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Mini-review

Atypical plasma lipid profile in cancer patients: Cause or consequence?

Rimsha Munir [a], Hina Usman [a], Shahida Hasnain [a], Karine Smans [b], Hubert Kalbacher [c,d], Nousheen Zaidi [a,*]

[a] Microbiology and Molecular Genetics, University of the Punjab, Lahore, Pakistan
[b] Department of Oncology, Janssen Research and Development, A Division of Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse, Belgium
[c] Medical and Natural Sciences Research Centre, University of Tubingen, Germany
[d] Interfacultary Institute of Biochemistry, University of Tubingen, Germany

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ABSTRACT

The aberrant blood lipoprotein levels in cancer patients are reported to be associated with cancer risk and mortality incidents however, there are several discrepancies in the previous reports. Hence the clinical usefulness of plasma/serum levels in risk stratification of a variety of cancers remains elusive. The present review highlights and compiles findings from different research groups regarding association of plasma lipoprotein levels with the risk of developing various types of cancer. We will discuss some prospective underlying mechanisms for this reported association. In addition to that the potential roles of plasma lipids in promoting carcinogenesis will be conferred.

Lipids comprise diverse classes of biomolecules that are known to play key roles in cellular energy storage, structure, and signaling. In the clinical settings blood plasma lipids are routinely assessed due to their widely established association with cardiovascular disorders. Cholesterol and TGs (triglycerides) are currently considered as the most significant plasma lipids in clinical terms [1]. Cholesterol, not only serves as a major component of the cell membranes, but also as a precursor for steroid hormones, vitamin D, oxysterols and bile acids [1]. It is also required for the activation of neuronal signaling molecules [2]. Whereas, TGs are a key energy source made up of free fatty acids (FFAs) ester-linked to a glycerol backbone. The hydrophobic nature of cholesterol and TGs require the presence of lipoproteins - complex aggregates of lipids and proteins - that assist the transport of lipids between the tissues. Broadly, lipoproteins have been classified on the basis of their densities as: chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins, low density lipoproteins (LDL), and high density lipoproteins (HDL). The clinical significance of plasma lipid levels in diagnosis and prognosis of certain diseases has been a long known fact. The plasma lipid disorders are found to be causally related to both atherosclerosis and coronary artery disease [3,4]. Researchers have also reported association of plasma/serum lipids and lipoproteins with different types of cancer (Table 1).

In general lipids are known to play a crucial role in tumor development and progression [5]. Briskly proliferating cancer cells require a constant supply of lipids for membrane biogenesis and protein modifications. Also, the cancer cells that are not rapidly proliferating require increased amounts of lipids for enhanced signaling and resistance against apoptosis [6]. Lipoproteins are the distributors of both endogenous as well as exogenous lipids across the tissues. It is therefore plausible that lipoproteins play a fundamental role in cancer progression *via* supplying lipids to malignant cells and tumors.

The present review focuses on association of serum/plasma lipoprotein levels with the risk of developing various types of cancer. In addition to that the potential roles of serum/plasma lipids in promoting carcinogenesis will be highlighted.

1. Overview of lipoprotein metabolism

The triglyceride-rich lipoproteins; chylomicrons and VLDL are synthesized in intestine and liver respectively. Chylomicrons are synthesized by enterocytes in the intestinal mucosa from the absorbed dietary fats and cholesterol. While VLDL particles are

Abbreviations: TGs, triglycerides; TG, triglyceride; FFAs, free fatty acids; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; LPL, lipoprotein lipase; LDL-R, low density lipoprotein receptor; FAs, fatty acids.

* Corresponding author. +92 3212371090.
E-mail address: nzzaidi@yahoo.com (N. Zaidi).

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Table 1
Overview of the previous studies aimed to evaluate the association between plasma/serum lipids and cancer.

Cancer type studied	Reference	Lipid fraction studied	Cancer subtype	Sample size	Major Findings/Comments
Overall/Several Cancers	[33]	Chl	–	$N = 577{,}330$	Lower serum Chl levels were associated with high-risk of all cancers in females. This association is also observed in males for several types of cancers.
	[25]	Chl and LDL	–	$n = 100$ $c = 103$	Significantly lower levels of total serum Chl, esterified-Chl and LDL were observed in patients in comparison to the control population.
	[18]	Chl	–	$n = 61$ $c = 610$	Lower levels of serum Chl were observed in patients in comparison to the control population.
	[34]	Chl	–	$c_{\text{(Stomach cancer)}} = 557$ $c_{\text{(Colorectal cancer)}} = 506$ $c_{\text{(Lung cancer)}} = 320$ $c_{\text{(Breast cancer)}} = 178$ $c_{\text{(Prostate cancer)}} = 164$ $c_{\text{(Liver cancer)}} = 125$ $c_{\text{(Cervical cancer)}} = 55$ $c_{\text{(Leukemia)}} = 50$	Lower levels of serum Chl were associated with high-risk of all cancers analyzed, particularly, stomach and liver.
	[26]	Chl	–	$c_{\text{(Non-Survivors)}} = 290$ $c_{\text{(Survivors)}} = 2173$	There was no significant difference between plasma Chl levels of the survivors and non-survivors. Nonetheless, increased mortality was associated with low plasma Chl levels in lung cancer patients but not in stomach, prostate or colon cancer patients.
	[27]	Chl and TGs	–	$n = 131$ $c = 131$	In comparison to the control population male cancer patients displayed lower whereas, female cancer patients displayed higher plasma Chl levels. TG levels were not significantly different between cancer patients and controls.
	[61]	LDL	–	$N = 6107$	In type 2 diabetes patients the association between LDL and cancer was V-shaped, whereby both low and high levels of LDL were associated with elevated risk of cancer.
	[28]	Chl	–	$N = 172{,}210$	High serum Chl levels were associated with lower cancer risk.
	[19]	Chl, LDL and TGs	–	$c_{\text{(Lymphomas)}} = 18$ $c_{\text{(Breast carcinomas)}} = 18$ $c_{\text{(Small-cell lung carcinomas)}} = 14$ $c_{\text{(Urothelial-cell carcinoma)}} = 7$	In this study various cancer patients undergoing chemotherapy were included. Patients that responded positively to chemotherapy demonstrated a significant increase in serum Chl, TG and LDL levels. While breast cancer patients responding positively to chemotherapy displayed a non- significant decrease in Chl and LDL.
	[20]	Chl, HDL, LDL, TGs, α-lipoproteins, Phospholipids and Total lipids	–	$n = 60$ $c = 115$	Serum Chl, HDL, LDL, total lipids, phospholipids and α-lipoproteins levels were significantly lower in patients as compared to the control group, whereas TG levels were found to be significantly elevated.
	[29]	Chl	–	$c = 160{,}135$	There was no strong or consistent association between low serum Chl level and overall cancer incidence. Lower serum Chl levels were only associated with elevated risks of cervical cancer and lymphoma in males.
	[30]	Chl, LDL and VLDL	–	$c = 4224$	Significantly lower plasma Chl values were observed in colorectal and gastric carcinoma patients as compared to the controls. While for other cancers no significant difference in plasma lipid fractions was observed.
	[31]	Chl, HDL, TGs and LDL	–	$n = 415$ $c_{\text{(Hematological malignancies)}} = 97$ $c_{\text{(Lung cancer)}} = 92$ $c_{\text{(Cancer of upper digestive system)}} = 108$ $c_{\text{(Colon cancer)}} = 103$ $c_{\text{(Breast cancer)}} = 32$ $c_{\text{(Cancer of the genitourinary system)}} = 32$	Significantly lower serum Chl, LDL and HDL levels were observed in all cancer patients in comparison to the controls. The lowest values of Chl, LDL and HDL were recorded in patients with hematological malignancies. Multiple regression analysis showed that cancer is also associated with high values of serum TG levels.
Bowel cancers	[51]	HDL	Gastric cancer	$c_{\text{(Normal-HDL)}} = 150$ $c_{\text{(Low-HDL)}} = 34$	In the low serum HDL group, lymphatic and vascular invasion was significantly increased in comparison to the normal serum HDL group.
	[35]	Chl	Colon cancer	$c = 691$	Low serum Chl levels were found to be associated with high incidence of cancer.
	[32]	Chl	Colorectal cancer	$n = 85$ $c = 85$	Serum Chl levels were significantly lower for the colorectal cancer group than for the control group.
	[58]	TGs, HDL, LDL, apoA-1 and apoB	Colorectal adenoma	$c_{\text{(With colorectal adenomas)}} = 5958$ $c_{\text{(non–advanced adenomas)}} = 5{,}504$ $c_{\text{(With advanced adenomas)}} = 454$	Higher levels of serum TG were significantly associated with increased prevalence of both advanced and non-advanced colorectal adenomas. Higher