Characteristics and clinical significance of lipid metabolism in patients with gastrointestinal stromal tumor

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Abstract

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

Methods: The clinical and pathological data of 694 GIST patients in Liyuan hospital and Union hospital from 2012 to 2016 were retrospectively analyzed. Blood lipid levels in patients with varying degrees of risk were compared.

Results: The findings showed that LDL-C, HDL-C, and CHOL increased significantly in women, and CD34 positive. In patients with tumors size less than 5 cm in diameter, TG, HDL-C, and CHOL were significantly higher. TG levels were significantly higher in DOG-1 (a marker and has a high specificity and sensitivity in the diagnosis of GIST) positive patients than in DOG-1 negative patients ($P < 0.05$). S-100 positive patients had lower HDL-C levels than S-100 negative patients ($P < 0.05$). Lipids indexes were found to be correlated with GIST risk stratification and tumor site ($P < 0.05$). TG/HDL-C was was significantly different among patients with GIST in different locations ($P < 0.05$).

Conclusion: The clinical and pathological characteristics of the patients with GIST are closely related to the level of blood lipids. To a certain extent, information about level of blood lipids can be helpful for distinguishing benign and malignant GIST.

Keywords: Gastrointestinal stromal tumor, Lipid metabolism, Clinical pathology, GIST, Lipid, Risk stratification

Background

Gastrointestinal stromal tumors (GISTs) originate from Cajal cells. GIST is the most common tumor originating from gastrointestinal mesenchymal tissue, with an incidence of approximately 0.128 per billion population in China [1, 2]. GIST, which can manifest itself anywhere through gastrointestinal tract, has the biggest incidence rate in stomach, followed by the duodenum. Lipid metabolism disorder has been related with a large of malignant tumors, such as thyroid cancer, lung cancer, liver cancer, stomach cancer, colorectal cancer, and so on [3]. Gastrointestinal stromal tumors can be classified into low, medium and high malignant levels according to their clinicopathological characteristics [4]. At present, it is difficult to differentiate benign from malignant gastrointestinal stromal tumors, and EUS-FNA (endoscopic ultrasonography-guided fine needle aspiration) is the most accurate, reliable, receptive, and safe testing method in clinical practice [5]. Only a few studies have been conducted to date on abnormal lipid metabolism in GIST patients and its association to the degree of malignancy. For the first time, 694 patients with gastrointestinal stromal tumors had their preoperative lipid levels measured.
levels retrospectively analyzed, to further elucidate the relationship between lipid levels and the clinicopathological characteristics of patients, which aids in the differentiation of benign from malignant GISTs.

Method

Patients
Seven hundred forty-one patients with gastrointestinal stromal tumors who underwent surgical surgery from 2012 to 2016 at Union Hospital and Liyuan Hospital of Huazhong University of Science and Technology were selected. All patients were diagnosed with gastrointestinal stromal tumors in accordance with the ESMO Clinical Practice Guidelines (2012) [6]. It is the accepted guideline for diagnosis and treatment of GIST. Risk stratification was performed using NIH 2008 modified classification and AFIP classification. The inclusion criteria were as follows: (1) clear pathological and immunohistochemical diagnosis; (2) complete clinical data; (3) no history of serious diabetes; and (4) no history of serious cardiopulmonary disease. The exclusion criteria were following: (1) absence of pathological data; (2) presence of other malignant tumors; (3) history of severe diabetes; (4) history of the severe cardiopulmonary disease; and (5) use of statins, fibrates or any other lipid-lowering medication. The risk of developing cancer was classified according to tumor size and its mitotic index [7]. The trial was conducted in accordance with the principles of the Declaration of Helsinki. It was approved by approved by the hospital ethics board. All information was accessed after receiving informed consent from the patients.

Specimen collection and detection
Each patient had 5 ml fasting venous blood drawn 1–2 days following admission to the hospital, and serum was prepared within 2 h. Triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol (CHOL), and TG/HDL-C were detected on serum specimens. TG was determined by the GPO-PAP method, HDL-C, and LDL-C by the direct method, and CHOL by the CHOD-PAP method. The Department of Clinical Laboratory, Union Hospital of Huazhong University of Science and Technology established the reference ranges for normal values: TG 0.050 ~ 1.700 mmol/L, LDL-C < 3.370 mmol/L, HDL-C 1.040 ~ 1.550 mmol/L, and CHOL 2.900 ~ 5.200 mmol/L.

Statistical method
Statistical analyses of the data were conducted on SPSS 23 software. The relationship between numerous factors and blood lipids was analyzed by one-way analysis of variance. P<0.05 was defined as significant statistical difference. The counting data were represented as (X ± s), while the measurement data were represented by the chi-square value. For data with more than two measurements, a single factor anova was used, and Graphpad was used to calculate the box graph illustrating the relationship between different risk stratifications and lipid levels.

Results

Clinical data of all included cases
Of the 741 patients with GISTs recruited in this study, 56 were using statins or other lipid-lowering drugs. According to the inclusion and exclusion criteria, a total of 694 patients with gastrointestinal stromal tumors were eligible, including 388 males and 306 females. According to the NIH 2008 modified version and AFIP classification, there were 340 cases classified as low-risk, 70 cases medium-risk, and 284 cases high-risk (Fig. 1). The mean age was 57.63 ± 10.94 years. Five hundred eighty-one patients were diagnosed with a single tumor, while 113 patients had multiple tumors. Tumors in the esophagus, stomach, duodenum, hollow ileum, colorectal and gastrointestinal tract occurred at a rate of 1.44, 55.19, 8.36, 18.59, 4.03 and 12.39%, respectively. The proportion of tumor tissue with a diameter less than 5 cm and greater or equal to 5 cm was 55.33 and 44.67%, respectively.

Relationship between clinical characteristics and various blood lipid indexes
The age of the patient and the presence of single or multiple tumors had no discernible effect on lipid levels. Female patients had higher levels of LDL-C, HDL-C, and CHOL levels than male patients. TG and TC levels in patients with tumor size ≥5 cm were higher than in tumor size < 5 cm. There were significant differences between serum lipids and TG/ HDL-C levels at distinct mesenchymal sites (all P < 0.05) (Table 1).

Relationship between tumor pathology and various lipid indexes
Tumor markers such as CD117, SMA, and Ki67 had no effect on preoperative serum lipid levels. Besides LDL-C, HDL-C and CHOL levels were higher in CD34 positive patients than in CD34 negative patients. TG levels were significantly greater in the DOG-1 positive patients than in DOG-1 negative ones (P < 0.05). S-100 positive patients had lower HDL-C levels than S-100 negative patients. TG/ HDL-C ratio was lower in CD34 or DOG-1 positive, compared to CD34 or DOG-1 negative patients (all P < 0.05) (Table 2).

Relationship between risk groups and various blood lipid indexes
Blood lipid levels were significantly different in GIST patients with varying degrees of malignancy (all P < 0.05)
(size effect: $\eta^2 = 0.21$). Compared to low-risk patients, high-risk patients had lower lipids levels, including TG, HDL-C, LDL-C, and CHOL. While TG/ HDL-C values did not exist any difference in patients with different risk levels (Fig. 2).

**Discussion**

The blood lipid levels of 694 patients with gastrointestinal stromal tumor were analyzed in this study. The findings suggested that multiple factors, including gender, tumor site, tumor size, CD34, CD117, and S-100 were related to blood lipid levels in patients with gastrointestinal stromal tumors. S-100 protein is a kind of the calcium-binding proteins, presenting in most gastrointestinal tumors. However, GIST is mostly negative for S-100. Patients with highly malignant gastrointestinal stromal tumors had lower lipids levels than in patients with other risk stratifications of stromal tumors. We

**Table 1** the relation between clinical significance and blood lipids in GISTs (X ± s)

|                | n  | TG (mmol/L) | P   | LDL-C (mmol/L) | P   | HDL-C (mmol/L) | P   | CHOL (mmol/L) | P   | TG/HDL-C | P   |
|----------------|----|-------------|-----|----------------|-----|----------------|-----|---------------|-----|-----------|-----|
| **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 | 0.188| 2.61 ± 0.82  | 0.000| 1.27 ± 0.36  | 0.000| 4.44 ± 1.06  | 0.000| 1.27 ± 1.55|
| **Age**        |    |             |     |                |     |                |     |               |     |           |     |
| < 60y          | 312| 1.27 ± 0.79 | 0.188| 2.49 ± 0.79  | 0.028| 1.17 ± 0.35  | 0.020| 4.17 ± 1.01  | 0.848| 1.25 ± 1.07| 0.276|
| ≥ 60y          | 382| 1.36 ± 1.07 | 0.090| 2.48 ± 0.77  | 0.033| 1.16 ± 0.33  | 0.034| 4.18 ± 0.99  | 0.035| 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 | 0.090| 2.60 ± 0.78  | 0.033| 1.22 ± 0.33  | 0.034| 4.35 ± 0.99  | 0.035| 1.24 ± 1.14|
| Duodenum       | 58 | 1.53 ± 1.18 | 0.08 | 2.35 ± 0.82  | 0.037| 1.07 ± 0.37  | 0.039| 4.02 ± 0.99  | 0.040| 1.79 ± 1.98|
| Jejunum        | 129| 1.33 ± 1.05 | 0.736| 2.21 ± 0.72  | 0.037| 1.03 ± 0.33  | 0.039| 3.79 ± 0.94  | 0.040| 1.51 ± 1.70|
| Colorectal     | 28 | 0.99 ± 0.34 | 0.090| 2.67 ± 0.97  | 0.033| 1.28 ± 0.27  | 0.034| 4.38 ± 1.03  | 0.035| 0.84 ± 0.49|
| External gastrointestinal tract | 86  |1.14 ± 0.46 | 0.090| 2.48 ± 0.78  | 0.033| 1.15 ± 0.34  | 0.034| 4.06 ± 0.94  | 0.035| 1.10 ± 0.59|
| **Tumor size** |    |             |     |                |     |                |     |               |     |           |     |
| < 5 cm         | 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|
| ≥ 5 cm         | 310| 1.21 ± 0.72 | 0.072| 2.43 ± 0.75  | 0.111| 1.11 ± 0.33  | 0.073| 4.03 ± 0.98  | 0.124| 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 | 0.090| 2.49 ± 0.79  | 0.117| 1.17 ± 0.35  | 0.147| 4.17 ± 1.02  | 0.132| 1.32 ± 1.38|
hypothesized that GIST patients had a lipid metabolism disorder, which could have an influence on the degree of malignancy of the tumor. Numerous studies have linked gastrointestinal stromal tumors to gene mutations in tyrosine kinase receptor (KIT) and platelet-derived growth factor receptor-alpha (PDGFRA). However, wild-type KIT /PDGFRA can be discovered in about 10–15% GISTs [8]. Clinicopathological characteristics of patients with GIST are complex and are influenced by several factors. KIT/PDGFRA may exert an effect on lipid metabolism via distinct signal transduction pathways [9]. Most tumor patients, such as those with thyroid cancer, lung cancer, or liver cancer, have lipid metabolism disturbance, and elevated lipid levels have been shown to promote the growth of multiple tumor types [10–12]. Obesity, on the other hand, has been demonstrated in some studies to play a protective effect on gastrointestinal stromal tumors [13]. In the 1920s, Warburg demonstrated, for the first time that tumor cells prioritize anaerobic fermentation even when oxygen supply is adequate, providing tumor cells with sufficient energy and prerequisite material for the synthesis of biological macromolecules, a phenomenon termed as the Warburg effect [14]. Warburg effect indicates that tumor cells require energy not only for growth but also for the synthesis of a vast number of macromolecules. Aerobic glycolysis not only increases tumor cells’ energy production efficiency, but also provides necessary conditions for the synthesis of biomolecular components necessary for growth, adhesion, metastasis, and other biological characteristics [15, 16]. Given the critical roles that lipids play in cellular membrane formation, energy and macromolecular metabolism, cellular signal transduction and other cellular activities, it is not surprising to find that associations between lipid metabolism and tumorigenesis have been discovered. In this study, by examining data from 694 GIST patients, we demonstrated that lipid metabolism was associated with tumor size, tumor site, tumor molecular markers, and the risk level in GIST patients.

|       | n   | TG (mmol/L) | P   | LDL-C (mmol/L) | P   | HDL-C (mmol/L) | P   | CHOL (mmol/L) | P   | TG/HDL-C | P   |
|-------|-----|-------------|-----|----------------|-----|---------------|-----|--------------|-----|----------|-----|
| 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 | 0.089 | 2.43 ± 0.59  | 0.05 | 1.05 ± 0.35  | 0.035 | 4.09 ± 0.92  | 0.092 | 1.31 ± 0.77 | 0.035 |
| 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 | 0.089 | 2.24 ± 0.70  | 0.000 | 1.02 ± 0.33  | 0.000 | 3.83 ± 0.96  | 0.000 | 1.62 ± 1.99 | 0.000 |
| 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 | 0.25 | 2.42 ± 0.69  | 0.09 | 0.99 ± 0.34  | 0.336 | 4.17 ± 0.91  | 0.277 | 4.31 ± 0.91 | 0.277 |
| 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 | 0.000 | 2.52 ± 0.77  | 0.000 | 1.17 ± 0.34  | 0.147 | 4.21 ± 0.99  | 0.198 | 1.26 ± 1.09 | 0.127 |
| 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 | 0.000 | 2.49 ± 0.77  | 0.000 | 1.17 ± 0.34  | 0.147 | 4.18 ± 0.99  | 0.198 | 1.30 ± 1.31 | 0.130 |
| 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 | 0.012 | 2.53 ± 0.82  | 0.13 | 1.13 ± 0.34  | 0.13 | 4.17 ± 1.09  | 0.13 | 1.30 ± 1.06 | 0.13 |
| Rank of risk |     |             |     |                |     |               |     |              |     |          |     |
| Extremely low risk | 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 risk | 224 | 1.48 ± 1.27 | 0.075 | 2.47 ± 0.75  | 0.173 | 1.17 ± 0.34  | 0.147 | 4.19 ± 0.97  | 0.198 | 1.46 ± 1.56 | 0.146 |
| Medium risk | 70  | 1.28 ± 0.60 | 0.000 | 2.64 ± 0.80  | 0.103 | 1.20 ± 0.32  | 0.13 | 4.38 ± 1.07  | 0.117 | 1.17 ± 0.69 | 0.117 |
| High risk | 283 | 1.20 ± 0.75 | 0.012 | 2.41 ± 0.79  | 0.13 | 1.11 ± 0.33  | 0.13 | 4.01 ± 0.99  | 0.13 | 1.24 ± 1.21 | 0.124 |

a Extremely low risk was defined as a GIST with tumor size ≤2 cm and arbitrary mitotic index, or 2 cm < tumor size ≤5 cm and mitotic index < 5 per 50 HPF. Low risk was defined as a GIST with 5 cm < tumor size ≤10 cm and mitotic index < 5 per 50 HPF. Medium risk was defined as a GIST with tumor size > 10 cm and mitotic index < 5 per 50 HPF, or 2 cm < tumor size ≤5 cm and mitotic index ≥5 per 50 HPF. High risk was defined as a GIST with tumor size > 5 cm and mitotic index ≥5 per 50 HPF.
There is more and more evidence that lipid metabolism has a vital role in tumor progression. The lipid raft, which is rich in neurolipids and cholesterol, is a unique small lipid domain on the cell membrane that acts as a selective signal transducer, regulating lipid metabolism, tumor cell growth, adhesion, and metastasis, and promoting tumor progression [17]. On the other hand, provide energy to tumor cells as well. To meet the needs of tumor cells’ rapid growth, lipid metabolism is expedited and lipid content is reduced. Fatty acid synthase overexpression may significantly contribute to the elevation of lipid levels in GIST patients [18]. In terms of nutritional support, abnormal host metabolism might result in the mobilization of host tissues and inefficient supplementation in patients with malignant tumors. Increased fat breakdown, decreased or increased fat production, increased free fatty acids (FFA) and glycerol turnover, and increased FFA-triacylglycerol circulation all contribute to lipid metabolism dysfunction [19]. Additionally, lipids are required for the synthesis of signaling molecules that can alter the microenvironment of tumor cells and promote tumor cell growth [20]. Additionally, HDL plays a critical role in maintaining proper intracellular cholesterol homeostasis by binding to cell membrane surface receptors and removing excess cholesterol from the cell [21].

Recent evidence suggests that TG/ HDL-C can be utilized as an independent risk factor for predicting the prognosis of breast cancer and gastric tumor and that its predictive value is superior to that of TG [22]. The ratio of TG/ HDL-C may be related to insulin resistance, which is associated with gastrointestinal tumors such as gastric cancer. The results of this study indicated that the ratio of TG/ HDL-C was different in gastrointestinal stromal tumors with varying clinical characteristics, implying that insulin resistance may be associated with gastrointestinal stromal tumors [23].

Compared with other studies, this study focuses on systematic analysis of laboratory examination data from a clinical perspective. As the number of cases included was large enough in this study, the results were more reliable in comparison to some other studies. The results of this study may have guiding significance for GIST patients’ dietary selection, suggesting that patients adhere to low-fat diet. In the future, the molecular mechanism of abnormal lipid metabolism in GIST patients may be further explored.
Strengths and limitations
This study innovatively analyzed the dyslipidemia of patients with GISTs. The limitation of this study is in that it failed to compare the changes in lipid levels in GIST patients before and after surgery. 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. Whether prior use of lipid-lowering drugs such as statins or betas had any effect on the study is unknown.

Conclusion
In general, patients with GISTs have varying degrees of lipid metabolism disorders. It also offers a new perspective for exploring abnormalities in GIST metabolism in this study. Therefore, both treatment and nursing on them should be taken seriously.

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Authors’ contributions
Xiaoling Liu participated in the process of data collection and screening, statistical analysis and manuscript drafting. Jun Hu participated in research design, data screening and manuscript drafting. Bende Liu participated in statistical analysis and manuscript drafting. All authors read and approved the final manuscript.

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This research was reviewed and approved by the Ethics Committee of Huazhong University of Science and Technology.

Consent for publication
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Competing interests
Conflict of interest relevant to this article was not reported.

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