The different notions about β-oxidation of fatty acids and ketonic bodies. The diabetic, acidotic coma as an acute deficiency of acetyl-KoA and ATP

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**Abstract.** The mechanisms of β-oxidation of fatty acids developed more than a century before have no compliance with actual physical chemical data. The oxidation of long-chain C 16:0 palmitic saturated fatty acid occurs not by sequential formation of eight molecules of acetyl-KoA but by force of formation of double bond and its hydrolysis on two short-chain C 8:0 fatty acids. Only short-chain fatty acids can become shorter under "chipping" of C 2-acetate with formation of C 4-butyric acid (butyrate) and its metabolites (β-hidroxibutirate, acetoacetate, acetone). The critical moment of oxidation is a hydrolysis of acetoacetate-KoA on two molecules of acetyl-KoA. The molecule of ATP is to be expended on hydrolysis. The foundation of nonspecific biological reaction of stress - ketoacidosis, - is a decrease in mitochondrions of acetyl-KoA pool formed both from glycogen and glucose and fatty acids. The oxalate acetate inputs into Krebs cycle inadequate amount of acetyl-KoA which limits synthesis of ATP. The insulin has no direct involvement into development of ketoacidosis but prepares conditions to facilitate nonspecific etiological factor to initiate diabetic ketoacidosis. These are the pooling of small amount of glycogen in cytozol and the predominance in cytozol of cells and adipocytes of palmitic triglycerides which are slowly hydrolyzed by hormone-dependent lipase to release non-esterified fatty acids into intercellular medium. The increase of their concentration in cytosol of cells and mitochondrions "are forced" to oxidize glucose. In these conditions, insulin enhances absorption of glucose by cells through glucose carriers - GLUT4. The derivatives of sulfonil-urea increase secretion of insulin by β-cells of islets. The biguanidines bond in cytosol covalently and irreversibly ketone bodies taking them away from oxidation in mitochondrions. The lipases, glitazones, flavonoids and flavones, lipoic ti-o fatty acids. The endogenous eicosanoids, derivatives ω-3 and ω-6 of essential polyolefinic fatty acids and conjugated unsaturated fatty acids are the antagonists of receptors of activation of proliferation of peroxisomes. In peroxisomes, they enhance α-, β- and ω-oxidation of all exogenous aphysiological fatty acids and excess of palmitic saturated fatty acid forming hypolipidemia in cytozol. The hypolipidemic pharmaceuticals with effect of β-blocker of oxidation stop absorption of fatty acids by mitochondrions. The ω-3 essential polyolefinic fatty acids, simultaneously with hypolipidemic effect, activate function of GLUT4. The decrease content of lipid substrates of oxidation in cytosol of cells and mitochondrions is determined by derangement of synthesis of phospholipids and function of GLUT4. It is valid to consider diabetes mellitus primarily as a pathology of metabolism of fatty acids and secondly as a pathology of content of glucose. It is necessary to take into account both under treatment (tactic activities) and strategic program of prevention of diabetes mellitus in population.

**Key words:** fatty acid, insulin, diabetes mellitus, mitochondrion, peroxisome, hyperglyceridemia

KL-1403-004

The clinical biochemistry of hyperlipemia and hyperglycemia. Insulin and metabolism of fatty acids. Hypoglycemic effect of hyperlipemic pharmaceuticals

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**Abstract.** The regulation of metabolism of glucose is billions years older than system of insulin and biological function of locomotion (function of motion). Hence hypoglycemic effect of hormone is mediated by alteration of metabolism of fatty acids. The insulin in physiological way deprives mitochondrions a possibility to metabolize ketone bodies, short chain, medium chain and long chain fatty acids and "forces" them to oxidize glucose which phylogenetically is not an optimal substrate. The relationships between fatty acids and glucose in the Rendle cycle have an effect only on autocrine level (in cell) determining alternation of biological reactions of exotrophia (after food intake) and endotrophia (beyond food intake) in biological function of alimentation (trophology). The most anti-diabetic pharmaceuticals are as insulin hyperlipemical by their mechanism of action. The decrease amount of lipid substrates of oxidation in cytosol of cells and mitochondrions "are forced" to oxidize glucose. In these conditions, insulin enhances absorption of glucose by cells through glucose carriers - GLUT4. The derivatives of sulfonil-urea increase secretion of insulin by β-cells of islets. The biguanidines bond in cytosol covalently and irreversibly ketone bodies taking them away from oxidation in mitochondrions. The lipases, glitazones, flavonoids and flavones, lipoic ti-o fatty acids. The endogenous eicosanoids, derivatives ω-3 and ω-6 of essential polyolefinic fatty acids and conjugated unsaturated fatty acids are the antagonists of receptors of activation of proliferation of peroxisomes. In peroxisomes, they enhance α-, β- and ω-oxidation of all exogenous aphysiological fatty acids and excess of palmitic saturated fatty acid forming hypolipidemia in cytozol. The hypolipidemic pharmaceuticals with effect of β-blocker of oxidation stop absorption of fatty acids by mitochondrions. The ω-3 essential polyolefinic fatty acids, simultaneously with hypolipidemic effect, activate function of GLUT4. In patients of middle age, the diabetes mellitus type II is a symptom of syndrome of atherosclerosis. The reason is that in cells the deficiency of essential polyolefinic fatty acids and is determined by derangement of synthesis of phospholipids and function of GLUT4. It is valid to consider diabetes mellitus primarily as a pathology of metabolism of fatty acids and secondly as a pathology of content of glucose. It is necessary to take into account both under treatment (tactic activities) and strategic program of prevention of diabetes mellitus in population.

**Key words:** fatty acid, insulin, diabetes mellitus, mitochondrion, peroxisome, hyperglyceridemia

KL-1403-014

The different notions about β-oxidation of fatty acids in peroxisomes, peroxisomes and ketonic bodies. The diabetic, acidotic coma as an acute deficiency of acetyl-KoA and ATP

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**Abstract.** The mechanisms of β-oxidation of fatty acids developed more than a century before have no compliance with actual physical chemical data. The oxidation of long-chain C 16:0 palmitic saturated fatty acid occurs not by sequential formation of eight molecules of acetyl-KoA but by force of formation of double bond and its hydrolysis on two short-chain C 8:0 fatty acids. Only short-chain fatty acids can become shorter under "chipping" of C 2-acetate with formation of C 4-butyric acid (butyrate) and its metabolites (β-hidroxibutirate, acetoacetate, acetone). The critical moment of oxidation is a hydrolysis of acetoacetate-KoA on two molecules of acetyl-KoA. The molecule of ATP is to be expended on hydrolysis. The foundation of nonspecific biological reaction of stress - ketoacidosis, - is a decrease in mitochondrions of acetyl-KoA pool formed both from glycogen and glucose and fatty acids. The oxalate acetate inputs into Krebs cycle inadequate amount of acetyl-KoA which limits synthesis of ATP. The insulin has no direct involvement into development of ketoacidosis but prepares conditions to facilitate nonspecific etiological factor to initiate diabetic ketoacidosis. These are the pooling of small amount of glycogen in cytozol and the predominance in cytozol of cells and adipocytes of palmitic triglycerides which are slowly hydrolyzed by hormone-dependent lipase to release non-esterified fatty acids into intercellular medium. The increase of their concentration in blood plasma precedes ketoacidosis which is developing in patients without diabetes mellitus too. When cells begin to oxidize unsaturated linoleic and linolenic acids with large number of double binds instead of medium-chain fatty acids, oleinic and palmitic fatty acids to support β-oxidation in mitochondrions and synthesis of ATP the amount of butyric acid, β-hidroxibutyril-KoA and acetoacetyl-KoA increases and of acetyl-KoA decreases. The cause of fatal outcome is the development of metabolic acidosis, hyperhydration of cerebral cells with development of edema and aphysiologic respiratory compensation of metabolic acidosis. The decarboxylation of acetoacetate and formation of acetone - initial stage of gluconeogenesis - formation of glucose from fatty acids - is manifested poorly both in primates and humans. From theoretical positions, to arrest ketoacidosis and to restore synthesis of AFT, it is reasonable to apply the infusion of...
optimal amount of acetyl-CoA which as nonpolar tioester can get over hematoencephalic barrier, plasma membrane and inner membrane of mitochondrions. It is supposed that diabetes mellitus is to be considered primarily as pathology of metabolism of fatty acids and only secondly as pathology of glucose.

**Key words:** diabetes mellitus; ketone bodies; ketoacidosis; fatty acids; β-oxidation.

**KL-1403-024**

The association of risk of development of cardiomyopathies with polymorphic variants of genes of angiotensin converting enzyme, glutathione-S-transferase, interleukins 8 and 10.

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**Abstract.** The article presents the results of study of association of risk of development and clinical course of cardiomyopathies with polymorphic variants of genes ACE, GSTM1, IL8 and IL10. The purpose of research was to find out molecular genetic markers of risk of development and clinical course of various types of cardiomyopathies. The analysis used the DNA samples extracted from lymphocytes of peripheral venous blood of patients with cardiomyopathies (N=89) and control group (N=426). The standard analysis techniques of polymerase chain reaction and restriction fragment length polymorphism were applied to detect polymorphic loci of genes candidates. It is established that genotype of DD-polymorphic locus of I/D geneACE is a marker of development of ischemic cardiomyopathy. The allele D is a marker of development of increased rate of manifestation of extra-systoles, growth of inter-ventricular septum and reduction of fraction of discharge in patients with cardiomyopathies.

**Key words:** cardiomyopathy, polymorphic variants of genes

**KL-1403-028**

The acoustic indicator of saliva under stress

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**Abstract.** The situation of stress affects various organs and systems that results in development of functional disorders and/or somatic diseases. As a result, different noninvasive, including salivary, techniques of diagnostic of stress conditions are in the process of development. The dynamics of acoustic indicator of saliva is studied during the period of passing the exams. The relationship of indicator with levels of potassium, sodium, glucose and protein of saliva was analyzed. The sampling consisted of 102 students of 5 and 6 academic years of medical university. To detect the acoustic indicator of saliva acoustic analyzer AKBa-01-“BIOM”® was applied. The level of potassium and sodium in saliva was detected using method of flame photometry. The level of glucose in saliva was detected by glucose oxidase technique using analyzer “EXAN-G”. The protein in saliva was detected by biuretic technique. The correlation between acoustic indicator of saliva and analyzed indicators of saliva was established.

**Key words:** stress, acoustic indicator of saliva

**KL-1403-029**

The analytic quality in laboratory medicine: problems and perspectives (a lecture)

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**Abstract.** The article considers the structure of analytical errors in clinical diagnostic laboratory analysis from the position of GOST R ISO 15189-2009 “Laboratories of medicine. Particular requirements to quality and competence”. The key value of metrologic traceability of analyses is emphasized. The role of official standard patterns, control materials and statistical methods applied in quality analysis are discussed. The international experience and applied methodical procedures to implement requirements of ISO 15189 concerning validation and verification of analytical quality are presented. The approaches of protocols E3 23-A, ER 15-A2, N59-A in the sphere of USA laboratory medicine developed by the institute of clinical and laboratory standards are demonstrated. The review of referent patterns and methods is given. The problem of optimization of requirements to quality of production for laboratory diagnostic is discussed. The expedience of organization of the National institute of laboratory standards is substantiated.

**Key words:** standardization, metrology, traceability, standard pattern, validation, verification, quality management
KL-1403-037

On the means of securing analytical reliability of laboratory results

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Abstract. The article is composed in the form of discussion with authors of another article published in the same issue of journal. The publication considers factors impacting analytical quality of results of clinical laboratory analyses. The cases in question are content of normative documents in force, expediency to complete them with more specific requirements to producers of laboratory analysis tools and recommendations for laboratories on implementation of verification of characteristics of techniques and medical tools for diagnostic in vitro. The article also considers requirements to metrologic traceability of control materials and necessity of formation of national reference system for laboratory medicine. The description of projects of methodical documents proposed to be considered by the profile expert commission on clinical laboratory diagnostic of Minzdrav of Russia is presented. These documents include complex of requirements to producers of medical tools for diagnostic in vitro. The proposal is expressed to develop a normative document of top status to establish a unified system of requirements implemented in all executive and methodical documents concerning regulation of access of medical tools for diagnostic in vitro, supporting security of application and quality of clinical laboratory analyses.

Key words: analytical quality, requirements, producer, tool, laboratory diagnostic, verification, characteristic, technique, medical, diagnostic, in vitro, traceability, control material, reference system, laboratory medicine

KL-1403-042

The fatty acids of membranes of erythrocytes in women with ischemic heart disease under effect of statins


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Abstract. The technique of evaluation of metabolism of fatty acids in vivo consists in detection of content of fatty acids in phospholipids of membranes of erythrocytes. The fatty acids are received with food, through synthesis on liver from carbohydrates and by katabolism of very long-chain polyolefinic fatty acids of food in peroxisomes of hepatocytes (oxidation, saturation and desaturation). In position sn-1 phospholipids more often than palmitic fatty acid (14%) stearic fatty acid is esterified (21% of all fatty acids). The palmitic, stearic and lignoceric saturated fatty acids are esterified in sn-1 phospholipids as 2:3:1. The simvastatin (80 mg per day) increased content of margarine, tricosanoic and hexacosanoic fatty acids by decrease of level of palmitic fatty acid. The ratio ω-3 polyolefinic fatty acids/ω-6 polyolefinic fatty acids reliably increased. The statins increase content of ω-3 polyolefinic fatty acids. In practice, it is necessary to differentiate the terms “atherosclerosis” and “atheromatosis”. The atherosclerosis is a syndrome of intracellular deficiency of polyolefinic fatty acids, derangement of function of cells in vivo under decrease of biological availability for all cells (absorption blockage). The atheromatosis is such most significant clinically symptom of atherosclerosis as accumulation of nonsaturated and polyolefinic fatty acids in pool of collection and utilization of biological “garbage” from blood plasma, in intima of elastic type arteries. The statins activate absorption of low density lipoproteins by cells and normalize biological availability of polyolefinic fatty acids which have a positive effect under atherosclerosis and on formation of atheromatosis.

Key words: fatty acids, phospholipids, erythrocyte, statins, atheromatosis

KL-1403-048

The immunologic predictors of effect of anti-B-cell therapy under rheumatoid arthritis

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Abstract. The article deals with results of study targeted to reveal laboratory biomarkers which can be useful in prognosis of effectiveness of rituximab therapy under rheumatoid arthritis. The sampling consisted of 34 patients with rheumatoid arthritis (31 women, average age 49 years, 42-64 years, mean duration of disease 66, 36-132 months). All patients were examined and received two infusions of rituximab intravenously with interval in 2 weeks against the background of standard therapy. The serum concentration of C-reactive protein, IgM rheumatoid factor, IgG, IgM, IgA were measured using immune nephelometric method. The level of cyclic citrullinated peptide antibodies, modified citrullinated vimentin antibodies and IgA rheumatoid factor was measured using method of immune enzyme analysis. The panel of 27 cytokines was measured using multiplex technology xMAP. Before rituximab therapy indices DAS28 (6,12; 5. 52-6. 81), SDAI (34.3; 23, 8-45, 9) and CDAI (31.3; 21, 8-38.5) corresponded to high activity of rheumatoid arthritis. Up to 24th week of therapy good response on criteria EULAR was registered in 15 patients, moderate response in 18 patients and was absent in 1 patient. The remission on DAS achieved more rarely in patients with initially negative/low positive values of IgM rheumatoid factor, basal level of IgM less than 2.4 g/l and duration of disease more than 40 months. In the group of patients who attained remission on CDAI up to 24th week of
therapy higher basal level of IL-1RA, IL-2, IL-8, IL-15, Eotaxin, GM-CSF, IFN-γ, MIP-1α and TNF-α was registered. In patients who attained remission on DAS 28 higher level of IL-1β, IL-2, IL-6, G-CSF, IFN-γ, MIP-1α and TNF-α was registered in comparison with patients with disease in active mode. The detection of basal level of IgM rheumatoid factor, IgM and also certain cytokines (IL-1β, IL-1RA, IL-2, IL-8, IL-15, GM-CSF, IFN-γ, MIP-1α, Eotaxin, TNF-α) can be useful in prognosis of effectiveness of rituximab therapy under rheumatoid arthritis.

**Key words:** rheumatoid arthritis, biomarker, rheumatoid factor, cytokine, anti-B-cell therapy.

**KL-1403-052**

*The ratio of hormones of system “hypophysis - thyroid” with level of dopamine and cyclic adenosine mono-phosphate of males in European North*

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**Abstract.** The study sampling consisted of 96 males from Arkhangelsk and 52 males from village of Nes. The examination was carried out to find out predominant regulative effect of dopamine on the system “hypophysis - thyroid” depending on territory of residence. In males of Zapolyarye, against the background of higher levels of T4, fT3 and TSH and cyclic adenosine mono-phosphate in blood occurs decreasing of levels of thyroglobulin and dopamine in comparison with males of circumpolar territories in case of registration of positive correlation between levels of dopamine and fT3. In males from circumpolar territories age-related decreasing of range of variations of level of dopamine and fT4 under increase of concentration of TSH was registered. At that, negative correlation between content of dopamine and T4 was registered. The age-related dynamics of alteration of level of cyclic adenosine monophosphate with tendency to increase in males of Zapolyarye at the age of 36-60 years in comparison with age group of 22-35 years.

**Key words:** hormone; male; North; age, global and free fraction of iodothyronin; thyrotropin; thyroglobulin; cyclic adenosine mono-phosphate; dopamine.