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Short communication

Changes in serum lipids and lipoproteins in cancer patients during chemotherapy

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Summary. We studied serum lipid and lipoprotein changes occurring during chemotherapy in 57 patients with chemosensitive cancers, including 18 malignant lymphomas, 18 breast carcinomas, 14 small-cell lung carcinomas, and 7 urothelial-cell carcinomas. Patients who responded favorably to chemotherapy demonstrated a significant increase in serum total cholesterol and LDL cholesterol values, with the singular exception of breast-cancer patients, who exhibited a nonsignificant decrease in both of these parameters. Serum levels of free cholesterol and HDL cholesterol did not show any significant changes. Finally, serum triglycerides tended to increase after effective chemotherapy, but this was of statistical significance only in breast-cancer patients. Although our findings were based on a rather small number of patients, they indicate that the lipid and lipoprotein disorders reported in cancer patients are reversible by effective treatment of the tumor, suggesting that these disorders are a secondary phenomenon of malignancy.

Introduction

Hypocholesterolemia has been associated with cancer in various reports [4, 10, 13], although the existence of a causative relationship has not yet been proven [1, 4, 9]. In a previous study, we have shown that untreated cancer patients as a group demonstrate a significantly lower level of serum cholesterol and low-density-lipoprotein cholesterol, the notable exception being breast-cancer patients [1]. In the present work, we studied the possible changes in serum lipids and lipoproteins occurring in cancer patients during chemotherapy and tried to correlate them to the type of response to treatment.

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Patients and methods

Patients. A total of 70 patients with various chemosensitive malignancies who had been consecutively treated in the Department of Medical Oncology, Evangelismos Hospital, between June 1987 and November 1989 were studied. Before their inclusion in the study, the following workup was performed in all patients: (1) estimation of body weight; (2) fasting and postprandial blood-glucose levels; (3) serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum γ-glutamyl transpeptidase (GT), alkaline phosphatase, prothrombin time, bilirubin, and serum protein levels; (4) 24-h urinary protein excretion; and (5) serum thyroid-stimulating hormone (TSH), T3 and T4 levels. On the basis of the above workup, we prospectively excluded from the study a total of 13 patients, 2 due to diabetes mellitus, 3 due to liver dysfunction, and 8 due to suspicion of liver metastases. None of the patients in our series showed evidence of nephrotic syndrome, hyperthyroidism, hypothyroidism, or cachexia carcinomatosa.

Parameters studied. The following parameters were determined in all eligible patients: (1) total serum cholesterol; (2) free and esterified cholesterol; (3) high-density-lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol; and (4) serum triglycerides. All of the above parameters were estimated prior to the administration of treatment as well as at 1 month after the completion of six monthly courses of chemotherapy. In 21 patients (37%), the same parameters were estimated during the follow-up at 12 months after the beginning of therapy.

Methods. Venous blood was drawn after a 12- to 14-h fasting period. Blood samples were immediately centrifuged at 4000 rpm for 10 min, and serum was collected and stored at 4° C. Serum triglycerides, total cholesterol, free cholesterol, and HDL cholesterol were determined within 2 h of blood collection by standard laboratory techniques [3, 8, 14] using Boehringer Mannheim kits. HDL cholesterol was calculated using Friedewald's formula, whereas esterified cholesterol was estimated as the difference between total and free cholesterol.

Response criteria. Responses to chemotherapy were defined as follows. A complete response (CR) represented the total disappearance of all tumors observed initially, normalization of all abnormal tumor markers, and no evidence of new areas of malignant disease for at least 2 months. A partial response (PR) represented a reduction by >50% in the sum of the products of the largest perpendicular diameters of all measurable indicator lesions and the absence of new lesions for a period of at least 2 months. Any responses amounting to less than a PR and any transient regressions lasting for <2 months were considered to represent failures.

Table 1. Patients' clinical characteristics

	Total	Men	Women	Response (CR+PR)
Number of patients	57	28	29	58%+32%
Median age (years)	50 (range 20–74)			
Malignant lymphoma	18	10	8	89%+ 5%
Small-cell lung carcinoma	14	13	1	64%+ 14%
Breast carcinoma	18		18	39%+50%
Urothelial-cell carcinoma	7	5	2	40%–60%

Results

Clinical characteristics of the 57 patients who were eventually included in the study are shown in Table 1. There were 18 patients with malignant lymphomas (ML), 18 with breast carcinoma (BC), 14 with small-cell lung carcinoma (SCLC), and 7 with urothelial-cell carcinoma (UCC). The median age of the whole group comprising 28 men and 29 women was 50 years (range, 20–74 years). In all, 17 patients (94%) with ML, 16 (89%) with BC, 11 (78%) with SCLC, and 7 (100%) with UCC who responded to the appropriate chemotherapy with either a CR (58%) or a PR (32%) were included in the following analysis.

The serum levels of cholesterol and its various fractions together with serum triglycerides measured before and after the completion of chemotherapy in all responders except the breast-cancer patients are summarized in Table 2. The mean level of total cholesterol measured after the completion of chemotherapy in the 35 responders was 215±50 mg/dl and was significantly higher (P <0.02) than the corresponding mean value (190±45 mg/dl) found before treatment. Likewise, the mean level of LDL cholesterol (146±46 mg/dl) was higher after chemotherapy than before treatment (126±39 mg/dl) and this difference was also significant (P <0.01). Mean values for total cholesterol (216±45 mg/dl) and LDL cholesterol (143±48 mg/dl) remained significantly higher (P <0.02) at 12 months during remission in the 14 patients in whom the estimations were repeated. The mean levels of serum-

Table 2. Serum cholesterol and its fractions as well as serum triglycerides measured before and after chemotherapy in the 35 patients with small-cell lung cancer, urothelial cancer, and malignant lymphomas who responded to chemotherapy

Period	Patiens (n)	TGs (mg/dl)	Serum cholesterol (mg/dl)			
			Total	Free	HDLc	LDLc
Before CT	35	140±65	190±46	55±15	37±14	126±39
After CT	35	156±66	215±50	56±16	37±12	146±46
Follow-up	14	156±79	216±45	61±12	42±13	143±48
P value		NS	<0.02	NS	NS	<0.01

CT, Chemotherapy; TGs, triglycerides; HDLc, high-density-lipoprotein cholesterol; LDLc, low-density-lipoprotein cholesterol; NS, not significant

Table 3. Serum cholesterol and its fractions as well as serum triglycerides measured before and after chemotherapy in the 16 patients with breast cancer who responded to chemotherapy

Period	Patients (n)	TGs (mg/dl)	Serum cholesterol (mg/dl)			
			Total	Free	HDLc	LDLc
Before CT	16	130±54	239±31	63±11	53±19	160±36
After CT	16	167±70	234±48	62±12	43±19	157±39
Follow-up	4	188	234	64	35	161
P value		0.05	NS	NS	NS	<0.05

For definitions, see Table 2

Table 4. Serum cholesterol and its fractions as well as serum triglycerides measured before and after chemotherapy in the 17 patients with malignant lymphomas who responded to treatment

Period	Patients (n)	TGs (mg/dl)	Serum cholesterol (mg/dl)			
			Total	Free	HDLc	LDLc
Before CT	17	146±70	159±38	50±14	30±11	102±35
After CT	17	152±50	200±53	51±15	34±11	135±46
Follow-up	8	138±45	211±40	59±13	46±11	137±35
P value		NS	<0.005	NS	NS	<0.05

For definitions, see Table 2

Table 5. Serum cholesterol and its fractions as well as serum triglycerides measured before and after chemotherapy in the 11 patients with small-cell carcinoma who responded to treatment

Period	Patients (*n*)	TGs (mg/dl)	Serum cholesterol (mg/dl)			
			Total	Free	HDLc	LDLc
Before CT	11	140±66	213±43	63±18	43±14	143±38
After CT	11	159±88	224±47	57±20	39±12	153±47
P value		NS	NS	NS	NS	NS

For definitions, see Table 2

Table 6. Serum cholesterol and its fractions as well as serum triglycerides measured before and after chemotherapy in the 7 patients with transitional-cell carcinoma who responded to treatment

Period	Patients (*n*)	TGs (mg/dl)	Serum cholesterol (mg/dl)			
			Total	Free	HDLc	LDLc
Before CT	7	133±61	225±25	59±12	44±13	154±17
After CT	7	161±74	235±46	70±12	38±11	165±46
P value		NS	NS	NS	<0.05	NS

For definitions, see Table 2

free cholesterol (56±16 mg/dl) and HDL cholesterol (37±12 mg/dl) measured after chemotherapy did not differ from the corresponding pretreatment values (55±15 and 37±14 mg/dl, respectively). Finally, the mean level of serum triglycerides (156±66 mg/dl) was higher after the completion of chemotherapy as compared with the value obtained before treatment (140±65 mg/dl), but this difference did not reach statistical significance.

The corresponding results for breast cancer are summarized separately in Table 3. The mean values for total cholesterol (234±48 mg/dl), HDL cholesterol (43±19 mg/dl), LDL cholesterol (157±39 mg/dl), and free cholesterol (62±12 mg/dl) were lower after the completion of chemotherapy than the corresponding values obtained before treatment (239±31, 53±19, 160±36, and 63±11 mg/dl, respectively), but these differences were not statistically significant, with the exception of LDL cholesterol (P <0.05). In contrast, the mean level of triglycerides (167±70 mg/dl) was significantly higher (P = 0.05) after the completion of chemotherapy as compared with the corresponding pretreatment value (130±54 mg/dl).

A separate analysis of the results obtained for ML, SCLC, and UCC demonstrated the following:

1. In the 17 patients with ML who responded to treatment (Table 4), the mean total cholesterol (200±53 mg/dl) and LDL cholesterol (135±46 mg/dl) values after successful chemotherapy were significantly higher (P <0.005 and P <0.05, respectively) than the corresponding pretreatment values (159±38 and 102±35 mg/dl, respectively). Mean values for total cholesterol (211±40 mg/dl) and LDL cholesterol (137±35 mg/dl) remained significantly higher at 12 months during remission in the 8 patients in whom the estimations were repeated. Serum-free cholesterol, HDL cholesterol, and triglyceride values observed after chemotherapy (51±15, 34±11, and 152±50 mg/dl, respectively) did not significantly differ from those obtained prior to treatment (50±14, 30±11, and 146±70 mg/dl, respectively).
2. In the 11 patients with SCLC who demonstrated a response to treatment (Table 5), the mean levels of total cholesterol (224±47 mg/dl) and LDL cholesterol (153±46 mg/dl) measured after successful chemotherapy were higher than the corresponding pretreatment values (213±43 and 143±38 mg/dl, respectively), although the differences were not significant. The mean value for serum triglycerides was considerably higher after chemotherapy (159±88 mg/dl) as compared with the mean pretreatment value (140±66 mg/dl), but here, too, the difference did not reach statistical significance. Serum-free cholesterol and HDL cholesterol demonstrated no consistent change after chemotherapy.
3. Finally, in the 7 patients with UCC who responded favorably to chemotherapy (Table 6), the mean levels of total cholesterol (235±46 mg/dl), LDL cholesterol (165±46 mg/dl), free cholesterol (70±12 mg/dl), and serum triglycerides (161±74 mg/dl) measured after treatment were higher, but not significantly so, than the corresponding values obtained before treatment (225±25, 154±17, 59±12, and 133±61 mg/dl, respectively). In contrast, the mean HDL cholesterol value was lower after chemotherapy (38±11 mg/dl) as compared with the corresponding pretreatment value (44±13 mg/dl), and the difference proved to be statistically significant (P <0.05).

Discussion

An analysis of our results showed that cancer patients who responded favorably to chemotherapy demonstrated a statistically significant increase in serum total cholesterol and

LDL cholesterol values, with the singular exception of breast-cancer patients, who exhibited a small, insignificant decrease in both of these parameters. The latter finding is in accordance with our previous observation that the pattern of serum lipid and lipoprotein disorders in breast-cancer patients is different from that in most other cancers [1]. Serum levels of free cholesterol and HDL cholesterol did not show any significant changes during chemotherapy. Finally, serum triglycerides tended to increase after effective chemotherapy, but this increase was of borderline significance ($P = 0.05$) only in breast-cancer patients.

A separate analysis of the findings according to the type of tumor and the type of response was also quite interesting:

1. The 17 patients with malignant lymphoma who achieved a CR demonstrated a statistically significant increase in total serum cholesterol and LDL cholesterol levels immediately after the completion of six courses of chemotherapy. These values remained high during remission at 12 and 18 months. As we have previously reported, total serum cholesterol and LDL cholesterol levels are significantly lower in patients with hematologic malignancies (175 ± 45 and 105 ± 37 mg/dl, respectively) as compared with the corresponding values (204 ± 49 and 130 ± 42 mg/dl, respectively) of normal controls of comparable age [1]. Serum HDL cholesterol and serum-free cholesterol did not change significantly after chemotherapy, and the same applies to serum triglycerides.
2. Likewise, serum cholesterol and LDL cholesterol values increased after six courses of chemotherapy in the 11 patients with small-cell lung cancer who achieved a CR, although this increase was not statistically significant, most probably because of the small number of patients studied. Nevertheless, another explanation of the nonsignificance of this increase may be inferred from our previous finding that lung-cancer patients show lower levels of total serum cholesterol and LDL cholesterol (205 ± 55 and 128 ± 44 mg/dl) as compared with normal controls (222 ± 47 and 142 ± 41 mg/dl), but this difference is not statistically significant [1]. A more pronounced increase was observed in the serum level of triglycerides, but this also failed to reach statistical significance. Serum HDL cholesterol and free cholesterol values demonstrated no consistent change after chemotherapy.
3. Serum total cholesterol, free cholesterol, and LDL cholesterol levels also increased in the 7 patients with transitional-cell carcinoma of the bladder who responded favorably to chemotherapy. Here, too, the number of patients was too small for valid statistical analysis. A more pronounced increase was observed in serum triglycerides. On the other hand, patients with bladder carcinoma were the only group of subjects showing significant changes in serum HDL cholesterol, which involved a decrease after the completion of chemotherapy.
4. Nevertheless, the most intriguing findings were made in the breast-cancer patients, who demonstrated an inverse pattern of changes after the completion of chemotherapy as compared with the other groups of patients. More specifically, total serum cholesterol, HDL cholesterol, LDL cholesterol, and free cholesterol levels decreased instead of increasing after the completion of chemotherapy in the 16 responders although only LDL cholesterol changes reached the level of statistical significance. An explanation for this discrepancy in the behavior of breast cancer is not easy to find, but it is interesting that untreated breast cancer is associated with hypercholesterolemia, in contrast to most other tumors, which demonstrate either hypocholesterolemia or normal values of serum cholesterol [1]. It is therefore possible that by minimizing the disease's activity, effective treatment reverses the thus far unknown causes of pretreatment hypercholesterolemia in breast cancer. The opposite effect is observed in the other tumors studied; effective chemotherapy apparently reverses the cause(s) of the observed pretreatment hypocholesterolemia.

The mechanism underlying the hypocholesterolemia that occurs in cancer patients remains speculative. It has been suggested that low serum cholesterol is a preexisting and even predisposing factor in cancer [2, 5, 10], whereas other investigators believe that it is a secondary phenomenon [1, 11–13]. Evidence has been provided in some reports that cancer hypocholesterolemia may be due to an increase in the activity of cellular LDL receptors [11–13]. The observed significant and prompt reversal of hypocholesterolemia in our lymphoma patients who achieved a CR after chemotherapy would be quite compatible with the hypothesis that lymphoma cells possess elevated LDL receptor activity, analogous to that described by Vitols et al. [13] in leukemic cells. Of course, a completely different mechanism must be responsible for the hypercholesterolemia associated with breast cancer. From this point of view, it is interesting that tamoxifen, a well-known antiestrogen and quite effective agent in the treatment of breast cancer, has recently been shown to reduce serum cholesterol levels [6, 7].

In conclusion, although our findings were based on a rather small number of patients, they indicate that serum lipid and lipoprotein disorders in cancer patients are reversible by effective treatment of the tumor. Further work on this subject is under way in our department.

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