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Serum lipid profile in gynecologic tumors: a retrospective clinical study of 1,550 patients

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Summary

Background: The study was performed to characterize and compare the serum lipid profile in gynecologic cancers and benign diseases. *Materials and Methods:* A total of 1,550 age-matched females were included in this study: 760 patients with gynecologic cancers and 790 patients with benign diseases. Serum levels of triglycerides (TG), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), total cholesterol (TC), and lipoprotein (a) were measured. *Results:* Compared to gynecologic benign disease group, gynecologic cancer group was associated with higher level of TG ($p = 0.0002$), as well as lower level of HDL-c ($p < 0.0001$), LDL-c ($p = 0.004$) and TC ($p = 0.003$). Compared to benign ovarian tumor group, ovarian cancer group had significantly lower levels of HDL-c ($p < 0.0001$), LDL-c ($p = 0.0009$), and TC ($p < 0.0001$), as well as a trend of higher level of lipoprotein (a) ($p = 0.10$). Compared to endometriosis group, endometrial cancer group showed higher levels of TG ($p < 0.0001$) and lower levels of HDL-c ($p = 0.002$). There was no significant difference in any lipid parameters between cervical cancer group and uterine leiomyomas group. *Conclusion:* In conclusion, compared with benign diseases, gynecologic cancers are associated with a disordered lipid profile characterized by higher TG and lipoprotein (a) levels, and lower HDL-c, LDL-c, and TC levels. The association is most conspicuous in ovarian cancers. Endometrial cancer is accompanied by alterations only in TG and HDL-c levels, while cervical cancer does not appear to be associated with disordered lipid profile.

Key words: Serum lipid; Ovarian cancer; Endometrial cancer; Cervical cancer.

Introduction

Lipid is a critical component of cell membranes and plays a key role in the maintenance of cell integrity [1, 2]. The development of cancer is usually associated with disordered lipid profile [1, 3]. Numerous studies have shown that disordered lipid profile was usually associated with many types of cancers, such as breast, prostate, gastrointestinal , kidney, liver, and lung cancer [4-10]. The growth of carcinoma utilizes lipids including triglycerides, cholesterol, and lipoproteins for new cancer cell membrane biogenesis. To fulfill these requirements, the cancer cell could either obtain the lipids from circulation and degradation of lipoprotein fractions or stimulate the synthesis of extra lipids through the metabolism [2]. Therefore the serum lipid profile may be modified [11].

Gynecologic disease is a threat to numerous females' health and quality of life all around the world. Gynecologic cancers mainly including ovarian, endometrial, and cervical cancer, are the most dangerous ones. Previous studies have suggested that other proliferative gynecologic disease such as polycystic ovary syndrome is accompanied by metabolic disease [12, 13]. Several large cohort studies and case-control studies have shown that metabolic syndrome, which is associated with disordered lipid profiles, is a potential risk factor of gynecologic cancers, including ovarian, endometrial, and cervical cancer [14-17]. However, no study has been conducted to investigate the differences in lipid profile between gynecologic malignant and benign diseases. The objective of this study was to characterize and compare serum lipid profile in gynecologic cancer and benign disease.

Materials and Methods

Ethics statement

This study was a retrospective and observational research, and all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 [5]. The blood samples used in this study were archival for routine biochemical indexes of hospitalized patients before operation. All blood samples and patient records were anonymized before use in this study. All blood samples and patients were from Gynecology Department of the First Affiliated Hospital of Nanjing Medical University, and other researchers did not collect human samples for this study.

Design and participants

A retrospective controlled study was designed for this research. From January 2006 to July 2013 and a total of 1,550 age-matched females were recruited from the inpatient Gynecology Department

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Table 1. — *Serum lipid profile of total gynecologic cancers and total gynecologic benign diseases (mean ± standard error).*

	Total gynecologic benign disease	Total gynecologic cancer	*p* value
Age (years)	49.65 ± 11.30	49.74 ± 12.19	0.87
Triglycerides (mmol/L)	1.249 ± 0.02581	1.404 ± 0.03242	< 0.001
HDL cholesterol (mmol/L)	1.325 ± 0.01002	1.230 ± 0.01139	< 0.001
LDL cholesterol (mmol/L)	3.052 ± 0.02459	2.944 ± 0.02770	< 0.01
Total cholesterol (mmol/L)	4.775 ± 0.03051	4.634 ± 0.03521	< 0.01
Lipoprotein (a) (mmol/L)	7.278 ± 0.2677	7.987 ± 0.2929	0.07

LDL: low density lipoprotein; HDL: high density lipoprotein;.

Table 2. — *Serum lipid profile of ovarian cancer and benign ovarian tumor (mean ± standard error).*

	Benign ovarian tumor	Ovarian cancer	*p* value
Age (years)	50.56 ± 13.79	51.09 ± 14.59	0.69
Triglycerides (mmol/L)	1.226 ± 0.04288	1.334 ± 0.04460	0.08
HDL cholesterol (mmol/L)	1.345 ± 0.01792	1.127 ± 0.02016	< 0.001
LDL cholesterol (mmol/L)	3.101 ± 0.04428	2.874 ± 0.05167	< 0.001
Total Cholesterol (mmol/L)	4.820 ± 0.05449	4.440 ± 0.06272	< 0.001
Lipoprotein (a) (mmol/L)	7.807 ± 0.5042	9.035 ± 0.5644	0.1

LDL: low density lipoprotein; HDL: high density lipoprotein.

Table 3. — *Serum lipid profile of endometrial cancer and endometriosis (mean ± standard error).*

	Endometriosis	Endometrial cancer	*p* value
Age (years)	55.11 ± 9.88	56.47 ± 9.80	0.13
Triglycerides (mmol/L)	1.305 ± 0.04523	1.703 ± 0.07329	< 0.001
HDL cholesterol (mmol/L)	1.319 ± 0.01794	1.239 ± 0.02123	< 0.01
LDL cholesterol (mmol/L)	3.153 ± 0.04366	3.145 ± 0.04831	> 0.05
Total Cholesterol (mmol/L)	4.898 ± 0.05260	4.935 ± 0.06410	> 0.05
Lipoprotein (a) (mmol/L)	7.552 ± 0.4792	7.713 ± 0.4961	> 0.05

LDL: low density lipoprotein; HDL: high density lipoprotein.

Table 4. — *Serum lipid profile of cervical cancer and uterine leiomyomas (mean ± standard error).*

	Uterine leiomyomas	Cervical cancer	*p* value
Age (years)	44.64 ± 7.48	43.54 ± 8.10	0.08
Triglycerides (mmol/L)	1.222 ± 0.04455	1.228 ± 0.04554	> 0.05
HDL cholesterol (mmol/L)	1.315 ± 0.01634	1.302 ± 0.01693	> 0.05
LDL cholesterol (mmol/L)	2.934 ± 0.03927	2.843 ± 0.04296	> 0.05
Total cholesterol (mmol/L)	4.644 ± 0.05024	4.550 ± 0.05379	> 0.05
Lipoprotein (a) (mmol/L)	6.639 ± 0.4107	7.255 ± 0.4562	> 0.05

LDL: low density lipoprotein; HDL: high density lipoprotein.

of the First Affiliated Hospital of Nanjing Medical University. Inclusion criteria were as follows: all the 1,550 age-matched patients had pathological results. No patient had been treated with surgery, chemotherapy or radiation before sample collection, had ever received cholesterol lowering agents, had a history of coronary artery disease, ischemia stroke, diabetes mellitus, thyroid disease, hepatopathy, nephrotic syndrome, polycystic ovary syndrome or any other diseases that were associated with dyslipidemia.

Among the included patients, 760 patients were gynecologic cancers and 790 patients were benign diseases. The gynecologic cancer group consisted of 229 ovarian cancers, 231 endometrial cancers, and 300 cervical cancers. The benign diseases group consisted of 233 benign ovarian tumors, 246 endometriosis, and 311 uterine leiomyomas.

Total gynecologic cancer was compared with total gynecologic benign disease, and benign ovarian tumor was set as a comparison to ovarian cancer. The difference between endometrial cancer and endometriosis, as well as cervical cancer and uterine leiomyomas, was also compared. Age showed no significant difference between any coupled groups (Tables 1-4).

Procedure

Fasting blood sample was collected in the coagulation-promoting tubes and then centrifuged at 3,000 revolution per minute (about 1,500 grams) for five minutes. Serum was separated and immediately analyzed. Serum levels (mmol/L) of triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), and

lipoprotein (a) were measured by using an automatic biochemical analyzer. According to the "Chinese guidelines on prevention and treatment of dyslipidemia in adults", the optimal target for serum lipid profile was as follows: TG < 1.7 mmol/L, TC < 5.18 mmol/L, LDL-c < 3.37 mmol/L, and HDL-c ≥ 1.04 mmol/L [18].

Statistical analysis

The Graph Pad Prism 5 Demo and SPSS v15.0 software package was used for statistical analyses and graphing. Unpaired Student's *t*-test was performed to evaluate the mean difference (MD) ± standard error (SE) and 95% confidence interval (CI) of parameters' value between groups, χ^2 test was performed to evaluate odds ratio (OR), multiple logistic regression analysis was performed to evaluate the risk factors, and a two-sided $p < 0.05$ was considered statistically significant.

Results

Gynecologic cancer

The comparison included 760 patients with gynecologic cancers and 790 patients with benign diseases. Gynecologic cancer group was associated with a higher level of TG (MD: 0.1550 ± 0.04127, 95%CI: 0.07413 to 0.2359, $p = 0.0002$) and lower level of HDL-c (MD: - 0.09483 ± 0.01514, 95%CI: - 0.1245 to - 0.06515, $p < 0.0001$), LDL-c (MD: - 0.1075 ± 0.03697, - 0.1799 to - 0.03503, $p = 0.004$) and TC (MD: - 0.1410 ± 0.04647, 95%CI: - 0.2320 to - 0.04986, $p = 0.003$) compared to gynecologic benign disease group (Table 2). The gynecologic cancer group had a trend of higher lipoprotein (a) level than gynecologic benign disease group (MD: 0.7093 ± 0.3964, 95%CI: -0.06736 to 1.486, $p = 0.07$) (Table 1). Multiple logistic regression analysis showed that high level of TG ($p = 0.011$) and lipoprotein (a) ($p = 0.008$), as well as low level of HDL-c ($p < 0.001$) and LDL-c ($p = 0.01$) were the independent risk factors for gynecologic cancers.

The ratio of higher level TG (≥ 1.7 mmol/L; OR: 1.61, 95%CI: 1.25 to 2.06, $p < 0.0001$) and lower level HDL-c (< 1.04 mmol/L; OR: 2.61, 95%CI: 1.96 to 3.46, $p < 0.0001$) were significantly higher in cancer group, which was consistent with the results of multiple logistic regression analysis ($p < 0.01$).

Ovarian cancer

The comparison included 229 patients with ovarian cancer and 233 patients with benign ovarian tumors. Compared to benign ovarian tumor group, ovarian cancer group had significant lower levels of HDL-c (MD: - 0.2182 ± 0.02695, 95%CI: - 0.2710 to -0.1654, $p < 0.0001$), LDL-c (MD: - 0.2269 ± 0.06796, 95%CI:- 0.3601 to - 0.09373, $p = 0.0009$) and TC (MD: - 0.3804 ± 0.08299, 95%CI: - 0.5431 to - 0.2177, $p < 0.0001$), as well as the trend of higher TG (MD: 0.1073 ± 0.06186, 95%CI: - 0.01396 to 0.2285, $p = 0.08$) and lipoprotein (a) levels (MD: 1.228 ± 0.7562, 95%CI: -0.2542 to 2.710, $p = 0.10$) (Table 2). Multiple logistic regression analysis showed that only low level of HDL-c ($p < 0.001$) was an independent risk factor for ovarian cancer, and high level of lipoprotein (a) was a potential risk factor ($p = 0.072$).

The ratio of lower level HDL-c (<1.04 mmol/L) was significantly higher in ovarian cancer group (OR: 6.40, 95%CI: 3.77 to 10.89, $p < 0.0001$), which was confirmed by multiple logistic regression analysis ($p < 0.001$). The ratio of higher level TG (≥ 1.7 mmol/L) was also higher in ovarian cancer group (OR: 2.11, 95%CI: 1.26 to 3.54, $p = 0.005$), but multiple logistic regression analysis suggested that TG was not an independent risk factor for ovarian cancer ($p = 0.662$).

Endometrial cancer

The comparison included 231 patients with endometrial cancer and 246 patients with endometriosis. Endometrial cancer group showed higher level of TG (MD: 0.3979 ± 0.08499, 95%CI: 0.2313 to 0.5644, $p < 0.0001$) and lower level of HDL-c (MD: - 0.07922 ± 0.02768, 95%CI: - 0.1335 to - 0.02497, $p = 0.004$) compared to endometriosis group. There was no significant difference of LDL-c, TC and lipoprotein (a) between two groups ($p > 0.05$) (Table 3). Multiple logistic regression analysis showed that only high level of TG was an independent risk factor for endometrial cancers ($p = 0.001$), and low level of HDL-c was a potential risk factor ($p = 0.10$).

The ratio of higher level TG (≥ 1.7 mmol/L; OR: 2.30, 95%CI: 1.51 to 3.50, $p < 0.0001$) and lower level HDL-c (<1.04 mmol/L; OR: 2.17, 95%CI: 1.32 to 3.57, $p = 0.002$) were significantly higher in endometrial cancer group, which was consistent with the results of multiple logistic regression analysis ($p < 0.01$).

Cervical cancer

The comparison included 300 patients with cervical cancer and 311 patients with uterine tumors. Cervical cancer group did not show any significant difference in level of TG, HDL-c, LDL-c, TC, and lipoprotein (a) compared to uterine leiomyomas ($p > 0.05$) (Table 4).

The ratio of both higher level TG (≥ 1.7 mmol/L) and lower level HDL-c (< 1.04 mmol/L) showed no significant difference between cervical cancer group and uterine leiomyomas group ($p > 0.05$)

Discussion

Lipids are hydrophobic molecules that are biologically important for energy storage, cell signaling, and cell membrane structure [2]. Lipids play a key role in the maintenance of cell integrity. Lipids are divided into several families including TG, sterols, fatty acyls, and so on. By binding to lipoprotein, lipids can travel in the blood. The most well known lipoproteins are HDLs and LDLs, and they are all essential for transporting lipids through-

out the body. Lipoprotein (a) is part of a subclass of lipoproteins that consist mostly of LDL-like particles [19]. Many previous studies suggested that the development of cancer is usually associated with disordered lipid profile and other metabolic disturbance [1-11], a nd multiple associations have been found between cholesterol metabolism and cancer with conflicting direction for various cancer types, though the mechanisms are still unclear [1, 20-22].

TG is transported by chylomicrons from the intestine to all cells. In agreement with some other studies [11, 14-19, 23], the present study showed higher levels of TG in endometriosis cancer and ovarian cancer than in benign diseases. High level of TG is usually accompanied by fat accumulation and abdominal obesity. The accumulated fat tissues secrete excessive aromatase, which could transform androgen into estrogen, and then extra estrogen could act as a mitogenic growth factor and is involved in the development of hormone-related cancers, such as endometrial cancer and some ovarian cancers [24].

HDL-c is not only responsible for transporting cholesterol from peripheral tissues to the liver, but also maintaining normal cell cholesterol homeostasis by removing excess cholesterol from intracellular pool [6]. Similar with the results of several previous studies [25], the present study showed that gynecologic cancer especially ovarian cancer and endometrial cancer had a lower level of HDL-c than benign diseases groups. However, the mechanism is still unclear. The possible explanation is that low level of HDL-c cannot remove excess cholesterol from intracellular pool efficiently, which induces the accumulation of cholesterol intracellular pool, and the accumulated cholesterol is then utilized by cancer cell for membrane biogenesis, which promotes the development and proliferation of cancer [20, 26].

TC is one of the critical cell membrane components [1, 25]. LDL-c is responsible in transporting lipids around the body and supply lipids to peripheral tissues [27, 28]. The results of different researches about the relationship between TC and gynecologic cancers remain inconsistent [21, 29, 30]. The present results showed that gynecologic cancer, especially ovarian cancer, had a significant lower concentration of TC and LDL-c compared with control group. The present authors speculate that the low levels of TC and LDL-c are secondary to cancer [30]. The growth of carcinoma utilizes lipids, especially TC and LDL-c, for new cancer cell membrane biogenesis, which could lead to the decreased level of TC and LDL-c [1, 2].

Lipoprotein (a) is an independent lipoprotein. The present study showed a higher level of lipoprotein (a) in gynecologic cancer group, especially in ovarian cancer. Lipoprotein (a) is considered to be associated with tumor angiogenesis, which is important for tumor proliferation and metastasis [10, 31].

The present study showed that gynecologic cancer is totally associated with a disordered lipid profile characterized by higher level of TG and lipoprotein (a), as well as lower level of HDL-c, LDL-c, and TC. Ovarian cancers' correlation is the most conspicuous.

Ovarian cancer is usually associated with a high degree of malignancy and is difficult to be diagnosed in its early stages. Advanced or terminal ovarian cancers could consume cholesterol, mainly TC and LDL-c, leading to a decreased level of TC and LDL-c. Furthermore, lipoprotein (a) may promote the proliferation and metastasis of ovarian cancer through its angiogenesis.

Endometrial cancer is accompanied by higher TG and lower HDL-c. Endometrial cancer is a hormone dependent carcinoma. As known, obesity and excessive estrogen increase the risk of endometrial cancer. Disordered lipid profile characterized by higher level of TG and lower level of HDL-c is usually accompanied by fat accumulation and abdominal obesity, and the accumulated fat tissues secrete excessive aromatase, which transforms androgen into extra estrogen.

Cervical cancer appears to have a slight disorder of lipid profiles. One reason for this association may be that cervical cancer is not a hormone-dependent carcinoma, and TG and HDL-c may not make a difference. Another explanation may be attributed to cervical cytological screening: cervical cancer can be diagnosed in early stage, and most of cervical cancers receive treatment in early stage;therefore, TC, LDL-c and lipoprotein (a) do not change secondarily.

So far, obesity has been identified as a risk factor for cancer development [32]. There have been several cohort studies and case-control studies concluding that metabolic syndrome, which is associated with disordered lipid profile, increases the risk of gynecologic cancers including ovarian, endometrial, and cervical cancer [11, 14-22].

Several potential limitations of the present study deserve mentioning. First, no healthy females were set as the control groups. Second, the stage of each gynecologic cancer was not distinguished to analyze the relationship between stage of cancer and lipids profiles.

In conclusion, gynecologic cancers are associated with a disordered lipid profile characterized by higher TG and lipoprotein (a) levels, and lower HDL-c, LDL-c, and TC levels, when compared with benign diseases. The association is most conspicuous in ovarian cancers. Endometrial cancer is accompanied by alterations only in TG and HDL-c levels, while cervical cancer appears not to be associated with disordered lipid profile.

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