumor cells to produce energy, but also provide necessary conditions for the synthesis of biomolecular molecules to meet their growth, adhesion, metastasis and other biological characteristics. The results in this paper may due to these mechanisms as follows. On the one hand, lipid is an important component of cell membrane, and there are increasing evidences that lipid metabolism plays an important role in tumor progression. Lipid raft, rich in neurolipids and cholesterol, is a unique small lipid domain on cell membrane, which acts as selective signal transduction to regulate lipid metabolism, tumor cell growth, adhesion, and metastasis, and promote tumor progression[12]. On the other hand, lipids are also an important source of energy for tumor cells. In order to meet the needs of rapid growth of tumor cells, lipid metabolism is greatly accelerated and lipid content is reduced. In terms of nutritional support in patients with malignant tumors, abnormal host metabolism can lead to mobilization of host tissues and ineffective supplementation. Increased fat breakdown, reduced or increased fat production, increased turnover of free fatty acids (FFA) and glycerol, and increased FFA-triacylglycerol circulation all contribute to the disorder of lipid metabolism[13]. Moreover, lipids are also the prerequisite for synthesizing signal molecules, which can change the

microenvironment of tumor cells and promote the development of tumor cells[14]. In addition, one of the main functions of HDL is to maintain normal intracellular cholesterol homeostasis by binding to receptors on the cell surface to remove excess cholesterol from the cell[15].

In recent years, there are evidences that TG/ HDL-C can be used as an independent risk factor for predicting the prognosis of triple negative breast cancer and gastric cancer, and its prediction effect is better than that of TG[16]. TG/ HDL-C may be related to insulin resistance, which is related to gastrointestinal tumors such as gastric cancer. The results in this study show that TG/ HDL-C is different in gastrointestinal stromal tumors with different clinical characteristics, which suggests that insulin resistance may be related to gastrointestinal stromal tumors[17].

The advantages of this study are that a large number of patients with gastrointestinal stromal tumors were included in the study, and multiple clinicopathological features of the patients and their blood lipid levels were statistically analyzed. The outcomes indicate that there is a close association between blood lipid levels and gastrointestinal stromal tumors, and it is of certain value in the judgment of benign and malignant tumors. The limitation of this study is that no prospective studies have been conducted to determine whether changes in lipid levels occurred before or after the tumor. In addition, the effect of serum lipid levels on the prognosis of patients with gastrointestinal stromal tumors is still unclear, and further studies are needed to confirm this in the future.

Declarations

Conflicts of Interests

Conflict of interest relevant to this article was not reported.

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Figures

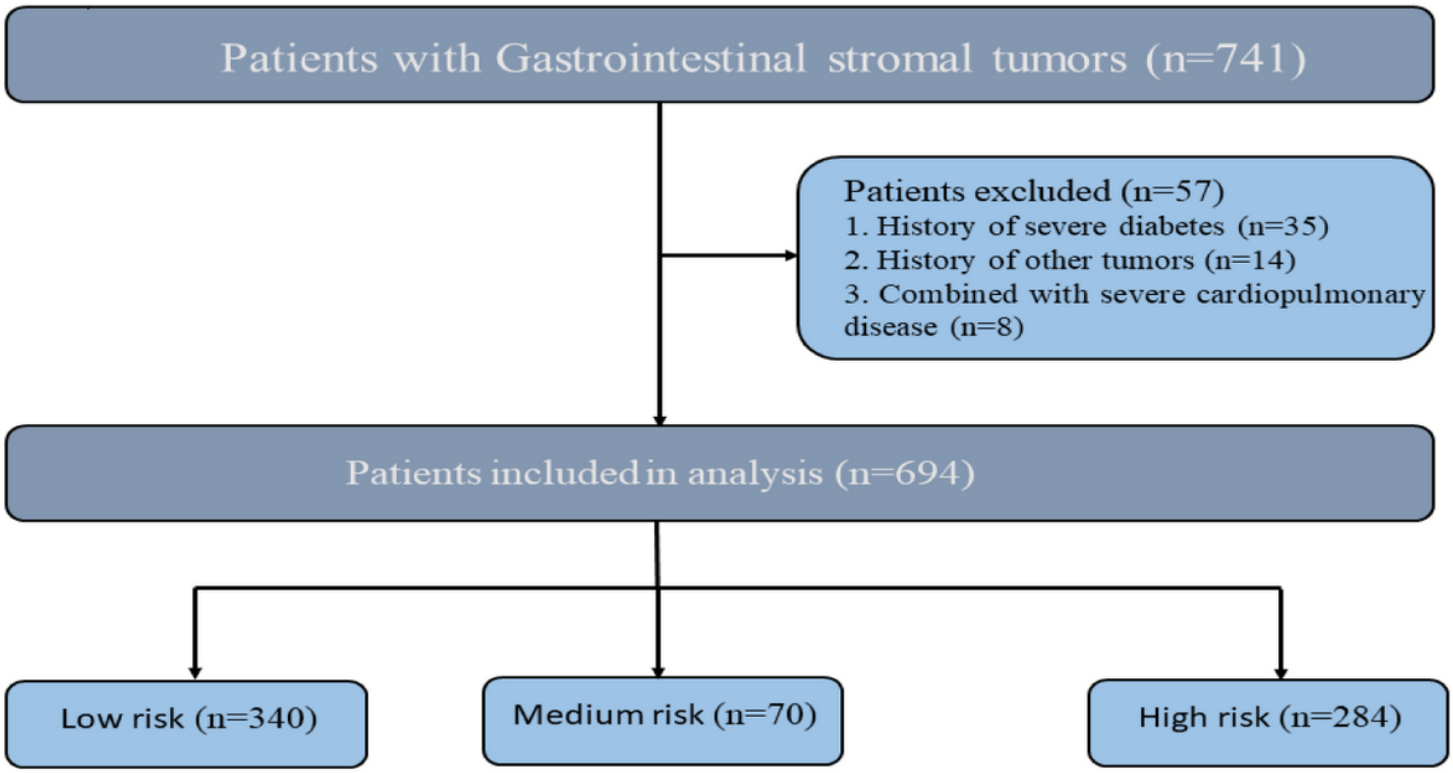

Figure 1

Flowchart of the patients with gastrointestinal stromal tumors selection. 694GISTs are included in this analysis, including 340patients in low risk, 70patients in medium risk, 284patients in high risk.

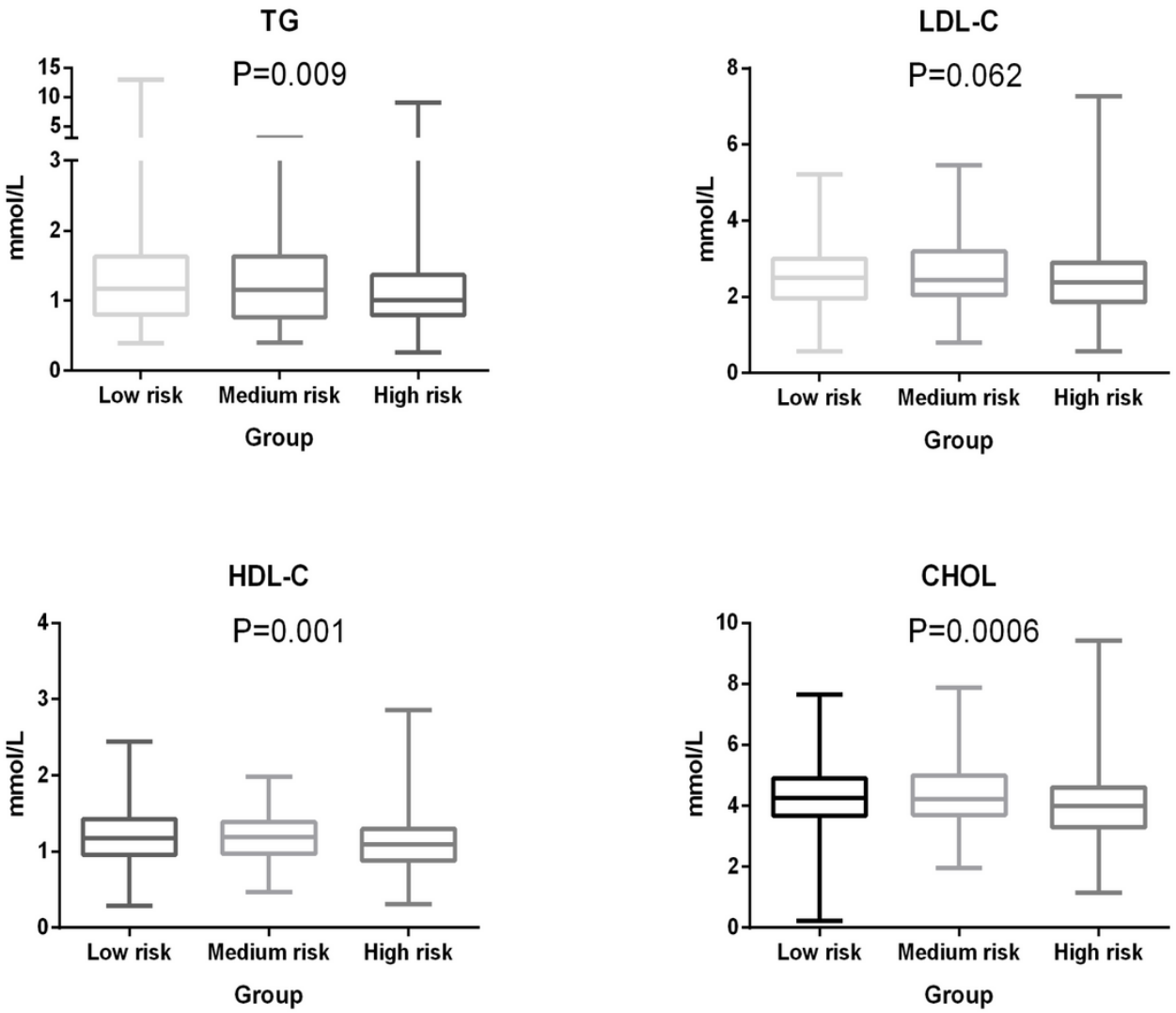

Figure 2

Differences in patients with different risk grades Box plot of the lipids level in various risk groups. There are significant difference in TG□HDL-C, and CHOL with risk sub-groups.