Clinica Chimica Acta 444 (2015) 43–49

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Revisiting the dyslipidemia associated with acute leukemia

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ARTICLE INFO

Article history:
Received 5 October 2014
Received in revised form 6 January 2015
Accepted 27 January 2015
Available online 11 February 2015

Keywords:
Acute leukemia
Plasma lipids
Tumor metabolism
Lipoproteins
Dyslipidemia

ABSTRACT

Background: Previous studies appreciate the leukemia-associated alterations in plasma lipid profiles but fail to provide a consistent pattern of lipid anomalies in leukemia patients. These inconsistencies could be due to overlooking the effects of related confounding risk-factors and comorbidities.
Methods: The plasma lipid profiles of acute-leukemia and control groups were compared.
Results: We observed that acute lymphocytic leukemia (ALL) patients display significantly higher triglycerides and very low-density lipoproteins, whereas, acute myeloid leukemia (AML) patients display significantly lower high-density lipoproteins. To assess the confounding effects of related risk factors gender-, age- and BMI-based analyses were performed. We observed that the aforementioned significant differences in the lipid profiles of leukemia patients were restricted to female participants of the respective groups. Moreover, a significant decrease in total cholesterol and low-density lipoprotein levels was observed only in male participants of the AML population. Various age-specific trends in plasma lipid profile of the leukemia patients were also observed. BMI-based analysis did not display many significant differences from the overall analyses. In addition to comparing the absolute values of plasma lipids in leukemia and control groups we also compared and observed significant differences in prevalence of various isolated- and mixed-dyslipidemias in these groups.
Conclusions: These findings may help in outlining the prevalence and types of dyslipidemia in leukemia patients that may emerge as diagnostic/prognostic factors for the management of acute leukemia.

1. Introduction

Irregularities in the plasma lipid profiles of leukemia patients have been widely observed. Most of the previous reports have demonstrated a decrease in total cholesterol (TC) [1–6] and various lipoprotein subfractions particularly, high-density lipoprotein cholesterol (HDL-C) [1–8], whereas an increase in the serum triglyceride (TG) concentrations of the leukemia patients is also a frequently observed phenomenon [1,3,4,6–8]. Nevertheless there are several inconsistencies in the previous reports [9]. For instance it has been reported that though the TC concentrations in leukemia patients are higher than the control group, this difference is not statistically significant [1]. Some other studies indicated no change or decrease in plasma TG concentrations [2,5]. Despite these inconsistencies in the literature the significance of plasma/serum lipids in the diagnosis or prognosis of leukemia has been pointed out by the previous workers. Interestingly the plasma lipid concentrations have been shown to have a significant prognostic potential for leukemia patients undergoing chemotherapy [5–7,10,11]. Serum lipid concentrations were shown to go back to the normal values after effective treatment [5,6]. These observations corroborate the correlation between abnormal serum lipid profile and disease activity. The most common observation in this regard was a significant increase in the serum concentrations of TC and HDL-C after effective chemotherapy [5,6,10].

Endogenous lipogenesis has historically been considered as the principal source of fatty acids (FAs) for cancer cells [12]. However, recent reports suggest that certain types of cancer cells also exploit the lipolytic pathways for attaining FAs [13,14]. These findings highlight the significance of plasma lipoproteins in carcinogenesis. Especially, the leukemic cells that are in circulation could attain more direct benefit from the plasma lipoproteins. As mentioned earlier, the previous works that indicated aberrant lipid profiles in leukemia patients do not provide consistent evidence. Some of these studies included both acute and chronic leukemia patients together as a single population [1]. This could be a possible reason behind the discrepant data as the number of cancerous cells in acute and chronic leukemia is vastly different. If the higher uptake of lipoproteins by cancerous cells is causing dyslipidemia in leukemia patients, the number of these cells could have a high impact on plasma lipid profiles of these patients. Some other studies overlooked certain clinical conditions or confounding factors that may affect the plasma lipid profile of the cancer patients. Patients with other metabolism related disorders display different types of dyslipidemias that

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http://dx.doi.org/10.1016/j.cca.2015.01.038
0009-8981/

include isolated lipid disorders, where only one of the lipid fractions is affected, or mixed-dyslipidemias, where two or more of these subfractions display abnormal values. The prevalence of isolated- or mixed-dyslipidemias is also not widely explored in the cancer patients. Due to these reasons a consistent and reliable plasma lipid profile of the leukemia patients has not emerged. Therefore, the clinical usefulness of plasma/serum lipoprotein concentrations in diagnosis or management of leukemia remains elusive. Further studies are required to clarify the ambiguities in this field of research.

2. Methodology

2.1. Study population, ethics and sample collection

For the present cross-sectional study we examined the patients that were clinically diagnosed for acute myeloid leukemia (AML) ($n = 25$) and acute lymphocytic leukemia (ALL) ($n = 32$). In addition to that healthy subjects ($n = 70$) were also included as control population. All the study subjects were above the age of 15 y. We excluded subjects with the following conditions: severe viral/bacterial infection, on anticoagulation therapy, suffering from bleeding disorder (e.g., hemophilia, low platelets, etc.) and aplastic anemia. Previous studies have reported that smoking status may affect the plasma lipid profile [15–17], therefore, smokers were excluded from the study population. In addition to that participants that had history of metabolic syndrome, diabetes mellitus, cardiovascular disease or any other cancer were also not included in the study population because these conditions could also interfere with plasma lipid concentrations [17–20]. The statin-users were also excluded from the study on the same grounds [21]. The study protocol for human subjects was approved by the Ethics Committee of School of Biological Sciences, University of the Punjab. Informed consent was obtained from each study-subject before sample collection. In order to obtain the basic personal information and medical history each participant was interviewed and completed a structured questionnaire. The medical history file of each patient was also thoroughly examined. Intravenous blood was collected from all the subjects after 10 ± 2 h of fasting. Blood samples were collected according to the guidelines of National Committee for Clinical Laboratory Standards [20] in vials containing EDTA-anticoagulant agent. The plasma was promptly separated (<4 h after collection of whole blood). For various analyses the study groups were classified into gender, BMI and age groups. For BMI-based analysis the study groups were categorized into two major BMI groups; BMI group-I (BMI $\leq$25, under-weight-normal) and BMI group II (BMI $\geq$ 25, overweight), according to the current National Institutes of Health (NIH) guidelines [22]. For age-adjusted analysis the study-population was categorized into following age groups; age group-I (15–19 y), age group-II (20–39 y) and age group-III ($\geq$40 y).

2.2. Determination of plasma lipid concentrations

Plasma total cholesterol (TC) and triglyceride (TG) concentrations were spectrophotometrically determined using commercially available kits (Analyticon Biotechnologies AG). For the estimation of high-density lipoprotein cholesterol (HDL-C), other lipoprotein fractions were precipitated using HDL-C precipitation reagent (Analyticon). HDL-C was then estimated using aforementioned Analyticon kit for the quantitative determination of cholesterol. For estimation of low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) we used recently described method by Martin et al. [23].

2.3. Cut-off values for plasma concentrations of various lipid and lipoprotein fractions

Atherogenic lipoprotein and lipid abnormality status was determined by utilizing the criteria given by the expert panel of the National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III) [24]. Cut-off values recommended by ATP III for various plasma lipid and lipoprotein fractions are given in Table S1. Hypocholesterolemia and lower than optimal concentrations of LDL-C were determined by utilizing the cut-off values described by previous works [25,26].

2.4. Statistical analysis

The results were analyzed by ANOVA followed by Dunnett's or Tukey's Multiple Comparison Test and z-test for two population proportions where applicable. A $p < 0.05$ were considered statistically significant. The data are presented as means $\pm$ S.D. unless otherwise indicated.

3. Results

3.1. Demographics of the study population

The demographics of the study groups are shown in Table 1. There were no statistically significant differences in age, height, weight and body-mass-index (BMI) among different sub-sets of the study population. The sex-ratio varied in the control and cancer groups.

3.2. Lipid profile of acute leukemia patients versus healthy subjects

We compared the major plasma lipoprotein fractions — total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides (TGs) and non-HDL-C in healthy subjects and overall acute leukemia (AL) patients — this group was comprised of both acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) populations. Plasma lipoprotein concentrations in the control group were also compared to ALL and AML patients separately. In addition to that lipid profiles of ALL and AML patients were compared to each other.

Plasma TC and LDL-C concentrations did not vary significantly between any sub-sets of the study-population (Fig. 1a–b, Supplementary Table S2). When plasma HDL-C concentrations were compared between the study-groups, it was observed that acute leukemia patients (AL) displayed significantly lower HDL-C concentrations from that in healthy subjects (Fig. 1c, Supplementary Table S2). This difference was even more striking when the plasma HDL-C concentrations in the healthy subjects were separately compared with that in AML subgroup (Fig. 1c, Supplementary Table S2), whereas, ALL subgroup did not display any significant difference for this lipoprotein fraction in comparison to the control group. The plasma HDL-C concentrations in the AML population were also significantly lower when compared to that in the ALL population (Fig. 1c).

Plasma VLDL-C and TG concentrations were significantly higher in overall AL or ALL population in comparison to the healthy subjects (Fig. 1d–e, Supplementary Table S2). No significant difference was observed when plasma non-HDL-C concentrations were compared among various sub-sets of the study-population (Fig. 1f, Supplementary Table S2).

Gender, age and BMI are previously shown to affect lipoprotein metabolism in healthy subjects [27–29]. Here, the study population was categorized into gender, BMI or age groups and plasma lipid concentrations in each patient group were compared to the respective control group. Gender-based analyses revealed certain significant differences between the lipid profiles of cancer and control groups, which were not noticeable in the overall analysis. For instance significantly lower TC and LDL-C concentrations were observed in the male participants of the AML group as compared to the respective control group (Supplementary Table S3). The two lipid sub-fractions, TGs and VLDL-C, that were observed to be significantly increased in AL or ALL patients in the initial evaluations (Fig. 1, Supplementary Table S2), were found to be significantly elevated only in the female participants of these two