sciendo

J Biomed Clin Res Volume 12 Number 2, 2019

DOI:10.2478/jbcr-2019-0013

Review

THE ROLE OF CHOLESTEROL IN ASSESSING THE CONDITION OF THE SURGICAL PATIENTS

Ralitsa P. Stavrova-Hristova

Department of Anesthesiology and Intensive Care, UMHAT "G. Stranski"- Pleven

Summary

Cholesterol is a white, waxy substance that always takes part in building each cell in the human body. The role of cholesterol in the normal functioning of the human body has been known for a long time, however, it is mainly due to its elevated levels and the health risk of it. It is less well known that low serum cholesterol levels are associated with serious health problems. When it comes to intensive care unit (ICU) patients, hypocholesterolemia may indicate infectious complications, impaired hepatic synthesis, significant bodily injury. Surgical patients are judged for operative trauma and perioperative stress, as well as for the resuscitation process.

Key words: hypocholesterolemia, perioperative stress, surgical patients

Introduction

Cholesterol is a white, waxy substance that always takes part in building each cell in the human body. The role of cholesterol in the normal functioning of the human body has been known for a long time, though more attention is paid to cholesterol levels higher than normal and their association with health risks. It is less well known that low serum cholesterol levels are associated with serious health problems.

Regarding ICU patients, hypocholesterolemia may be related to infectious complications, impaired hepatic synthesis, and significant bodily injury. Surgical patients are assessed for operative trauma and perioperative stress, as well as for the resuscitation process.

The aim of this comprehensive review was to summarize data on the role of cholesterol as a predictor of severity of perioperative stress and prognosis. The biochemical aspects and the regulatory and physiologic role of cholesterol in stress conditions are discussed.

Term and Definition of Cholesterol

Cholesterol comes from Greek (chole – bile and stereos – solid). It was first identified in gallstones in 1769, by François Poulletier de la Salle, but its name was given in 1815 by Michel Eugène Chevreul (1786-1889), who called it cholesterin. Later, in 1859, Marcelin Berthelot (1827-1907, 79) proved its alcoholic structure and the name was changed to cholesterol. Now both cholesterol

Corresponding Author:
Ralitsa P. Stavrova-Hristova
Department of Anesthesiology and Intensive Care, UMHAT "G. Stranski" – Pleven
Bulgaria
e-mail: rstavrova@abv.bg

Received: August 04, 2019
Revision received: December 01, 2019
Accepted: December 02, 2019

and cholesterin are used [1-3]. From a chemical point of view, calling the substance "cholesterol" is correct, since it is a polycyclic alcohol [1].

Structure of cholesterol

Cholesterol is an organic molecule. By its structure, it is a polycyclic alcohol (Figure 1). It is a sterol, or a modified steroid, a type of lipid molecule, found in all animal cells.

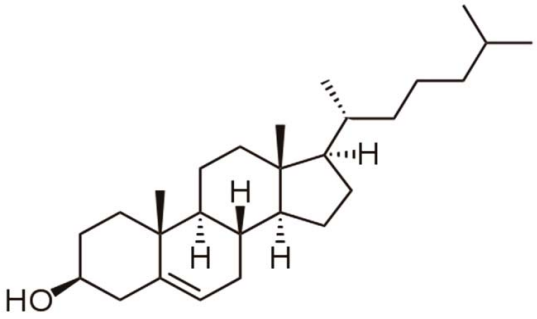

Figure 1. Cholesterol. Chemical structure.

Function of cholesterol

Cholesterol is a vital compound, found in all tissues of the human body. It is essential for the structure of cell membranes and myelin sheaths of nerve cells [4]. It is also the precursor molecule for the synthesis of steroid hormones, bile acids and Vitamin D [5].

Biosynthesis of cholesterol

There are two types of cholesterol in the organism: exogenous and endogenous. Exogenous cholesterol enters with plant-based nutrients, around 400-500 mg (plant-based sterols cannot be digested by the gastrointestinal tract) and is around 20% of the total cholesterol in the human organism. The other 80% are endogenous, i.e. they are synthesized by the organism itself, 9-12 mg/kg [6]. Cholesterol is mainly synthesized in the liver – 1 gram/day [7], the small intestine, adrenal gland, gonads, and the skin.

Cholesterol synthesis is a complex process, which can shortly be presented in the following way (Figure 2.).

Synthesis of cholesterol is carried out in the cytoplasm, with acetyl coenzyme A (acetyl CoA), Nicotinamide adenine dinucleotide phosphate (NADH) and Adenosine triphosphate (ATP) needed in significant amounts. The process starts with 2 molecules of acetyl CoA, condensing to form acetoacetyl-CoA. It binds to a third molecule acetyl CoA, and β-Hydroxy β-methylglutaryl-CoA is formed. The reaction is catalyzed by β-Hydroxy β-methylglutaryl-CoA synthase [8,9].

The next reaction is irreversible and rate-limiting. It is catalyzed by the enzyme β-Hydroxy β-methylglutaryl-CoA reductase, and mevalonate is produced from β-Hydroxy β-methylglutaryl-CoA reductase [8,9]. Six molecules of mevalonate condense to form squalene: the process begins with a 2-step phosphorylation of mevalonate. Those reactions are catalyzed by two phosphokinases, and 2 ATP molecules are needed. The product is activated mevalonate - mevalonate pyrophosphate(8). The next reaction also requires one molecule of ATP – isopentyl pyrophosphate (also called active isoprene) is formed under the effect of the enzyme diphosphomevalonate decarboxylase.

Isopentyl pyrophosphate converts to dimethyl pyrophosphate with the help of isopentyl pyrophosphate isomerase [10]. The next step

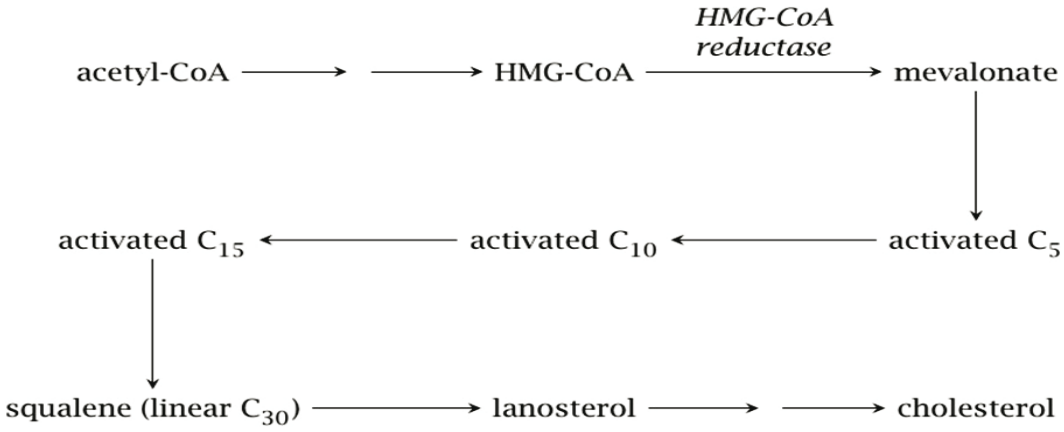

Figure 2 Cholesterol synthesis (5)

of the squalene formation is the condensation of isopentyl pyrophosphate with dimethylallyl pyrophosphate, to form geranyl pyrophosphate. As shown in Figure 3, it condenses with another molecule isopentyl pyrophosphate and forms farnesyl pyrophosphate. When two molecules farnesyl pyrophosphate condense, squalene is formed [11].

Under the effect of the enzyme squalene monooxygenase and in the presence of O2, NADPH and soluble protein activator, 2,3-oxidosqualene is formed from squalene. With the help of another enzyme, also found in the endoplasmic reticulum – 2,3-oxidosqualene-lanosterol cyclase, lanosterol is formed (Figure 4) [8,10].

Conversion of lanosterol into cholesterol includes 20 consecutive reactions. Enzymes that take part in those reactions are located in the endoplasmic reticulum [10].

Regulation of cholesterol synthesis

Cholesterol synthesis and degradation take place in the liver, bile ducts and mucous membrane of the small intestine [7].

In cholesterol synthesis, conversion of 3-hydroxy-3-methylglutaryl-CoA in mevalonate is an irreversible and rate-limiting reaction. It is catalyzed by the enzyme HMG-CoA reductase (HMGCR) [12], i.e., the mechanisms that take part in regulating this enzyme's activity have a key significance for defining the speed of

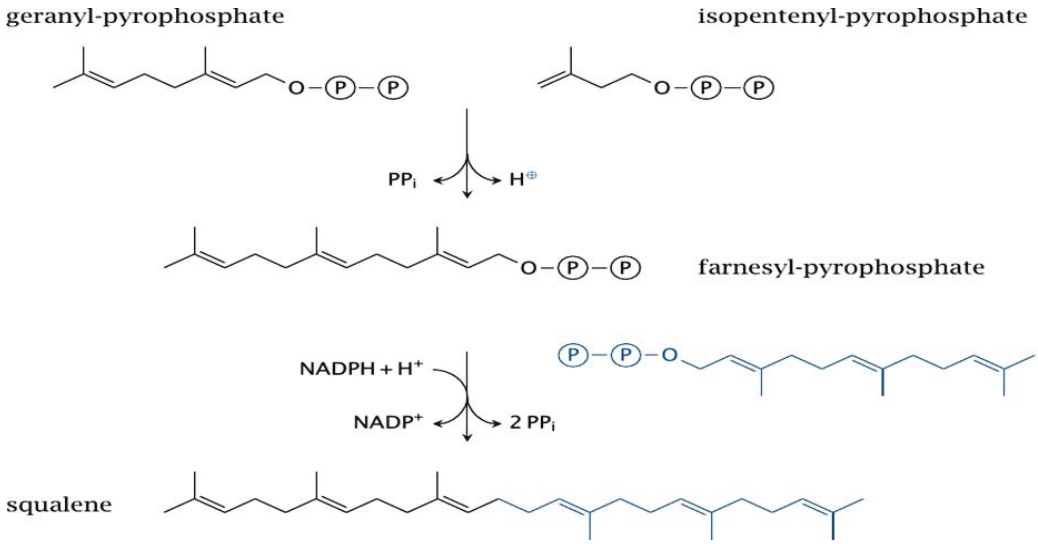

Figure 3. Formation of intermediate compounds with 15 and 30 carbon atoms (5)

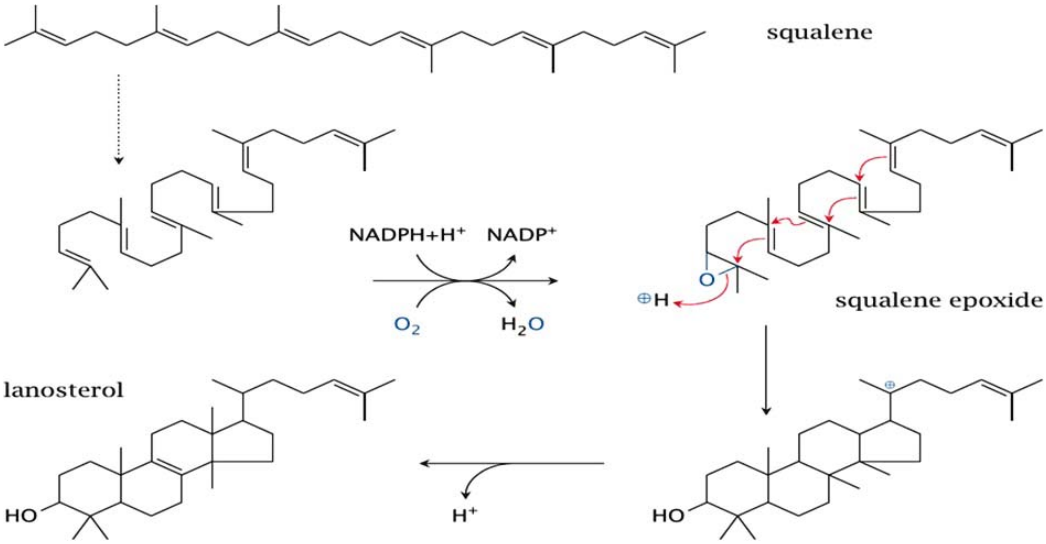

Figure 4. Formation of the first intermediate sterol compound.(5)

cholesterol synthesis.

Inactivation of 3-hydroxy-3-methylglutaryl-CoA reductase has a half-life of 3 hours, and its half-life depends on cholesterol level, i.e. if the level is high, the enzyme has a shorter half-life(10) . Degradation of HMGCR is also stimulated by oxidized derivatives of cholesterol, bile acids, mevalonate and farnesol [7,13,14]. Some hormones also affect the activity of this hormone. Insulin and thyroid hormones activate it, glucocorticoids and glucagon suppress it [7,15].

The level of cholesterol controls the quantity of messenger ribonucleic acid (mRNA), which codes HMGCR. If the cholesterol level is high, the quantity of mRNA is reduced [10].

Excess intracellular free cholesterol is regulated by a change of activity of acyl-coenzyme A:cholesterol acyltransferase (ACAT) [8].

The level of plasma cholesterol is regulated by low-density lipoprotein (LDL) receptors-related intake and high-density lipoprotein (HDL)-receptors-related reverse transport [8].

Exogenous cholesterol intake inhibits the liver sterol synthesis at the level of the HMG-CoA conversion to melavonate. Continuous intake of cholesterol, however, suppresses liver sterol synthesis in the following steps, after mevalonate synthesis [14].

Cholesterol is the main substance for higher eukaryotes, including those in humans. It is a component of the cell membranes and is important for their stability, fluidity and permeability [16]. It is a precursor of oxysterols, steroid hormones, including estrogen, progesterone, testosterone and cortisol, and also of Vitamin D and bile acids[12]. Cholesterol is irreplaceable for the normal development of the brain. It is also necessary for the formation of myelin, synapses and dendritic branches of the nerves [12]. Furthermore, cholesterol is important for the absorption of nutrients, reproductive biology, stress response, electrolyte balance and calcium metabolism [17]. In the plasma, around one-third of cholesterol is free, and two-thirds are in the form of esters. Some intermediate products such as steroids and signal proteins play a key regulatory and mediatory role [18].

Cholesterol is a vital compound for the human organism, but both hypocholesterolemia and hypercholesterolemia are linked to the presence of a disease [16]. Cholesterol taken with the food is absorbed by the intestines and included in chylomicrons, which are synthesized by the intestinal mucous membrane. From there it is transferred to the liver. The liver and other tissues also synthesize cholesterol. Part of the cholesterol is excreted with the bile and resorbed again by the intestinal mucous membrane. The greater part of cholesterol in the liver is bonded with proteins – lipoproteins with very low density and, in the form of those complexes, circulates the bloodstream [19]. The cholesterol molecule is hydrophobic, and to be delivered to all cells in the body, it needs to bond with special macromolecules in the plasma – lipoproteins (chylomicrons, very low-density lipoprotein (VLDL), LDL, HDL). The LDL-cholesterol complex circulates from the liver to all organs and tissues and delivers the cholesterol they required. Excess cholesterol, in the form of HDL complexes, is transported back to the liver. In case of dysfunction in cholesterol metabolism, it is possible that cholesterol from the LDL-cholesterol complex is not assimilated by the cells or is released from the complex too early [10,20]. Cholesterol can be oxidized, which can form cholesterol oxidation products. Those products are responsible for diseases like atherosclerosis, not the cholesterol itself. Excess cholesterol oxidation products lead to a change in the stability and permeability of the cell membrane, which makes the latter susceptible to cytotoxic, mutagenic, carcinogenic and atherosclerotic changes [16]. Conditions like Smith-Lemli-Opitz syndrome, Niemann-Pick type C, Alzheimer's disease are linked to metabolic disorders [12].

When we speak of cholesterol and its link to problems and diseases, most people think of hypercholesterolemia, while in reality, a big part of patients in surgical wards, intensive care units and traumatology departments have low levels of serum cholesterol. Furthermore, the lower the values, the longer is the hospital stay, more often, the infectious complications are present and the outcome is worse. Hypocholesterolemia is also related to worse outcome or infectious complications in trauma, burns and sepsis [18]. Cholesterol lowers in the first post-operative day due to the acute phase reaction. Vyroubal. et al. (2008) reported that none of the patients with cholesterol that dropped under 1.6 mmol/l

survived. Cholesterol has an important role in maintaining immunity and protection against different infections in critical patients [21]. Cholesterol is the main precursor for the steroid synthesis in the adrenal medulla, where there is no cortisol reserve. Therefore, in the case of prolonged hypocholesterolemia, there may be insufficient cortisol production [22].

Cholesterol is often one of the routine tests for elderly patients and is used as a marker for malnutrition and poor health status [23]. Authors believe that hypocholesterolemia, seen after abdominal surgery, is usually caused by infusion of water-electrolyte solutions and by the hemodilution. Other reasons for low levels of plasma cholesterol include surgical stress, reduced or missing intake of nutrients and more importantly, fats, as well as reduced liver cholesterol synthesis and liver and intestinal synthesis of low-density lipoproteins.

Surgery is not just a local tissue trauma but also leads to metabolic and hormonal changes in the organism, which can be designated as postoperative disease or post-aggression syndrome [24]. Different phases can be defined, depending on the stage of trauma, the onset of postoperative complications and the patients' reaction to treatment. The observed hypocholesterolemia [25-27] is related to reduced LDL amounts, but also a lower level of HDL. Therefore, there is a correlation between the severity of surgical intervention and the rapid reduction of cholesterol-containing lipoproteins in the serum. Researchers have concluded that hypocholesterolemia is not a result of hemodilution or insufficient nutrient intake,and such a conclusion is also confirmed by the test results of triglycerides, hematocrit and albumin. They also observed a reduced half-life of lipoproteins, which more likely points towards redirecting of lipoproteins to traumatized tissues for the regeneration of water-insoluble membranes and wound healing [24].

Hypocholesterolemia is seen in patients after severe trauma, surgery, multi-organ failure, and burn injuries. Results reported by many authors confirm that cholesterol levels correlate with the severity of organ damage and the presence of sepsis. This is mainly explained by the reduced synthesis in the liver, hemodilution, loss of lipoproteins and accelerated metabolism [23,28,29]. Hypocholesterolemia in surgical patients in critical condition is related to the reduced liver protein synthesis [30,31].

Hypocholesterolemia is seen not only after surgery, but also after trauma, sepsis, burn injuries and liver dysfunction [32,33]. Lee et al. (2018) observed significantly more pronounced hypocholesterolemia in the beginning of the study in deceased patients and following reduction of the values of serum cholesterol on the following days in the same patients, while for patients who got better, after the initial hypocholesterolemia, a gradual increase of the serum levels of cholesterol was found [32,34]. Hypocholesterolemia is a prognostic marker for increased morbidity and mortality in a variety of pathological conditions [21]. Hypocholesterolemia can be used as a predictor for early hospital mortality even before the clinical events occur [32].

Bakalar et all. (2003) studied the changes in cholesterol and its precursors on the first days after severe traumas [35]. Hypocholesterolemia was found as a prerequisite for prolonged mechanical ventilation, increased risk of infections, multi-organ failure and prolonged hospital stay. Cholesterol synthesis is an energy-dependent process, which consists of around 200 enzyme steps. Many tissues produce cholesterol – skin, intestines, adrenal gland, adipose tissue, while the liver is capable of secreting cholesterol in the blood in the form of lipoproteins. Authors suggest that hypocholesterolemia may occur as a result of reduced cholesterol synthesis in the first days after the trauma. This may be due to the complexity of the synthesis, sensibility of some of the enzymes and the prevalence of catabolic processes with high production of hormones with antilipogenic effect. Other authors reached the same conclusion: the liver has a key role in cholesterol homeostasis, and hypocholesterolemia after trauma and surgery is caused by temporary liver function failure [29, 36]. These were also our observations on patients with trauma affecting the liver [37].

Our observations on traumatically ill patients indicated that determining cholesterol levels is essential for assessment of the severity of the trauma and choosing its treatment. Plasma cholesterol lowering in patients with multiple traumas below the age of 50 may be considered a poor prognosis. In patients older than 50 years, this indicator is less informative [37]. Also, the positive dynamics of cholesterol in patients with

trauma indicates a favorable clinical outcome of the trauma [37].

In acute trauma there is a temporary decrease in cholesterol levels. The more severe the damage and therefore the greater the stress on the body, the lower these levels are, and the harder it is for the body to cope with stress. The lower the compensatory reserves, the lower the values, and the longer these values remain [37].

The dynamics of changes in cholesterol levels testify to the severity of the trauma and are a predictive sign of its outcome. Early restoration to normal cholesterol values may be one of the signs that a recovery process has started [8].

Conclusions

Cholesterol is a key element in the construction and support of the cell membrane, and is irreplaceable in the development of the nervous system. It is necessary for the synthesis of steroid hormones, bile acids and Vit. D. In patients, who underwent surgery and patients in intensive care, monitoring the dynamics of serum cholesterol levels allows to evaluate the recuperative process. Cholesterol levels can be used as an additional source of information about the severity of the patient's condition, the presence or likely occurrence of complications, and the outcome of the disease.

References

1. Cholesterol. MedlinePlus. [cited 2019 Jul 27]. Available from: https://medlineplus.gov/cholesterol.html
2. Cholesterol. Wikipedia, The Free Encyclopedia. [cited 2019 Jul 27]. Available from: https://en.wikipedia.org/wiki/Cholesterol
3. Cholesterin. Wikipedia, The Free Encyclopedia. [cited 2019 Jul 26]. Available from: https://de.wikipedia.org/wiki/Cholesterin
4. Ma H. Cholesterol and human health. Nat Sci. 2004;2(4):17-21.
5. Cholesterol metabolism [Internet]. [cited 2019 Jul 26]. Available from: http://watcut.uwaterloo.ca/webnotes/Metabolism/Cholesterol.html
6. Šmahelová A, Hyšpler R, Haas T. Relation of cholesterol metabolism and non-cholesterol sterols to insulin resistance. Physiol Res. 2007;56(6):749-55.
7. Severin ES, ed. [Biochemistry]. Moscow: GEOTAR –MED; 2004. Russian
8. Omoigui S. The Interleukin-6 inflammation pathway from cholesterol to aging - Role of statins, bisphosphonates and plant polyphenols in aging and age-related diseases. Immun Ageing. 2007;4:1-22.
9. Argirova T, ed. [Lectures on medical biochemistry]. Sofia: Medical University - Sofia; 2010. Bulgarian
10. Moss D. Pressure Vessel Design Manual. 3rd ed. Oxford: Elsevier; 2004.
11. Yeagle P, editor. Biology of cholesterol. CRC Press: Boca Raton, FL; 1988.
12. Orth M, Bellosta S. Cholesterol: Its Regulation and Role in Central Nervous System Disorders. Cholesterol. 2012;2012:1-19.
13. Voet D, Voet JG. Biochemistry. 4th ed. John Wiley & Sons; 2010.
14. Feingold KR, Wiley MH, MacRae G, Siperstein MD. The effect of decreased plasma cholesterol concentration on circulatinga mevalonate metabolism in rats. J Lipid Res. 1981;22(6):990-7.
15. Shin DJ, Osborne TF. Thyroid Hormone Regulation and Cholesterol Metabolism Are Connected through Sterol Regulatory Element-binding Protein-2 (SREBP-2). J Biol Chem. 2003;278(36):34114-8.
16. Vicente SJV, Sampaio GR, Ferrari CKB, Torres EAFS. Oxidation of Cholesterol in Foods and Its Importance for Human Health. Food Rev Int. 2012;28(1):47-70.
17. Tabas I. Cholesterol in health and disease. J Clin Invest [Internet]. 2002;110(5):583-90.
18. Porter JA, Young KE, Beachy PA. Cholesterol modification of hedgehog signaling proteins in animal development. Science. 1996;274(5285):255-9.
19. Maxfield FR, Tabas I. Role of cholesterol and lipid organization in disease. Nature. 2005;438(7068):612–21.
20. Suter PM. Checkliste Ernährung. 3rd ed. Georg Thieme Verlag; 2008.
21. Vyroubal P, Chiarla C, Giovannini I, Hyspler R, Ticha A, Hrnciarikova D, et al. Hypocholesterolemia in clinically serious conditions--review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2008;152(2):181-9.
22. Yamano S, Shimizu K, Ogura H, Hirose T, Hamasaki T, Shimazu T, et al. Low total cholesterol and high total bilirubin are associated with prognosis in patients with prolonged sepsis. J Crit Care. 2016;31(1):36-40.

23. Sun X, Oberlander D, Huang J, Weissman C. Fluid resuscitation, nutritional support, and cholesterol in critically ill postsurgical patients. J Clin Anesth. 1998;10(4):302-8.
24. Aufenanger J, Walter H, Kattermann R. Untersuchungen zum Lipid-und Lipoproteinstoffwechsel beim Menschen nach operativen Eingriffen. Langenbecks Arch Chir, 1993;378(1):41-8
25. Eriksen N, Benditt EP. Trauma, high density lipoproteins, and serum amyloid protein A. Clin Chim Acta. 1984;140(2):139-49.
26. Goodman DS, Noble RP, Dell RB. Three-pool model of the long-term turnover of plasma cholesterol in man. J Lipid Res. 1973;14(2):178-88.
27. Lindh A, Lindholm M, Holmquist L, Carlson LA. Time course for the changes of serum lipoproteins and apolipoprotein T concentrations after major surgical trauma in man. J Parenter Enter Nutr. 1986;10(3):265-73.
28. Gui D, Spada PL, Gaetano A De, Pacelli F. Hypocholesterolemia and risk of death in the critically ill surgical patient. Intensive Care Med. 1996;22(8):790-4.
29. Memiş D, Gursoy O, Tasdogan M, Süt N, Kurt I, Türe M, et al. High C-reactive protein and low cholesterol levels are prognostic markers of survival in severe sepsis. J Clin Anesth. 2007;19(3):186-91.
30. Giovannini I, Boldrini G, Chiarla C, Giuliante F, Vellone M, Nuzzo G. Pathophysiologic correlates of hypocholesterolemia in critically ill surgical patients. Intensive Care Med. 1999;25(7):748-51.
31. Marques MB, Langouche L. Endocrine, metabolic, and morphologic alterations of adipose tissue during critical illness. Crit Care Med. 2013;41(1):317-25.
32. Lee SH, Lee JY, Hong TH, Kim BO, Lee YJ, Lee JG. Severe persistent hypocholesterolemia after emergency gastrointestinal surgery predicts in-hospital mortality in critically ill patients with diffuse peritonitis. PLoS One. 2018;13(7):1-15.
33. Giovannini, I., Chiarla, C., Greco, F., Boldrini, G., & Nuzzo, G. Characterization of biochemical and clinical correlates of hypocholesterolemia after hepatectomy. Clin chem. 2003;49(2):317-9.
34. Dunham CM, Fealk MH, Sever WE. Following severe injury, hypocholesterolemia improves with convalescence but persists with organ failure or onset of infection. Crit Care. 2003;7(6):R145-53.
35. Bakalar B, Hyspler R, Pachl J, Zadak Z. Changes in cholesterol and its precursors during the first days after major trauma. Wien Klin Wochenschr. 2003;115(21–22):775-9.
36. Oster P, Muchowski H, Heuck CC, Schlierf G. The prognostic significance of hypocholesterolemia in hospitalized patientsDie prognostische Signifikanz einer Hypocholesterinämie bei stationären Patienten. Klin Wochenschr. 1981;59(15):857-60.
37. Stavrova R, Radeva-Dafinova N, Radev V, Marinchev N, Getov I. Changes in serum cholesterol levels in patients with combined trauma. Anesteziologiâ i intenzivno lečenie. 2009;3
38. Stavrova R, Radeva-Dafinova N, Getov I, Bogdanov S, Maneva N, Radev V, et al. Dynamics in serum cholesterol and cortisol levels in trauma patients, National Congress of Anesthesiology and Intensive Care with international participation, Sofia, October 1-4, 2009