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The Valuable Role of Measuring Serum Lipid Profile in Cancer Progression

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ABSTRACT

Objective: Serum lipid levels are not only associated with etiology, but also with prognosis in cancer. To investigate this issue further, we aimed to evaluate the serum levels of lipids in association with the most important prognostic indicators in cancer patients at the start of chemotherapy. ***Methods:*** In a retrospective cross-sectional study, using existing medical records obtained from 2009–2014, the data of all incident cancer cases in Iranian patients referred to the Semnan oncology clinic for chemotherapy were analyzed. Data on demographics, cancer type, prognostic indicators (e.g. lymph node involvement, metastasis, and stage of disease), as well as the patient's lipid profile were collected. We used multiple logistic regression models to show the relationship between prognosis indicators and lipid profile adjusting for age, gender, and type of cancer. ***Results:*** The data of 205 patients was gathered. We found a significant difference in the lipid profile between different types of cancers (breast, colon, gastric, and ovarian). With the exception of high-density lipoprotein levels in women, which were higher than in men, the means of other lipid profiles were similar between the genders. There was a significant association between higher levels of low-density lipoprotein (LDL >110mg/dL) in the serum and metastasis (adjusted odds ratio=2.4, 95% CI 1.2–3.5). No significant association was reported between lipid profile and lymph nodes involvement and stage of the disease. ***Conclusion:*** Our study suggested a benefit of measuring serum levels of lipids for predicting cancer progression. Increased LDL levels can be considered a predictive factor for increasing the risk of metastasis.

The main goal of early diagnosis and treatment of lipid disorders is globally improving the quality of life, minimizing serious complications of cardiovascular disorders, and increasing survival. It is now well demonstrated that hyperlipidemia is a major problem and a potential risk factor for various metabolic, cardiovascular and even genetic-based disorders.[1,2] Recently, the importance of treating hyperlipidemia was clearly identified as a fundament for treating coronary atherosclerotic disorder. Anti-hyperlipidemic medications also have a major role in therapeutic regiments for malignant disorders.[3-5]

It is well-known that malignancy is the second cause of death worldwide with a high disability rate in affected patients.[6] In this regard, identifying both genetic and environmental risk factors for different types of malignancies is on the agenda of governments and scientists. Some genetic polymorphisms and also factors associated with lifestyle including smoking, alcohol consumption, obesity, physical inactivity, low fruit and vegetable consumption, unsafe sex, air pollution, indoor smoke from domestic fuels, and contaminated injections have all been identified as risk factors for cancers.[6-8]

Some studies have documented the changes in lipid levels in the etiology and prognosis of cancer.[9,10] For instance, high cholesterol and low-density lipoprotein (LDL) levels are one of the most important and influential factors in the etiology of cardiovascular disease and has recently been considered as possible risk factor in the etiology of different types of cancers. However, in some types of malignancies, such as oral cancers, reduction of cholesterol is alarming for the progression of cancerous lesions.[11]

Given the contradictory results regarding the association between lipid levels and cancer progression, it seems that the pointed association may be potentially influenced by the type of tumor and also by role of lipids in the pathophysiological mechanisms related to cancer progression.

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In our study, we aimed to evaluate serum levels of lipids and lipoproteins in patients diagnosed with cancer and who were referred to an oncology clinic to clarify the association between hyperlipidemia and the most important progression indicators in different cancer types.

METHODS

This cross-sectional study was performed on 500 consecutive patients with various types of cancers with positive pathological examinations who were referred to the oncology clinic in Semnan Hospital over a five-year period (from 2009 to 2014).

Following an initial assessment, 350 patients with breast, ovary, gastric, or colon cancer were included in the study. One hundred and fifty patients with blood, prostate, lung, esophageal, renal, bladder, and head and neck cancer were excluded due to the small number of people with each cancer. Patients who had no record of serum lipid level at the first visit were also excluded. Of the 350 included patients, 145 patients were excluded because of incomplete files. Finally, 205 patients were assessed. All baseline characteristics including demographics (age and gender), type of cancer, prognostic indicators (e.g. lymph node involvement, metastasis, and stage of disease) as well as the patient's lipid profile (i.e. serum triglyceride, cholesterol, LDL, and high-density lipoprotein (HDL)) were collected and recorded at the start of chemotherapy. Results were presented as mean and standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using the Student's *t*-test or ANOVA test and/or non-parametric Mann-Whitney or Kruskal-Wallis H test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were compared using the chi-square test. Multiple logistic regression models were used to determine the relationships between the variables adjusting for sex, age, and type of cancer.

SPSS Statistics (SPSS Inc., Chicago, US) version 16.0 was used for the statistical analysis. A *p*-value of 0.050 or less was considered statistically significant.

RESULTS

Of our 205 study patients, 107 (52.2%) had breast cancer, 49 (23.9%) had colon cancer, 31 (15.1%) had gastric cancer, and 18 (8.8%) had ovarian cancer. In total, 78.5% were female, and 21.5% were male. Among all patients, 37.1% had stage II cancer or lower, and 62.9% had stages III or IV, 77.1% were diagnosed with lymph node involvement. Evidence of metastasis was seen in 38.5% of patients.

No significant differences were observed in the levels of triglyceride, LDL, and HDL between the age groups. However, the lowest and the highest serum cholesterol levels were found in fifth and sixth decades of life, respectively, with a significant difference between the subgroups [Table 1]. With the exception of HDL levels, which were higher in women than in men, the mean of other lipid profiles were similar in both genders [Table 1]. We found a significant difference in the serum levels of lipids between the different types of cancers with the

Table 1: Serum levels of lipids by sex and age (n=205).

Characteristics (n)	Serum triglyceride	Serum cholesterol	Serum LDL	Serum HDL
Age (years)				
<40 (27)	131.4±62.4	179.1±39.1	30.5±5.9	48.0±11.5
40–49 (38)	149.7±72.1	158.8±34.8	29.0±4.7	47.1±10.2
50–59 (72)	168.3±88.9	201.8±46.2	41.0±4.8	48.1±14.2
60–69 (36)	161.6±75.3	186.1±40.2	32.5±5.4	49.5±16.3
≥70 (32)	143.4±60.8	174.6±51.5	32.5±5.4	43.3±9.0
p-value	0.200	0.023	0.477	0.352
Gender				
Male (161)	139.2±55.0	183.0±41.5	106.5±38.0	43.9±9.1
Female (44)	159.2±81.3	190.7±44.7	111.7±35.1	48.3±13.7
p-value	0.126	0.126	0.392	0.046

Data presented as mean±SD.
LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Table 2: Serum levels of lipids by cancer type (n=205).

Cancer type (n)	Serum triglyceride	Serum cholesterol	Serum LDL	Serum HDL
Breast (107)	156.8±78.5	196.3±43.4	118.3±43.4	49.5±14.2
Colorectal (49)	137.0±57.6	184.5±45.9	94.5±40.3	45.6±12.6
Gastric (31)	148.5±71.9	170.1±35.0	80.1±30.2	42.7±9.0
Ovarian (18)	203.9±101.2	188.8±49.2	108.0±32.1	47.8±9.2
p-value	0.015	0.027	0.003	0.049

Data presented as mean±SD.
LDL: low-density lipoprotein; HDL: high-density lipoprotein.

highest and the lowest serum triglyceride levels in ovarian and colorectal cancers (203.9±101.2mg/dL vs. 137.0±57.6mg/dL), the highest and the lowest serum cholesterol levels in breast and gastric cancers (196.3±43.4mg/dL vs. 170.1±35.0mg/dL), the highest and the lowest serum LDL levels in breast and gastric cancers (118.3±43.4mg/dL vs. 80.1±30.2mg/dL), and the highest and the lowest serum HLD levels in breast and gastric cancers (49.5±11.2mg/dL vs. 42.7±9.0mg/dL).

As shown in Table 2, there was a significant difference observed between patients with ovarian and colorectal cancers and serum triglyceride levels (66.9±20.8mg/dL, p=0.008); between patients with breast and gastric cancers and serum cholesterol levels (26.2±8.9mg/dL, p=0.018); between patients with breast and gastric cancers and serum LDL levels (24.2±7.1mg/dL, p=0.004), and between patients with breast and gastric cancers and serum HDL levels (6.8±2.6mg/dL, p=0.048).

The assessment of the serum level of lipid profiles according to presence or absence of lymph nodes involvement [Table 3] showed no significant differences in the serum levels of triglyceride, cholesterol, LDL, and HDL between cancerous patients with and without lymph nodes involvement. We found no differences in the serum levels of triglyceride, cholesterol, LDL, and HDL between cancerous patients with and without metastasis [Table 3]. There were also no differences in the serum levels of triglyceride, cholesterol, LDL, and HDL between the different cancer stages. Multiple logistic regression models [Table 4] with the presence of baseline variables including age, gender, serum level of lipids and types of cancers showed that none of these parameters could predict involvement of lymph nodes. Only serum LDL greater than 110mg/dL could predict cancer metastasis to lymph nodes (odds ratio 2.39, 95% CI, 1.22–3.47; p=0.007). Serum lipid levels of none of the lipid particles could predict the stage of the disease; however, the presence of gastric cancer or colon cancer was accompanied by higher stages of the disease.

DISCUSSION

Lipid profile is not only associated with etiology but also with prognosis in cancer. In the present study,

Table 3: Serum levels of lipids by lymph node involvement, metastasis, and cancer stage (n=205).

Prognosis indicator (n)	Serum triglyceride	Serum cholesterol	Serum LDL	Serum HDL
Lymph node involvement				
Yes (158)	155.3±78.5	189.0±44.7	109.8±34.4	47.7± 13.9
No (47)	153.7±71.4	188.3±42.5	113.1±40.0	46.4±8.8
p-value	0.905	0.923	0.577	0.536
Metastasis				
Yes (79)	152.3±75.7	191.8±45.3	113.0±36.5	46.6±13.4
No (126)	126.5±77.7	187.0±43.3	109.0± 35.2	47.8±12.7
p-value	0.701	0.447	0.424	0.517
Disease stage				
II or lower (76)	161.4±76.6	187.3±41.3	106.6± 33.2	47.2±8.8
III and IV (129)	151.1±76.9	189.7±45.8	112.9± 37.0	47.5 ±14.9
p-value	0.351	0.709	0.218	0.886

Data presented as mean±SD.
LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Table 4: The odds ratios* for prognosis indicators associated with lipid profile adjusted for age, gender and type of cancer.**

Prognosis indicator	*p*-value	Odds ratio	95% Confidence Interval	
Lymph node involvement				
Age >53 years	0.379	0.7	0.4	1.5
Male	0.315	0.6	0.2	1.8
TG >150	0.625	0.8	0.4	1.7
LDL >110	0.510	1.3	0.6	2.5
HDL <47	0.071	1.9	0.9	3.9
Ovarian cancer	0.749	0.8	0.2	2.8
Gastric cancer	0.828	1.2	0.3	5.3
Colon cancer	0.167	3.4	0.6	19.5
Metastasis				
Age >53 years	0.499	1.2	0.5	1.4
Male	0.501	0.7	0.6	1.2
TG >150	0.511	0.8	0.4	1.2
LDL >110	0.007	2.4	1.2	3.5
HDL <47	0.559	1.2	0.8	1.5
Ovarian cancer	0.907	0.9	0.9	1.0
Gastric cancer	0.317	2.0	0.4	2.0
Colon cancer	0.013	6.1	1.1	8.6
Disease stages III and IV				
Age >53 years	0.493	0.8	0.4	1.5
Male	0.273	0.6	0.2	1.6
TG >150	0.222	0.7	0.4	1.3
LDL >110	0.064	1.8	1.0	3.3
HDL <47	0.090	1.1	0.6	2.1
Ovarian cancer	0.205	2.0	0.7	5.6
Gastric cancer	0.015	5.1	1.4	19.3
Colon cancer	0.005	8.4	1.9	36.7

TG: triglyceride; LDL: low-density lipoprotein; HDL: high-density lipoprotein.
**Multiple logistic regression models.*
*** Reference group: breast cancer.*

we evaluated the serum levels of lipids associated with the most important prognostic indicators in patients who suffered from breast, ovarian, or gastrointestinal cancer at the start of chemotherapy. Because of unavailability of correct and reliable data on other types of cancer, we had to ignore other types of malignancies.

In the first step of our assessment, we found different levels of serum lipids among various types of cancer. The highest and the lowest serum triglyceride levels were revealed in ovarian and colorectal cancers, respectively. Additionally, breast cancer was related to the highest levels of cholesterol and lipoproteins, while the lowest ranges of these profiles were shown in gastric cancer. In fact, the increased lipid levels could have a major role in the pathophysiological appearance and progression of cancers associated with women, including breast and ovarian cancers, while lower level of lipids and lipoproteins may be valuable markers for discriminating gastric cancer. The association of lipids and lipoproteins with ovarian and breast cancer is exclusively assessed in some previous studies.[12,13] In some studies, it has been shown that a higher intake of dietary lipids, systemic lipid metabolism malfunction, and abnormal serum lipid levels are related to ovarian cancer. Over-expression of some lipid metabolic enzymes was found in ovarian cancer. Several case–control and cohort studies have found positive associations between ovarian cancer and an intake of foods with high levels of saturated fats or cholesterol, such as red meat, eggs, and dairy.[14-16] Pan et al,[17] reported that ovarian cancer risk is positively associated with higher consumption of dietary cholesterol and eggs, and inversely associated with a higher intake of vegetables and cruciferous vegetables and with supplementation of vitamin E, beta-carotene, and vitamin B complex. High consumption of fats may increase circulating estrogen levels, thus increasing the possibility of cell damage and proliferation, which is responsible for cancerous growth.[18] Risch et al,[12] suggested that dietary cholesterol may influence the risk of ovarian cancer through elevated circulating estrogen or progesterone. Also, in agreement with Llanos et al,[13] we found an association between high HDL levels and increased risk of breast cancer. However, contrary to that study that documented an inverse association between serum cholesterol level and risk for breast cancer, our study found a direct association between cholesterol level and risk for breast cancer. In another study, low HDL, as part of the metabolic syndrome, was associated with increased postmenopausal breast cancer risk.[19] It seems that the association between serum HDL level and risk for breast cancer can potentially be influenced by menopausal status so it has been shown that premenopausal cases have mean HDL levels lower than matched controls, whereas postmenopausal cases had levels higher than the controls.[20] We also showed higher serum triglyceride in patients with ovarian cancer, while the association between triglyceride level and colon cancer was the inverse. Although a high level of serum triglycerides does not appear to be mechanically involved in the development of most cancers, a reduction of serum triglyceride and intensive surveillance with total colonoscopy in colon cancer may have benefits for men with hypertriglyceridemia.[21] McKeown–Eyssen[22] has also reported an association between high serum triglyceride and colon cancer.

We showed that not only was a change in serum lipids and lipoproteins associated with the presence of some types of cancers, but that there was a direct association between high LDL level and increased risk for lymph nodes metastasis. Angiogenesis is a key factor for growing cancer and metastasis, so that with an increase in the size of the tumor, the nutritional requirements of the tumor also increase. The growth of tumor and metastasis can be stopped by inhibiting angiogenesis and metastasis. LDL can successfully inhibit the enzymes necessary for angiogenesis.[23]

Our article is based on a cross-sectional study in which temporality is not measurable, and this is one of the most significant limitations. Therefore, the direction of a relationship path between cancer progression and changes in blood levels of lipids cannot be stated decisively just by the results of this kind of study. For instance, some studies showed a decrease in plasma lipid levels in patients with cancer. This may be consequent upon an increased utilization of blood lipids by malignant cells as a competing factor.[24] In a cross-sectional study, we can hardly consider competing risks as another inherent limitation of the study. Therefore, conclusions should be made concerning these limitations.

CONCLUSION

We showed a benefit of measuring serum levels of lipids and lipoproteins for predicting different cancer types and their progression. High triglyceride levels were found in patients with ovarian cancer and high levels of cholesterol or HDL in breast cancer patients. Low levels of cholesterol and lipoproteins were reported in gastric cancer patients. Increased LDL levels were significantly associated with metastasis.

Disclosure

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