

# Cholesterol Metabolism in Patients with Gastric Cancer

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## Abstract

Gastric cancer is one of the leading causes of death in the world among cancer diseases. Frequently, the asymptomatic course of the disease and the deficit in screening are the cause of late diagnosis. The implication of this is a drastic reduction in the effectiveness of treatment due to the presence of distant metastases. The cholesterol metabolism disorders have been observed in patients with gastric cancer for years. There are significant changes in the level of lipid parameters that can be attributed to prognostic significance in gastric cancer. Alignment of cholesterol metabolism disorders can have a positive effect on the treatment, and learning about its mechanisms may allow to set new therapeutic goals. This review article reviews literature data on lipid profile in patients with gastric cancer prior to surgery and after gastrectomy. The influence of changes in cholesterol metabolism on the therapy and course of the disease was also discussed.

**Key words:** Cholesterol; Metabolism; Gastric Cancer

## Introduction

The importance of cholesterol metabolism in the development of cancer is considered for a long time. Already at the beginning of the 20th century cholesterol was observed to accumulate in cancer cells. White [1] suggested then that this could have an effect on the regulation of cell proliferation. In the 1970s, it was noticed that since sterol synthesis is required in normal conditions for cell proliferation, disturbances in sterol synthesis may contribute to uncontrolled proliferation, i.e. the development of a malignant state [2]. Since then - in the scientific community - one can observe an increase in interest in the role of cholesterol metabolism in the process of neoplastic transformation.

The presence of cholesterol - a component of plasma membranes - is essential for maintaining the proper conditions of the internal environment of cells. Various regulatory pathways are involved in maintaining optimal cholesterol levels [3-6]. Cholesterol influences the dynamics of the structure of plasma membranes, regulates their fluidity. The degree of fluidity of the cell membrane depends on which molecules can diffuse through it. As a consequence, this is about cell homeostasis. Cholesterol also regulates lipid rafts - signal platforms contained in plasma membranes. Modifications of lipid rafts components are

important for cell viability in their response to cytotoxic stimuli [7, 8]. In addition, cholesterol plays an important role in the human body, as a precursor in the synthesis of vitamin D, sex hormones and steroid hormones in the adrenal cortex. Being a component of bile salts, it participates in the process of digestion of fats and absorption of vitamins soluble in them [8, 9]. The cholesterol also acts as a mediator in inflammatory processes and promotes cell migration, which is why it can be considered as one of the factors contributing to cancer transformation [10]. The source of cholesterol is diet and de novo synthesis, which takes place mainly in the liver. Due to lipophilicity, cholesterol is transported in plasma inside lipoproteins of different density (chylomicrons, VLDL, IDL, LDL, and HDL). Lipoproteins - synthesized in the liver and intestine - are carriers of lipids from the intestine to the liver and between the liver and the body's cells [3, 11]

Cancer cells show altered cellular metabolism, adapted to their increased metabolic requirements and achieve the goal of uncontrolled proliferation and the acquisition of malignant traits [12-14]. In the last few years, disturbances of lipid homeostasis in cancer cells, which undergo intensive cell divisions, use cholesterol for their growth are more and more observed [15-17]. Numerous studies have shown the relationship between disorders of lipid metabolism and the onset and progression of tumors, among others lung, prostate, breast, brain, liver, ovary, colon and stomach. An inverse relationship was observed between total cholesterol and the risk of some cancers, depending on their location and type [18, 19]. The results of research carried out by Lim et al. [20] suggest that cholesterol may be a signal regulator in modulating cell viability in gastric cancer; and normal levels of cell cholesterol may promote inhibition of carcinogenesis within this organ.

Stomach cancer is in the second place among cancer diseases that cause death in the world [21]. High mortality in patients is associated with malignancy of this cancer and late diagnosis. Usually metastases in distant organs are present at the time of diagnosis - most often in the liver, lungs and bones. Due to the detection of gastric cancer in the advanced, inoperable phase, only 20% of patients have a 5-year survival. Such statistics are initially facilitated by the asymptomatic nature of the ongoing cancer process and the deficit in screening [22, 23]. Numerous

risk factors for gastric cancer are known, however the etiology of this cancer remains insufficiently clarified. Cancer transformation in the stomach is supported by a salt-rich diet, nitrites, smoked and preserved products, hot meals, as well as smoking, alcohol, obesity, and persistent infection with *Helicobacter pylorii* [22-25].

Also interesting is the importance of the occurrence of metabolic syndrome for the development of gastric cancer. Wei et al. [26] showed that the metabolic syndrome is associated with a better differentiation of tumor cells in patients with early stage gastric cancer. Metabolic syndrome has been recognized as a significant, independent and beneficial prognostic factor for survival in elderly patients (> 50 years) or in the early stage of cancer [26].

According to the researchers, hyperlipidaemia may decrease cellular immunity and lead to neoplastic transformation [27]. It has been found that disturbances of lipid metabolism negatively affect DNA repair mechanisms and, as a consequence, promote tumor growth. Therefore, it is suggested that in the prophylaxis and treatment of cancer, nutritional and pharmacological measures to correct cholesterol metabolism disorders should be used [28].

Gastric dysplasia is often the stage preceding carcinogenesis within this organ [29]. Jung et al. [30] demonstrated that elevated LDL-C is associated with a greater risk of gastric dysplasia. Zhou et al. [31] found, however, that the measurement of low density lipoproteins (LDL) may be useful in predicting the chemical sensitivity of locally advanced gastric cancer to the use of NAC (neoadjuvant chemotherapy). Kim et al. [32] also emphasized that hypercholesterolemia is a risk factor for the occurrence of gastric dysplasia, and therefore the control of the lipid profile may be of protective importance for gastric cancer.

### Lipid profile in patients with gastric cancer before surgery

There are discrepancies between the results obtained so far, however, it is suggested that the serum cholesterol level is one of the factors affecting the risk of gastric cancer [33, 34]. What's more, the researchers point to a clear inverse relationship between the total cholesterol (TC) level and the incidence and mortality from gastric cancer [33,35].

Zhou et al. [36] conducted an analysis regarding the prognostic significance of lipid parameters in neoplastic transformation. In their studies, they determined that the values of TC and HDL-C concentrations are significantly related to the survival time of patients with cancer. They noticed that the survival time - in people with higher HDL-C levels - was longer and the risk of relapse after treatment was lower [36]. HDL lipoproteins have anti-inflammatory and antioxidant properties, which is why they can play a protective role in the body before neoplastic transformation [37-39]. In the same studies, it was shown that elevated LDL lipoprotein levels, resulting from increased cholesterol transport to tissues, can be considered as a prognostic factor increasing the risk of metastases in cancer, which is also confirmed by other authors [19, 36, and 40].

Tamura et al. [41] in a retrospective study of a group of patients before gastrectomy showed a positive correlation between low pre-operative HDL-C levels in serum and prognosis in patients with gastric cancer. The researchers also found that the prognosis of patients who had HDL-C levels within the reference limits before the resection was significantly better than in the group of patients with decreased HDL-C pre-operatively. In addition, significantly increased lymphatic and vascular invasion was noted in patients with decreased HDL-C. Based on the conducted studies, it was suggested that serum HDL-C may be a clinical prognostic factor in the treatment of gastric cancer [41].

Guo et al. [42] performed a retrospective study on a group of 501 patients with gastric cancer prior to surgical treatment, in which they showed a relationship between decreased HDL-C concentration and high TC / HDL-C index and the stage of disease severity - degree of involvement of lymph nodes. It was noted that patients with lymph node metastasis are characterized by significantly lower HDL-C levels than those with metastatic gastric cancer. Researchers found that in patients with gastric cancer, pre-operative low serum HDL-C or a high ratio of TC / HDL-C are independent risk factors and potential biomarkers for the advanced stages of pN2-3, especially in patients with a histologically diverse type of gastric cancer [42].

In another study, Kitayama et al. [43] noted that the incidence of lymph node metastases is significantly higher in patients with early gastric cancer with present hypercholesterolemia (TC 220 mg / dl or more) or hypertriglyceridemia (TG 150 mg / dl or more). This dependence mainly concerned men. It was recognized that hypertriglyceridemia may be an independent risk factor for lymph node metastasis in this group of patients. Finally, it was found that hyperlipidemia may be conducive to the development of lymph node metastases in men in the early stage of gastric cancer [43,44].

### Lipid profile in patients with gastric cancer after gastrectomy

Lee et al. [45] analyzed changes in metabolic parameters in patients with early gastric cancer (EGC) after gastrectomy. All subjects had a decrease in body weight, significant decrease in triglycerides and LDL-C levels and a significant increase in HDL-C levels. It has been found that gastrectomy in patients with EGC reduces mortality in these patients for cardiovascular reasons [45].

In other studies, Lee et al. [46] showed that total resection of the stomach compared to subtotal resection has a greater impact on changes in the lipid profile. On the basis of the conducted tests, it was found that patients after resection show a decrease in body weight, a decrease in TC, LDL-C and an increase in HDL-C. In contrast, the concentration of TG does not change. The observed changes were more pronounced in patients after total gastrectomy [46].

In the light of the presented studies, it seems necessary to clarify the relationship between changes in the lipid profile after gastrectomy and recurrence of the disease or metastases.

## The role of apolipoprotein AI in neoplastic transformation

Apolipoprotein AI (apoAI) is the major protein of high density lipoproteins (HDL). It makes it possible to maintain normal homeostasis of cellular cholesterol by taking part in the removal of cholesterol from peripheral tissues. It has also been proven that apoAI has anticancer activity - affecting the immune system, it causes regression of tumor and distant metastases [47].

The antitumor effect of apolipoprotein AI has been observed in studies of various types of cancer, including gastric cancer [47, 48]. One of the hypotheses explaining the anti-tumor effect of apoAI / HDL indicates the ability of these molecules to influence signaling pathways by modulating the content of cholesterol in lipid rafts of immune cells or cell membrane [49].

HDL lipoprotein and apoAI have the ability to control the rate of carcinogenesis and immunomodulatory properties, which slow down the proliferation of tumor cells, reduce neoangiogenesis and the extent of metastasis [47,49]. The introduction of apoAI determination to routinely performed tests may also be important for predicting the course of the disease in people with gastric cancer.

## Conclusions

In patients with gastric cancer, cholesterol metabolism disorders are observed. According to the aforementioned scientific reports, the values of certain lipid parameters and calculated lipid parameters can be considered as prognostic factors in gastric cancer.

Cholesterol control used in the prevention and therapy of gastric cancer, aimed at taking corrective actions of abnormalities, may contribute to the effectiveness of the therapy. Examination of the lipid profile - both before and after treatment can be important in predicting the course of the disease. Accurately investigating and identifying the mechanisms responsible for abnormal cholesterol metabolism in patients with gastric cancer can allow a deeper explanation of the etiology of this disease and understanding of potential therapeutic goals.

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