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Serum Lipids and Lipokines as Prognostic/Diagnostic Biomarkers in Common Cancers

Nikolaos Dogkas[1,2], Maria Trapali[2], Christine Fountzoula[2], Georgios Albert Karikas[2], Petros Karkalousos[2]

[1]Biochemistry Laboratory, General Anticancer Hospital of Piraeus "METAXA", Piraeus, Greece
[2]Department of Biomedical Sciences, School of Health and Care Sciences, University of West Attica, Athens, Greece
Email: petef@uniwa.gr

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Abstract

Total cholesterol (CHOL) levels have been shown in many studies, to be higher in people with several types of cancer. Similar results are observed for both triglycerides (TG) and low-density cholesterol (LDL), as opposed to high-density cholesterol (HDL). Chemotherapy seems to reduce CHOL and LDL, leading to a reduction. Furthermore, the recurrence of high levels of CHOL, TG and LDL, as well as low levels of HDL, after receiving treatment, or when patients appear to have been cured, are signs of a possible recurrence of the disease. Lipoprotein *α* (Lpa), occurs at higher levels in patients than in healthy people, whereas lipokines resistin and bisfatin, "hormonal" products of adipose tissue exhibited high levels in cancer cases, compared to control groups.

Keywords

Cancer, Total Cholesterol, Triglycerides, HDL, LDL, Resistin, Visfatin

1. Introduction

Lipids are necessary for the maintenance of cell structure and providing the production of energy to cancer cells. Lipoprotein distributors of both endogenous and exogenous lipids to tissues and "lipokines" or "lipocytokines" are involved in regulating many processes.

Present sort review article, presents the important role and biosynthesis of a number of basic lipids (CHOL, LDL, HDL, TG) Lp (a), as well as the lipokines resistin and visfatin in health and pathological conditions. More specific, latest

data concerning the close relation between lipid serum concentrations, with several common types of cancers are proposed, as prognostic and diagnostic potential biomarkers. Above bibliographic data are suggested to be taken into account in an auxiliary way, without replacing the specific biomarkers for each type of disease.

2. Adipose Tissue-Lipid Chemistry, Biosynthesis and Pathology

Adipose tissue is the main store house of energy, having the ability to store fuel of high energy content (triglycerides), when there is an excess of nutrients. In addition, another important function is the thermal insulation of the body. Its ability to store large amounts of energy is due to the properties of its basic functional unit, the fat cell. The fat cell is the only cell type, perfectly adapted to store fat, without affecting its function, having the appropriate enzymes for the synthesis of fatty acids (lipogenesis), their storage in the form of triacylglycerols and their mobilization, when needed (lipolysis) [1].

In addition, it is recognized as a complex endocrine and paracrine organ by releasing more than 20 hormones and signaling molecules called "lipokines" or "lipocytokines". Under normal circumstances, lipocytokines are involved in the regulation of many physiological processes that play an overall role in appetite and energy balance, such as lipid metabolism, glucose homeostasis, insulin resistance, angiogenesis, arterial pressure regulation and various inflammatory processes. In the case of obesity, deregulation of fat cells and alteration of normal processes are observed. Obesity-related diseases are of global interest including cancer, as it is estimated that 20% of cancers are caused by being overweight [2].

Lipids include a number of small biomolecules that differ from the other three basic biological macromolecules (proteins, nucleic acids and polysaccharides) in their chemical architecture, since they are macromolecular polymers. In contrast, lipids are distinct chemical compounds, with a great structural variety. Although there is no widely accepted definition, they are often described as natural compounds, insoluble in water (hydrophobic) and thus soluble only in polar solvents [3].

In living cells, lipids are essential for maintaining cellular structure, providing energy, and being involved in cellular signaling. Their metabolism produces a number of bioactive molecules, the so-called biological mediators [4]. Many of these mediators play a role in various cell signaling pathways, such as growth, proliferation, differentiation, survival, apoptosis and membrane homeostasis [5].

Lipids are classified into eight sub-categories:

1) Fatty acids;

2) Glycerolipids;

3) Glycerophospholipids;

4) Sphingolipids;

5) Lipids of sterol;

6) Lipids of prenol;

7) Saccharolipids (glycolipids);

8) Polyketides [6].

Changes in lipid metabolism can lead to modifications in cell membrane composition and permeability, contributing substantially to the development and progression of many diseases, including cancer. Fatty acids, glycerolipids, glycerophospholipids, sphingolipids and sterol lipids are most associated with cancer development [7]. Lipids play also a critical role in tumor growth and development. Cancer cells, due to their increasing proliferative capacity, require a constant supply of lipids in order to biosynthesize membranes and modify proteins. On the other hand, cells that do not have a corresponding capacity, need increased amounts of lipids for improving signaling and resistance to apoptosis. The distribution of both endogenously and exogenously derived lipids to the tissues is accomplished by lipoproteins. Thus, lipoproteins play a fundamental role in the progression of cancer via the delivery of lipids to malignant cells and tumors [8].

The main source of fatty acids (Fat acids or FAs) for cancer cells is the endogenous lipogenesis. In many cancers, there is an increase in *de novo* fatty acid biogenesis, which is independent of the circulating lipid levels. This is reflected in the significantly increased activity of several lipogenic enzymes in cancer cells and in particular that of fatty acid synthase (FASN). This poly-enzymatic system is responsible for the final catalytic step in the synthesis of fatty acids and the change in its expression occurs in most human malignancies [9].

However, it has also been suggested that cancer cells can use exogenously derived fatty acids. In this case, the enzyme lipoprotein lipase (Lipoprotein lipase or LPL) is activated, which is responsible for lipolysis, as well as the transmembrane channel for the entry of fatty acids into the cell. In addition, classic lipogenesis factors, such as the fatty acid synthase mentioned above, must be added [10].

Cholesterol (Cholesterol or CHOL) and triglycerides (Triglycerides or TGs) are considered the most important plasma lipids from a clinical point of view [11]. Cholesterol, in addition to being a major component of cell membranes, is also a precursor for steroid hormones, vitamin D, oxysterols and bile acids. It is also required for the activation of neuronal signaling molecules. Triglycerides are the main source of energy. The hydrophobic nature of these biomolecules requires the presence of lipoproteins (complex lipid aggregates and proteins) which transport lipids between tissues. Based on their density, lipoproteins are classified into the following categories: chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins or IDLs, low density lipoproteins (LDL), and high density lipoproteins (HDL) [11]. In clinical practice, blood plasma lipids are regularly evaluated for their unequivocal association with atherosclerosis and coronary heart disease [12]. In addition to their primary role, a correlation of lipid and lipoprotein levels with plasma/serum lipoproteins

has been reported [13].

Connecting Obesity with Cancer: Tumor Microenvironment and Inflammation

The tumor microenvironment resembles that of a healing wound [14]. Tissue injury and the ensuing inflammation promote enhanced cellular proliferation via influx of immune cells, production of proinflammatory mediators and growth factors, tissue remodeling, and angiogenesis [15]. The initiating events in response to tissue injury include platelet activation and aggregation, and stimulation of the coagulation cascade. In addition to achieving hemostasis, these initiating events also lead to the production and secretion of several proteins that stimulate a local inflammatory response. For example, platelet-derived growth factor, transforming growth factor-b, and several complement factors stimulate neutrophil chemotaxis [15]. Once engaged, neutrophils continue the cascade by producing cytokines and chemotactic factors that recruit and activate effector cells. Specifically, factors such as platelet-derived growth factor, transforming growth factor-b, monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)-1b, tumor necrosis factor-a (TNF-a), and others guide circulating mononuclear phagocytes to the site of injury [15]. Once present, these progenitor cells differentiate into mature macrophages, which assume the main role of cytokine and growth factor production. These macrophage products have profound effects on the local microenvironment, including stimulation of angiogenesis and modulation of the ECM. Chronic tissue injury, such as adipose tissue inflammation, can stimulate the same wound healing mechanisms and generate a proneoplastic microenvironment [16]. Once established, malignant cells may co-opt the inflammatory mechanisms responsible for tissue repair and instead promote tumor growth and invasion. Obesity is a common cause of chronic inflammation, both systemically and at the tissue level [17]. Locally, white adipose tissue (WAT) in patients who are obese is infiltrated by immune cells, including macrophages and lymphocytes. In this manner, the obese fat pad resembles chronically injured tissue and can be a rich source of proinflammatory mediators, potentially fostering tumor growth.

3. Factors Contributing to High Levels of Drug Resistance

Drug resistance continues to be the principal limiting factor to achieving cures in patients with cancer. The problem of drug resistance in cancer is challenged by highly proliferating intrinsic or extrinsic aggressors. Cancer therapy targets a population of cancer cells within a particular host environment. The pharmacological properties of the therapy, together with intrinsic and acquired physical and molecular parameters of cancer cells and extrinsic environmental factors, result in the spectrum of clinical responses. In practice, many tumours are or become resistant owing to overlapping combinations of the following factors:

1) Tumour heterogeneity

Cancer cells acquire genomic alterations through a variety of mutational processes that generate spatial and temporal genetic diversity [18]. These processes occur at different evolutionary speeds—from the relatively slow rate of age-related mutations, to frequent editing of genes by APOBEC enzymes (a process that increases over the course of tumour evolution), to bursts of dramatic and catastrophic events that are induced by genomic instability, chromothripsis and chromosomal instability [19] [20] [21]. Large chromosomal alterations can be taken into account as macro-evolutionary events and in some circumstances probably represent a point of no return in the development of resistance, illustrating the importance of early therapeutic intervention.

2) Physical obstacles

Cancer cells can create obstacles within tumours that prevent adequate blood flow, thereby creating a pro-tumorigenic hypoxic environment and decreasing the effective exposure of a tumour to drugs. Alternative evidence suggests that anti-angiogenic agents may also normalize vascular structure and function, facilitating the delivery of systemic agents such as chemotherapy or even targeted therapy [22] [23]. Cancer cells may colonize and proliferate in specific sites, or anatomical spaces in which systemically administered drugs do not reach therapeutic concentrations.

3) Tumour and growth kinetics

There is a correlation between tumour burden and curability [24]. In many tumour types, the size of the tumour at diagnosis is perhaps the most frequently used variable to estimate prognosis; larger tumours correlate with increased metastatic risk [25]. This inverse correlation between size and curability was not entirely anticipated in the infancy of chemotherapy. Mathematical models propose that combining multiple drugs that individually kill a logarithmic fraction of cells over multiple cycles would permit sequential decreases in tumour burden until the disease was fully eradicated [26]. This is true in tumours that are highly sensitive to chemotherapy, such as some lymphomas and germ cell tumours, but does not hold across many other cancer types.

4) Immune system and tumour microenvironment

The tumour microenvironment (surrounding space composed of immune cells, stroma and vasculature) may mediate resistance by several mechanisms, including preventing immune clearance of tumour cells, hindering drug absorption and stimulating paracrine growth factors to signal cancer cell growth [27].

5) Genomic drivers

Despite a growing number of successes in efforts to target oncogenic driver mutations, some of the most formidable oncogenes and tumour suppressor genes remain undruggable, including MYC, RAS and TP53. Several approaches are being explored to address these targets, including miniproteins that prevent MYC dimerization [28], allele-specific inhibitors that trap and inactivate mutant KRAS (G12C) [29] and small molecules that covalently bind to p53 to restore its normal (wild-type) function [30].

4. Cancer Types and Lipid Markers

Among various types of cancer, there is heterogeneity regarding the levels of total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol.

There are studies towards breast cancer, which claim that there is no difference in the levels of total cholesterol, between the groups of patients and healthy people [31] [32]. In other cases (cancer types), however, there was an increase in cholesterol with a statistically significant difference [33] [34] [35] [36]. The level increase is in some cases characterized as a prognostic indicator of the occurrence of this malignancy [37], as well as a reccurence after treatment [38]. Nevertheless, this is not detected in premenopausal women [39]. Finally, total cholesterol levels are found low after chemotherapy [40]. Regarding other parameters, an increase in triglycerides levels [32] has been reported among cancer patients and non-cancer patients [32], as well as a decrease in LDL [34] and a decrease in HDL [41] are observed. Other studies actually suggest that cancer is not accompanied by a significant difference in the levels of the above parameters [31] [32] [34] [35]. On the other side, chemotherapy does not affect triglycerides and HDL levels, but it seems to have a decreasing effect in LDL [40]. The number of chemo sessions does not appear to play a crucial role, as the results are similar. The increasing effect in triglycerides levels has been suggested as a prognostic factor [37] [38] [42] [43], while a similar interpretation is given for LDL [37] [43]. Correspondingly, low levels of HDL [42] [44] [45] are reported. Increased triglycerides levels have been suggested as an indicator of reoccurrence of the disease.

In ovarian cancer, it has been argued that there is no difference in total cholesterol and the lipoproteins HDL and LDL concentrations, between healthy and sick people [33].

In a large study by Lindemann *et al.* in 2009 [46], high conc. of triglycerides was suggested as a risk factor for endometrial cancer, but this was not the case for other lipid parameters. In endometrial cancer, total cholesterol levels rise and HDL [47] levels fall.

Concerning prostate cancer, data are limited, where the appearance of high triglycerides levels is suggested as a risk of reoccurrence after prostatectomy, while, there seems to be no difference for total cholesterol, HDL and LDL [48]. High triglycerides levels with low HDL levels, are also associated with disease severity [49], whereas high conc. of total cholesterol, triglycerides and LDL are associated with post-operative risk in patients with prostatectomy [50]. In addition, researchers have argued that the serum lipid levels of patients undergoing radical prostatectomy may not be associated with a risk of reoccurrence [51].

In small cell lung cancer as well as squamous epithelium, the of total cholesterol and HDL conc. are reduced [52] [53]. To this finding, low triglycerides values are added, but only for squamous cell carcinoma [49]. In small cell carcinoma there is also no statistically significant difference for the LDL [54]. The above findings relate to studies between healthy and patient groups.

In a study between among groups of healthy people and colorectal cancer pa-

tients, total cholesterol as well as LDL conc. were found to be lower in patients [55]. However, there was no statistically significant difference, for triglycerides and HDL [56]. People who had a relapse showed low blood serum levels for HDL. No statistically significant changes were found for TG and LDL [57] [58]. Very high triglyceride levels were associated with the prevalence of both non-advanced and advanced cases of colorectal adenoma, while high HDL levels were associated only with non-advanced cases [59].

4.1. Lp (a)

Lp (a) is produced exclusively by the liver and its catabolism appears to be involved in the kidney [60]. The normal role of LP (a) has not been fully elucidated. People who have low plasma levels do not perform any deficiency syndromes. Lp (a) high levels, however, are an independent prognostic factor for the development of cardiovascular atherosclerosis and peripheral arterial disease [61].

Wound healing, vascular remodeling and the promotion of tissue repair are among its normal functions. Indeed, Lp (a) accumulates in endothelial lesions, binds to various components of the vessel wall and sub-endothelial plexus, stimulates chemotactic activation of monocytes/macrophages and regulates angiogenesis [62].

Lp (a) and Cancer

Unfortunately, existing data for the association of lipoprotein *α* with cancer are both scarce and controversial [63]. Contans *et al.* attempted to assess Lp (a) levels and prostate cancer, suggesting that patients with high blood Lp (a) levels had a higher risk for developing aggressive disease in compared to those with low levels [64]. In a similar study, high Lp (a) values were associated with a higher risk of colorectal cancer [65].

In contrast, in hepatocellular carcinoma, the levels of Lp (a) were low [66]. This may be justified by the close relationship of Lp (a) with the liver, although high values have also been reported [67].

Patients with primary lung cancer showed significantly high levels of Lp (a). In addition, its positive correlation with stages I-III of the disease was proposed, as well as that of IV, but the patients had levels lower than stage III [68].

In breast cancer, a study showed that patients had higher levels than the no-patient group [68] [69]. Results that contrast with those of another study, where levels appear reduced [70]. In the case of the ovaries, the few elements present do not appear to affect lipoprotein *α* levels [71].

4.2. Resistin

Resistin belongs to the lipokines. Is a small protein with M.W. of 12 kDa [72]. Apart from fat cells, resistin is produced also by muscle cells, pancreatic cells, mononuclear cells and macrophages [73]. Its main actions in humans are related to immunity, inflammation and insulin resistance. Its inflammatory action is

mediated by the NF-κβ protein and seems to induce the expression of inflammatory cytokines (TNF-α, IL-6, IL-1, etc.) and adhesion molecules. Due to the fact that it is more expressed in adipocytes that penetrate adipose tissue, its levels are more likely to be associated with the inflammatory condition of the individual [74]. Thus, it has been implicated as one of the lipocytokines that can lead to the development of cancer. Resistin has been shown to link obesity to increased inflammatory status and the development of inflammation to subsequently affect tumor growth [75].

Resistin and Cancer

In comparative studies between groups of healthy and breast cancer, postmenopausal women, serum resistin conc. was statistically significantly measured higher in patients [76] [77] [78] [79]. Similar results were found in women who had not entered menopause [80]. This fact characterized the determination of resistance as a parameter of prognostic value. However, data from similar studies should not be ignored, with no a statistically significant difference, but refer to measurements made in the plasma of postmenopausal [80] or premenopausal [80] women. Nevertheless, the resistance was increased compared to the control groups. Higher levels of resistin were also found in patients with breast cancer and high body mass index, compared to healthy and similar index [81] [82]. However, in none of the above cases, the body mass index was linked as a primary factor for the appearance of high levels of resistance.

Increased serum resistin may be a risk factor for developing colorectal cancer. In a study among healthy and patients, resistin levels were found to be significantly higher in patients with colorectal cancer without any association with the stage or location of the lesion [83]. On the contrary, a connection with the stage was seen in the study of Nakajima *et al.* in 2010 [84]. In another study between healthy and patients, resistin conc. was found significantly higher in patients with colorectal cancer [85]. As in the case of breast cancer, no correlation between high levels and body mass index was detected.

In cases of gastroesophageal cancer, serum resistin values were found higher in the diseased group compared with the healthy group [86].

4.3. Visfatin

Visfatin is another small lipokine of 52 kDa, which is expressed almost exclusively in adipose tissue and its levels are increased during the differentiation of prolipocytes to mature adipocytes. It was first discovered as a growth factor of early B-lymphocytes (PBEF) (pre-B cell colony-enhancing factor) by Samal *et al.* [87]. Apart from its expression in bone marrow, liver and skeletal muscle, visfatin was also found in large quantities in visceral adipose tissue. Similar to visfatin is Nampt (nicotinamide phospho-ribosyl-transferase) which was first discovered by Preiss *et al.* in 1957 [88]. The correlation between the molecular indentification of the growth factor PBEF and Nampt, was later made by Rongvaux *et al.* [89]. Nampt was eventually renamed to visfatin. It is involved in various pro-

cesses such as the immune cell signaling (PEBF form) [90], the insulin mimicking [91] and the biosynthetic pathway of NAD (Nampt form) [92]. Recent studies suggest that visfatin is mainly expressed in macrophages that infiltrate adipose tissue [93]. It is therefore possible that visfatin is released by macrophages in response to inflammatory stimuli, rather than adipocytes. It acts as an insulin-repellent protein, since, its intravenous administration can decrease glucose levels without affecting insulin levels. Visfatin acts by binding to different region of insulin receptor itself, thus activating the insulin pathway and signaling the uptake of glucose by adipocytes. Furthermore, it activates the differentiation of fat cells, increases the production of triglycerides from glucose, while increasing the gene expression of PPAR-*γ*, fatty acid synthase, diacyl-glycerol acyltransferase and antiponectin [94].

Visfatin and Cancer

In several studies, performed in breast cancer patients, serum levels were found, higher in pre-treatment patients than in control group [76] [77] [95]-[100]. This finding suggests that the detection of serum visfatin can be considered a diagnostic parameter, for the occurrence of breast cancer. Considering if the participants were pre- or post-menopausal cases, visfatin levels were significantly higher in postmenopausal patients, in comparison with the controls [76] [77] [95] [96] [97] [101], while in premenopausal patients serum visfatin was found either slightly increased [101] or without any statistically significant change [99]. The prognostic value of visfatin is shown by the fact that patients who passed the disease and survived for a long time, had low levels of this lipokine [76] [99], as well as by the fact that its levels were lower after surgery, in comparison to women before surgery [100].

In endometrial cancer, visfatin conc. is detected higher in patients compared to control group [101] [102] [103] [104] [105]. In addition, high levels of visfatin are associated with both disease recurrence and a short patient survival time, along with the poor prognosis [101] [103] [105].

In colorectal cancer, visfatin levels are detected higher in patients than in the control group. Additionaly, to the above results visfatin high conc. is found to gradually related on tumor evolution [106] [107]. According to these results, it can be said that visfatin may be proved as a good future biomarker of colon cancer.

As for hepatocellular carcinoma, Yifan et al, found that serum visfatin in patients was detected higher than in the control group [108]. They also found that high levels of visfatin could be associated with a high risk of developing hepatocellular carcinoma as well as tumor size and disease stage [108], a finding supported and enforced by the results of another study [109]. Similar findings were also registered for gastric cancer by Lu *et al.* [110].

Preliminary results, concerning lymphoblastic leukemia showed that the most frequently observed disorder was the significant reduction of HDL and the elevation of LDL. These measurements seem to recurrent to normal values, during remission [111].

Table 1. Changes of total cholesterol, HDL, LDL, TG, Lp (a), resistin and visfatin serum conc. in several types of cancer. (*Survival for a short time-bad prognosis).

		Total holesterol	Triglycerides	HDL	LDL	Lp (a)	Resistin	Visfatin
Ca breast	premenopause	↑ 33 - 36	↑ 32	↓ 41	↑ 34	↑↓ 68, 69 but 70	↑ 78	↑ 76, 77, 96 - 101
	postmenopause	↑ 33 - 36	↑ 32	↓ 41	↑ 34	↑↓ 68, 69 but 70	↑ 76 - 79	↑ 76, 77, 96 - 100
	chemotherapy	↓ 40			↓ 40			
	bad prognosis*	↑ 37	↑ 36, 38 - 40	↓ 42, 44, 45	↑ 37, 43		↑ 76 - 79	↑ 76, 99, 100
	return	↑ 38	↑ 37, 38, 42, 43					
Ca gastric	disease	↓ 55			↓ 55		↑ 83	↑ 84, 107
	bad prognosis*			↓ 57, 58				
	return					↑ 65		
Ca prostate	prostatectomy	↑ 48	↑ 48		↑ 48			
	seriousness		↑ 49	↓ 49				
Ca ovaries	disease							↑ 101 - 105
	bad prognosis*							↑ 102, 103, 105
	return	↑ 47	↑ 46	↓ 47				↑ 102, 103, 105

5. Results and Conclusions

Table 1 shows in abstract existing data, regarding increase/decrease values of total cholesterol, HDL, LDL, TG, Lp (a), resistin and visfatin serum conc. in relation to breast, gastrointestinal, prostate and ovaries cancers/stages (bibliography in numbers).

In summarizing, bibliography survey, so far, showed that serum levels for total cholesterol, triglycerides and HDL and LDL fractions, differ between different types of cancer. Furthermore, no one-size-fits-all pattern, that can be directly matched to any form, is observed. Thus, it can be that it is not yet possible to fully link these increased or decreased values, regarding the occurrence, prognosis, risk or recurrence of the disease. Nevertheless, these data can be used as auxiliary indicators, taking into account the individuality of each patient, with the notorious complexity of the disease, expecting in which or which of these parameters significant changes will be observed. Lp (a) few findings should be, still under careful re-examination. As a final crucial point, more research has still to be done, due to the fact that the controversy over detected lipid changes in cancer remains unclear, while present data on resistin and visfatin can be considered, so far as reliable indicators both as potential diagnostic and prognostic biomarkers.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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