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Prognostic impact of lipid profile in adult Egyptian acute leukemia patients

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Abstract

Introduction: Acute leukemia is a malignant disorder which results from clonal proliferation of lymphoid and myeloid blast cells. Several studies have reported changes in lipid metabolism at the time of diagnosis of leukemia. Although investigators have reported decreased total cholesterol, decreased high-density lipoprotein, and elevated triglyceride (TG) in leukemic patients, there is a lack of agreement about these changes among different types of leukemia and between children and adult patients, in addition to different data about their impacts on prognosis. In this study, lipid profile has been examined at the time of diagnosis of acute leukemia in order to correlate it with response to therapy.

Material and methods: This is a prospective study carried out at the Oncology Center at Mansoura University, Egypt between 2018 and 2019. Fifty patients newly diagnosed with *de novo* acute leukemia were included. Thirty-four patients were diagnosed with acute myeloid leukemia (AML) (68%), while 16 patients were diagnosed with acute lymphoblastic leukemia (ALL) (32%). Lipid profile and body mass index (BMI) data was obtained.

Results: Overweight/obese patients showed a more statistically significant association with female patients than with male patients (p = 0.009). By comparing the lipid profile between overweight/obese patients and other patients, there was no statistically significant association. 76.7% of AML patients were overweight or obese (p = 0.015), and 81.3% of ALL patients showed hypertriglyceridemia (p = 0.014). There was no statistically significant association between lipid profile and complete response (CR) rate; however, there was a marginally significant association between non-CR rate and overweight and obese patients (p = 0.051). In addition, there was no impact of BMI or lipid profile on overall survival among acute leukemia patients.

Conclusions: Female, and acute myeloid leukemia, patients were more commonly associated with overweight and obesity, and high TG level was found to be associated with acute lymphoid leukemia. Changes in lipid profile showed no impact on complete response rate or on overall survival in acute leukemia patients.

Key words: acute leukemia, AML, ALL, TG, CR

Introduction

An association between hypocholesterolemia and various malignant tumors such as colon, pancreatic, ovarian, and lung cancer has been determined [1]. In addition, alterations in lipid profile in hematological malignancies including leukemia have been demonstrated in the course of disease and treatment. Acute leukemia is a neoplastic transformation where there is proliferation of hematopoietic progenitor cells in the bone marrow, blood and extramedullary sites. Several studies have reported changes in the lipid's metabolism at the time of a diagnosis of leukemia. Although investigators have reported decreased total cholesterol (TC), decreased high-density lipoprotein (HDL), and elevated triglyceride (TG) in leukemic patients, there is uncertainty about these changes regarding different types of leukemia and differences between children and adults [2]. Some studies have demonstrated that lipid profile in patients with leukemia can be considered as a possible prognostic factor, and might be used as a simple test to follow the response to chemotherapy [3–5]. This study was carried out to evaluate the lipid

profile among Egyptian patients who had been diagnosed with acute myeloid and lymphoid leukemia, at the time of their diagnosis and the impacts on their prognosis.

Material and methods

This is a prospective study conducted on patients with acute leukemia admitted to the Oncology Center at Mansoura University, Egypt in 2018 and 2019.

A total of 50 adult patients)25 males and 25 females), diagnosed with *de novo* acute leukemia on the basis of peripheral blood morphology, bone marrow (BM), and flow cytometry,were included. Immunophenotyping (Coulter Epics XL Flow Cytometer PN 42372238 B, Coulter Corporation, Miami, FL, USA) was used to confirm the diagnosis; Cyt. MPO, CD 13, CD 33, and CD 117 were the primary panel for myeloid lineage, CD14, CD36, and CD11b for M4 and M5, CD61 and glycophorin A for M6, and CD41 and CD42 for M7. CD20, CD10, CD79a, CD3, CD5, CD7, and TDT were the panel for lymphoid lineage.

Blood specimens for lipid profile assessment were collected after a conclusive diagnosis, and segregated serum was kept in a freezer for lipid testing. Blood specimens were collected without anticoagulant and serum was separated from red blood cells (RBCs) by centrifugation. Triglyceride and total cholesterol were determined using laboratory kits. Direct analysis of high-density lipoprotein cholesterol (HDL-C) was done using kits (ELITECH, France). LDL-cholesterol direct SL kits also from ELITECH were used for direct analysis of low-density lipoprotein cholesterol. All measurements were done by an open system HITACHI 902 autoanalyzer automatically.

All patients received intensive induction therapy (there was no control group): cytarabine 100 mg/m^2/day for 5–7 days i.v. continuous infusion and doxorubicin 30 mg/m^2 for 2–3 days i.v. for acute myeloid leukemia (AML), Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) or augmented BFM (Berlin–Frankfurt–Münster) for acute lymphoblastic leukemia (ALL) [max. chemotherapy dosage not exceeding surface area (SA) = 2]. Patients were classified according to their body mass index (BMI) as overweight and obese patients (29 patients), or others (16).

The study design was approved by The Institutional Review Board of the Faculty of Medicine, Mansoura University, Egypt (code number: R.19.09.607)

Statistical analysis

Data was analyzed using SPSS (Statistical Package for Social Scientists) 16. A two-tailed *p* value of <0.05 was considered statistically significant. For descriptive statistics of qualitative variables, the frequency distribution procedure was run with calculation of the number of cases and percentages. For descriptive statistics of quantitative variables, the mean and standard deviation or the median and range was used. An association between categorical variables was tested by a Chi square test, or by Fishers exact test if the assumptions of Chi square were violated. Survival and relapse-free survival analyses were calculated using the Kaplan-Meier method. Comparisons of survival were performed using a log-rank test.

Results

This prospective study analyzed 50 *de novo* acute leukemia patients [25 (50%) males, and 25 (50%) females]. Mean age was 39.5 years (range 16–69). 34 (68%) patients were AML, and 16 (32%) were ALL. Five patients (10%) had diabetes, and eight (16%) had hypertension. In the ALL patients, t(9;22) was done in four patients (positive in one (25%) and negative in three (75%), and 11q23 re-arrangement was done in four patients (negative in all). In the AML patients, inv 16 was done in 12 patients (positive in three (25%) and negative in nine (75%), t(8;21) was done in 11 patients [positive in two (18.2%) and negative in nine (81.8%)], and t(15;17) was done in three AML (M3) patients [positive in all (100%)]. 29 (58%) patients were overweight or obese based on their body mass index (BMI). Basic data is set out in Table I.

Table I. Descriptive data of acute leukemia patients

Variables		**No**	
Gender	M:F	25:25	50:50%
Leukemia type	AML	34	68%
	ALL	16	32%
CBC and PB	WBC	66.5	0.6–498
	Hb	8.5	3.8–13.6
	PLT	56.3	5–296
	BLAST	69.3	20–100
BMI	Overweight + obese	29	58%

	Others	16	32%
	Missing	5	10%
TG level	Hypertriglyceridemic	28	56%
	Normal	22	44%
Cholesterol level	Hypercholesterolemic	25	50%
	Normal	25	50%
HDL level	Low level (risky)	22	44%
	Normal	28	56%
LDL level	Elevated	23	46%
	Normal	27	54%
Total cholesterol/HDL ratio	High risk	21	42%
	Normal and borderline	**29**	**58%**

M — male; F — female; AML — acute myeloid leukemia; ALL — acute lymphoblastic leukemia; CBC — complete blood count; PB — peripheral blood; WBC — white blood cells; Hb — hemoglobin; PLT — platelets; BMI — body mass index; TG — triglycerides; HDL — high-density lipoproteins; LDL — low-density lipoproteins

Overweight/obese patients showed a statistically more significant association with female patients than male patients (65.5%, $p = 0.009$). Female patients were statistically significantly associated with high cholesterol level (64%, $p = 0.048$), low HDL level (60%, $p = 0.023$), and elevated LDL level (60%, $p = 0.047$) (Table II).

Table II. Comparative lipid profile pattern regarding gender in all 50 patients

Variables		**Male**	**Female**	***p***
BMI*	Overweight/obese	10 (34.5%)	19 (65.5%)	0.009
	Others	12 (75%)	4 (25%)	
TG level	Hypertriglyceridemic	14 (56%)	14 (56%)	1
	Normal	11 (44%)	11 (44%)	
Cholesterol level	Hypercholesterolemic	9 (36%)	16 (64%)	0.048
	Normal	16 (64%)	9 (36%)	
HDL level	Low level (risky)	7 (28%)	15 (60%)	0.023

	Normal	18 (72%)	10 (40%)	
LDL level	Elevated	8 (32%)	15 (60%)	0.047
	Normal	17 (68%)	10 (40%)	

*50 cases included in analysis, except for body mass index (BMI) where only 45 cases included (five missed BMIs); TG — triglycerides; HDL — high-density lipoproteins; LDL — low-density lipoproteins

In comparing the lipid profile between overweight/obese patients and other patients, there was no statistically significant association (Table III).

Table III. Comparative lipid profile pattern regarding body mass index in 45 patients

Variables		**Overweight–obese**	**Others**	***p***
TG level	Hypertriglyceridemic	15 (51.7%)	10 (62.5%)	0.48
	Normal	14 (48.3%)	6 (37.5%)	
Cholesterol level	Hypercholesterolemic	12 (41.4%)	9 (56.3%)	0.33
	Normal	17 (58.6%)	7 (43.8%)	
HDL level	Low level (risky)	14 (48.3%)	7 (43.8%)	0.77
	Normal	15 (51.7%)	9 (56.3%)	
LDL level	Elevated	11 (37.9%)	8 (50%)	0.43
	Normal	18 (62.1%)	8 (50%)	

TG — triglycerides; HDL — high-density lipoproteins; LDL — low-density lipoproteins

76.7% of AML patients were overweight or obese ($p = 0.015$), while 81.3% of ALL patients showed hypertriglyceridemia ($p = 0.014$) (Table IV).

Table IV. Comparative lipid profile between acute leukemia patients

Variables		**ALL**	**AML**	***p***
BMI*	Overweight/obese	6 (40%)	23 (76.7%)	0.015
	Others	9 (60%)	7 (23.3%)	
TG level	Hypertriglyceridemic	13 (81.2%)	15 (44.1%)	0.014
	Normal	3 (18.8%)	19 (55.9%)	

Cholesterol level	Hypercholesterolemic	10 (62.5%)	15 (44.1%)	0.2
	Normal	6 (37.5%)	19 (55.9%)	
HDL level	Low level (risky)	7 (43.8%)	15 (44.1%)	0.9
	Normal	9 (56.2%)	19 (55.9%)	
LDL level	Elevated	9 (56.2%)	14 (41.2%)	0.32
	Normal	7 (43.8%)	20 (58.8%)	
Total cholesterol/HDL ratio	High risk	8 (50%)	13 (38.2%)	0.75
		Normal and borderline	8 (50%)	21 (61.8%)

*50 cases included in analysis, except for body mass index (BMI) where only 45 cases included (five missed BMIs); ALL — acute lymphoblastic leukemia; AML — acute myeloid leukemia; TG — triglycerides; HDL — high-density lipoproteins; LDL — low-density lipoproteins

There was no statistically significant association between lipid profile and complete response (CR) rate, although there was a marginally significant association between non-CR rate and overweight and obese patients ($p = 0.051$) (Table V). In addition, there was no impact of BMI or lipid profile on overall survival among acute leukemia patients.

Table V. Impact of body mass index (BMI) and lipid profile on complete response rate among acute leukemia patients

Variables		**CR**	**Non-CR**	***p***
BMI*	Overweight/obese	13 (52%)	16 (80%)	0.051
	Others	12 (48%)	4 (20%)	
TG level	Hypertriglyceridemic	17 (65.4%)	11 (45.8%)	0.16
	Normal	9 (34.6%)	13 (54.2%)	
Cholesterol level	Hypercholesterolemic	11 (42.3%)	14 (58.3%)	0.25
	Normal	15 (57.7%)	10 (41.7%)	
HDL level	Low level (risky)	10 (38.5%)	12 (50%)	0.41
	Normal	16 (61.5%)	12 (50%)	
LDL level	Elevated	10 (38.5%)	13 (54.2%)	0.26
	Normal	16 (61.5%)	11 (45.8%)	

*50 cases included in analysis, except for body mass index (BMI) where only 45 cases included (five missed BMIs); CR — complete response; TG — triglycerides; HDL — high-density lipoproteins; LDL — low-density lipoproteins

Discussion

The high rate of expansion and metabolism in cancer cells associated with decreased intracellular cholesterol and other lipids may lead to LDL receptor overexpression. For example, in myeloblast cells, LDL uptake can increase by up to 100-fold. Many attempts have been made to evaluate the correlation between serum lipids in leukemic patients and disease activity and response to chemotherapy [3, 6].

Epidemiological data suggests a significant association between increased BMI and hematological neoplasms [7]. Several large studies have revealed an association between a high incidence of leukemia and being overweight, and suggested that obesity is a poor prognostic factor for leukemia [8, 9]. In our study, 76.7% of AML patients were overweight or obese, as opposed to 40% of ALL patients ($p = 0.015$).

Our data showed that female patients were significantly overweight/obese ($p = 0.009$), and were more associated with increased TC level ($p = 0.048$), low HDL level ($p = 0.023$), and elevated LDL level ($p = 0.047$) than male patients. This data accords with that of Mehrabani et al. [9] who found that the incidence of obesity and overweight was higher in females than in males, and of Safford et al. [10] who found that females have higher TC and LDL levels than males.

In comparing the lipid profile in overweight/obese patients to that of others, no significant difference was found. 81.3% of ALL cases were associated with hypertriglyceridemia compared to 44.1% of AML cases ($p = 0.014$). Babu et al. [11] demonstrated that only TC and LDL cholesterol showed significant differences between obese and non-obese individuals, and other parameters like HDL and TG did not show any significant difference.

On the other hand, Einollahi et al. [12] reported hypertriglyceridemia and a decline in TC, HDL and LDL among leukemic patients. Also, similar results have been observed by Naik et al. [8] (in 55 leukemic patients) and Tao et al. [13] (in 86 ALL patients).

As regards response rate and BMI, 80% of patients who did not achieve complete response were obese or overweight ($p = 0.051$), which aligns with Orgel et al. [14] who found that obesity was associated with residual leukemia following induction therapy for childhood B-precursor acute lymphoblastic leukemia, and with Elazab et al. [15] who reported that overweight

and obesity were associated with decreased complete response rates in adult AML patients (p = 0.004).

Targeting the metabolic profiles in leukemia cells could improve the outcome of leukemia patients. Statins possess several anti-leukemia effects such as apoptosis, anti-proliferation, and autophagy. Preliminary data has suggested that statins have anti-leukemia activities [16–18]. Two clinical trials have further revealed that statins can improve the efficacy of standard therapy in AML [19, 20].

Conclusions

Female, and acute myeloid leukemia, patients were more commonly associated with overweight and obesity, and a high TG level was found to be associated with acute lymphoid leukemia. Changes in lipid profile showed no impact on the complete response rate in acute leukemia patients. However, 80% of patients who did not achieve complete response were obese or overweight.

Further studies are needed to understand the correlations between metabolic profile and leukemia to help in developing new therapeutic approaches.

Conflict of interest

The author declares no conflict of interest.

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References

1. Fiorenza AM, Branchi A, Sommariva D. Serum lipoprotein profile in patients with cancer. A comparison with non-cancer subjects. Int J Clin Lab Res. 2000; 30(3): 141–145, doi: 10.1007/s005990070013, indexed in Pubmed: 11196072.
2. Halton JM, Nazir DJ, McQueen MJ, et al. Blood lipid profiles in children with acute lymphoblastic leukemia. Cancer. 1998; 83(2): 379–384, indexed in Pubmed: 9669823.

3. Ghalaut VS, Pahwa MB, Ghalaut PS. Alteration in lipid profile in patients of chronic myeloid leukemia before and after chemotherapy. Clin Chim Acta. 2006; 366(1-2): 239–242, doi: 10.1016/j.cca.2005.10.022, indexed in Pubmed: 16386722.
4. Gokhale CD, Udipi SA, Ambaye RY, et al. Post-therapy profile of serum total cholesterol, retinol and zinc in pediatric acute lymphoblastic leukemia and non-Hodgkin's lymphoma. J Am Coll Nutr. 2007; 26(1): 49–56, doi: 10.1080/07315724.2007.10719585, indexed in Pubmed: 17353583.
5. Zalewska-Szewczyk B, Matusiak I, Wyka K, et al. [Changes in the lipid profile in children with acute lymphoblastic leukaemia — the influence of the disease and its treatment]. Med Wieku Rozwoj. 2008; 12(4 Pt 2): 1035–1040, indexed in Pubmed: 19531822.
6. Spiegel RJ, Schaefer EJ, Magrath IT, et al. Plasma lipid alterations in leukemia and lymphoma. Am J Med. 1982; 72(5): 775–782, doi: 10.1016/0002-9343(82)90543-5, indexed in Pubmed: 7081275.
7. Lichtman MA. Obesity and the risk for a hematological malignancy: leukemia, lymphoma, or myeloma. Oncologist. 2010; 15(10): 1083–1101, doi: 10.1634/theoncologist.2010-0206.
8. Naik PP, Ghadge MS, Raste AS. Lipid profile in leukemia and Hodgkin's disease. Indian J Clin Biochem. 2006; 21(2): 100–102, doi: 10.1007/BF02912921, indexed in Pubmed: 23105623.
9. Mehrabani J, Ganjifar ZK. Overweight and obesity: a brief challenge on prevalence, complications and physical activity among men and women. Women's Health. 2018; 7(1), doi: 10.15406/mojwh.2018.07.00161.
10. Safford MM, Gamboa CM, Durant RW, et al. Race-sex differences in the management of hyperlipidemia: the REasons for Geographic and Racial Differences in Stroke study. Am J Prev Med. 2015; 48(5): 520–527, doi: 10.1016/j.amepre.2014.10.025, indexed in Pubmed: 25891050.
11. Babu SV, Jagadeesan A, Ramalingam J. A comparative study of lipid profile in obese and nonobese men attending master health checkup. Indian J Med. 2017; 21(2): 73–75, doi: 10.5005/jp-journals-10054-0024.

12. Einollahi N, Alizadeh S, Nabatchian F, et al. Serum lipid profile alterations in acute leukemia before and after chemotherapy. IJBC. 2013; 6(1): 3–9.
13. Tao LJ, Qin YQ. [Alteration of serum lipids in patients with acute leukemia and its clinical significance]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2002; 10(4): 371–372, indexed in Pubmed: 12513777.
14. Orgel E, Tucci J, Alhushki W, et al. Obesity is associated with residual leukemia following induction therapy for childhood B-precursor acute lymphoblastic leukemia. Blood. 2014; 124(26): 3932–3938, doi: 10.1182/blood-2014-08-595389, indexed in Pubmed: 25349177.
15. Elazab A, Denewer M, Mabed M. PB1818: Influence of body mass index on the outcome in patients with acute myeloid leukemia. HemaSphere. 2022; 6(Suppl): 1698–1699, doi: 10.1097/01.hs9.0000850124.98624.52.
16. Li HY, Appelbaum FR, Willman CL, et al. Cholesterol-modulating agents kill acute myeloid leukemia cells and sensitize them to therapeutics by blocking adaptive cholesterol responses. Blood. 2003; 101(9): 3628–3634, doi: 10.1182/blood-2002-07-2283, indexed in Pubmed: 12506040.
17. van der Weide K, de Jonge-Peeters SD, Kuipers F, et al. Combining simvastatin with the farnesyltransferase inhibitor tipifarnib results in an enhanced cytotoxic effect in a subset of primary CD34+ acute myeloid leukemia samples. Clin Cancer Res. 2009; 15(9): 3076–3083, doi: 10.1158/1078-0432.CCR-08-3004, indexed in Pubmed: 19383813.
18. Minden MD, Dimitroulakos J, Nohynek D, et al. Lovastatin induced control of blast cell growth in an elderly patient with acute myeloblastic leukemia. Leuk Lymphoma. 2001; 40(5-6): 659–662, doi: 10.3109/10428190109097663, indexed in Pubmed: 11426537.
19. Advani AS, McDonough S, Copelan E, et al. SWOG0919: a phase 2 study of idarubicin and cytarabine in combination with pravastatin for relapsed acute myeloid leukaemia. Br J Haematol. 2014; 167(2): 233–237, doi: 10.1111/bjh.13035, indexed in Pubmed: 25039477.
20. Kornblau SM, Banker DE, Stirewalt D, et al. Blockade of adaptive defensive changes in cholesterol uptake and synthesis in AML by the addition of pravastatin to idarubicin + high-dose Ara-C: a phase 1 study. Blood. 2007; 109(7): 2999–3006, doi: 10.1182/blood-2006-08-044446, indexed in Pubmed: 17158228.