МЕХАНИЗМЫ РАЗВИТИЯ КАХЕКСИИ ПРИ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

(ОБЗОР ЛИТЕРАТУРЫ)

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МЕХАНИЗМЫ РАЗВИТИЯ КАХЕКСИИ ПРИ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ (ОБЗОР ЛИТЕРАТУРЫ). ЖКМП.-2025.-Т.3.-№3.-С

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Аннотация: В данной статье проанализированы результаты наблюдений и научных исследований, проведенных в последние годы в мире, посвященных относительно малоизученному тяжелому осложнению хронической сердечной недостаточности кахексии. В ней представлена роль факторов, участвующих в развитии кахексии, современные подходы к диагностике и лечению. В то же время было показано, что существует множество спорных вопросов в развитии кахексии, и их изучение является актуальной проблемой медицины.

Ключевые слова: *хроническая сердечная недостаточность, кахексия, хроническая почечная недостаточность, витамин Д.*

SURUNKALI YURAK YETISHMOVCHILIGIDA KAXEKSIYA RIVOJLANISHINING MEXANIZMLARI

(ADABIYOTLAR SHARXI)

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Annotatsiya: Ushbu maqolada surunkali yurak yetishmovchiligining nisbatan kam o‘rganilgan og‘ir asorati kaxeksiyaga bag‘ishlangan jaxonda so‘ngi yillarda amalga oshirilgan kuzatuv va ilmiy tadqiqot ishlari natijalari taxlil qilingan. Unda kaxeksiyaning rivojlanishida ishtirok etuvchi omillarning o‘rni, tashxislashga va davolashga zamonaviy yondashuvlar keltirilgan. Shu bilan bir qatorda kaxeksiya rivojlanishida munozarali masalalar ko‘pligi va ularni o‘rganish tibbiyotning dolzarb muammosi ekanligi ko‘rsatilgan.

Kalit so‘zlar: *surunkali yurak yetishmovchiligi, kaxeksiya, surunkali buyrak yetishmovchiligi, vitamin D.*

MECHANISMS OF DEVELOPMENT OF CACHECIA IN CHRONIC HEART FAILURE

(LITERATURE REVIEW)

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Abstract: This article analyzes the results of observations and scientific research conducted in recent years in the world devoted to cachexia, a relatively poorly studied severe complication of chronic heart failure. It presents the role of factors involved in the development of cachexia, modern approaches to diagnosis and treatment. At the same time, it is shown that there are many controversial issues in the development of cachexia, and their study is an urgent problem of medicine.

Keywords: *chronic heart failure, cachexia, chronic kidney failure, vitamin D.*

Chronic heart failure (CHF) represents the ter-minal stage of the cardiovas-cular continuum and ulti-mately results in death. Its prevalence is reported to be 4–10.3 times higher compared with that observed in the general healthy population [26].

According to the literature, CHF has been iden-tified in 1.0–2.6% of the Eu-ropean population, 2.2% in the United States, and 7% in Russia, with its incidence increasing in parallel with advancing age. This severe complica-tion occurs not only in elderly patients but also among middle-aged individuals. Approximately 1.4 million patients younger than 60 years have been diag-nosed with CHF, with 2% of them being between 40 and 59 years of age. In the United States, each year more than one million new patients with CHF are admitted to hospitals, with similar figures reported across Europe. In the Russian Federation, 16.7% of all hospitalized pa-tients are diagnosed with CHF, while in European coun-tries this figure averages around 5% [29].

In Uzbekistan, ischemic heart disease and ar-terial hypertension—major causes of CHF—are wide-spread among the population. Therefore, CHF can reasonably be considered one of the leading causes of hospi-tal admissions in our country.

It is well established that CHF is a severe com-plication in which the body's adap-tive reserves become depleted, leading to the development of numerous patho-logical changes. These include car-diac arrhythmias, disturbances of mineral metabolism, anemia, cachexia, and oth-ers. Among these complications, cachexia is especially noteworthy in patients with advanced func-tional classes of CHF, being one of the least studied yet clinically significant manifestations.

According to some data, cachexia occurs in 5–15% of such patients and is regard-ed as a highly unfavorable prognostic marker [32]. At the "Cachexia Consensus" Conference held in Washington in 2008, ca-chexia was defined as an unintentional loss of ≥5% of body weight within 12 months, accompanied by fatigue, depression, anemia, and other characteristic features [25].Given the increasing prevalence of chronic diseas-es, particularly CHF, ca-chexia has been increasingly recognized not only in developing but also in indus-trialized nations. At present, an estimated 6–12 million individu-als worldwide suffer from cachexia, with 1.5–2 million deaths annually attributed to this syndrome [17]. In their 2022 publication, Jandjirachaya Tanalolsart and colleagues pre-sented primary and secondary diagnos-tic criteria for cachexia. The primary crite-ria include the presence of chronic diseases (e.g., CHF, chronic kid-ney disease, etc.), and either unintentional body weight loss of more than 5% over the preced-ing 12 months or a body mass index (BMI) below 20 kg/m² in the absence of edema. The secondary criteria comprise fatigue, an-orexia, loss of lean body mass, reduced muscle strength, hemoglobin levels below 12 g/dL, serum protein con-cen-tration below 3.2 g/dL, elevated interleukin-6 (IL-6) above 4.0 pg/mL, and C-reactive protein (CRP) levels exceeding 5.0 mg/L [41].

A diagnosis of cachexia is established when ≥5% weight loss (without ede-ma) within 12 months is combined with at least two major and three minor crite-ria. However, owing to the heterogeneity of existing definitions, precise epidemi-ological estimates of ca-chexia prevalence remain inconsistent across studies.

Globally, cachexia is estimated to affect about 1% of the general patient population. In oncology, its prevalence may rise to 50–80%, and up to 80% of cancer patients die within one year after diagnosis [33].

Cardiac cachexia is a complex, severe, and mul-tifactorial pathological pro-cess that in nearly all cas-es develops as a consequence of chronic heart failure (CHF). Its presence is considered a marker of adverse clinical outcomes, substan-tially increases the cost of treatment, and significantly reduces life expectancy [18]. Importantly, cachexia in CHF can occur regardless of patient age, ventricu-lar function, or functional classifi-cation of the disease In cachexia, the weakening of both skeletal and cardiac muscles is closely associated with profound metabolic alterations.

These disturbances interact with one another, leading to a further decline in cardi-ac function and pump efficiency. As a result, the supply of oxygen and nutrients to all tissues and organs of the body becomes impaired. Concurrently, the pro-gressive wasting of skeletal muscle mass combined with the presence of ede-ma in-terferes with venous return and ventricular filling, thereby causing a marked dete-rioration of cardiac pump performance [8].

Clinically, patients present with fatigue, sensations of breathlessness, and anorexia. Early fatigability is among the most frequently observed symptoms in both heart failure and cachexia. This symptom reflects insufficient energy availability, decreased metabolic reserves, and impaired autonomic as well as neutral regulatory mechanisms. Its etiology is regarded as multifactorial,encompassing both physiological and pathological causes. Contributing factors include reduced left ventricular pump function, impaired tissue perfusion and diffusion, alterations in the autonomic nervous system, endothelial dysfunction, and overall deterioration of physical condition.

Breathlessness in chronic heart failure (CHF) patients exacerbates fatigue and contributes to anorexia and dysphagia. Dietary restrictions, polypharmacy, and intestinal edema further aggravate satiety, nausea, and nutrient malabsorption [24]. Anorexia is observed in up to 72% of CHF patients with cachexia and is often linked to fatigue, drug dependence, depression, or gastrointestinal disorders [1].

Anemia is common in CHF-associated cachexia (24–70%), worsening oxygen delivery, exercise tolerance, overall condition, and mortality [2]. Cachexia is also associated with aging-related comorbidities such as frailty, anorexia, depression, and dementia. Hormonal imbalances (testosterone, cortisol, 17β-estradiol) further contribute to its pathogenesis [15,19,20,39]. Frailty and sarcopenia in elderly CHF patients predict poor outcomes, with weakness serving as a key diagnostic and prognostic marker [15].

Depression, closely linked with cortisol dysregulation, accelerates CHF and cachexia progression [30,37]. Circulating cytokines, particularly leptin, also play an important role by influencing the central melanocortin system [27,38].

Cachexia in CHF is multifactorial, involving altered protein metabolism, endocrine dysfunction, micronutrient imbalance, vitamin D deficiency, inflammation, and malabsorption. Cardiac hypertrophy initially acts as a compensatory mechanism but later becomes maladaptive, with reduced myocardial mass, ventricular thinning, and impaired contractility, leading to progression of heart failure [34,40].

Although cardiomyocytes can function throughout life, their proteins and organelles undergo constant renewal. Cardiac proteins regenerate about every 30 days, with amino acids reused for new protein synthesis [10]. They include structural, nuclear, enzymatic, and contractile proteins essential for pumping [35]. Turnover of actin and myosin prevents accumulation of damaged proteins [10]. Protein synthesis in skeletal and cardiac muscle depends on dietary intake and anabolic signaling [44].

In cachexia, reduced insulin sensitivity and endothelial dysfunction impair protein metabolism, with decreased insulin-like growth factor-1 (IGF-1) levels also seen in sarcopenia [6]. Physical loading may stimulate anabolism, but excessive stress lacks benefit [35].

Protein degradation involves autophagy, the ubiquitin–proteasome system (UPS), and the calcium-dependent calpain system. Ubiquitinated proteins contribute to impaired contractility and apoptosis [6]. Hyperactivation of UPS is key in cachexia-related atrophy, while inhibition of deubiquitinases enhances protein breakdown [48]. Calpains degrade cytoskeletal proteins, disrupt contraction, and contribute to titin degradation in heart failure, though regulated by calpastatin [44,47].

Inflammation and reactive oxygen species (ROS) activate FoXO and other catabolic pathways. Mitochondrial turnover via fusion, fission, and mitophagy maintains contractile function, but chronic inflammation, oxidative stress, and hyperglycemia disturb these processes, driving cachexia [51,52].

Hormonal dysregulation also shifts anabolic–catabolic balance. Insulin, IGF-1, leptin, ghrelin, melanocortins, neuropeptides, and growth hormone act as regulators [6]. Anabolic disruption (insulin, IGF-1, GH) and excess catabolic hormones (catecholamines, cortisol, DHEA) aggravate wasting [13]. Insulin is a major anabolic factor, activating PI3K–AKT–mTOR signaling, stimulating satellite cell proliferation and contractile protein synthesis [9].

In CHF patients with cachexia, elevated norepinephrine, adrenaline, cortisol, and increased renin–aldosterone activity are observed [14]. Pathological hypothalamic responses further impair energy homeostasis.

Leptin and ghrelin exert opposite cardiovascular effects: leptin activates the sympathetic system, raises blood pressure, and promotes pro-inflammatory, proliferative, and pro-thrombotic processes, while ghrelin reduces sympathetic activity, improves vasodilation, and has protective anti-inflammatory effects [31,36]. Despite hormonal fluctuations, energy utilization remains stable due to pro-opiomelanocortin activity and reduced neuropeptide signaling [21]. Vitamin D, synthesized mainly in the skin under UV exposure and partly obtained from diet, is metabolized in the

liver and kidneys to its active form, 1,25-dihydroxyvitamin D, which acts on multiple organs including the heart, muscles, and intestines [50]. In cachexia, vitamin D deficiency impairs intestinal absorption, often aggravated by long-term NSAID therapy and magnesium deficiency. Since magnesium is essential for vitamin D activation, combined deficiencies promote inflammation and muscle atrophy [22].

Vitamin D receptors are distributed in muscle tissue depending on age, sex, and the presence of pathological processes. Moreover, vitamin D deficiency and reduced receptor levels influence muscle size, strength, and relaxation capacity. Consequently, these factors play an important role in the development of cachexia [16].

Cachexia is also characterized by deficiencies in macro- and micronutrients, including calcium, zinc, iron, thiamine, vitamins E and K, and folic acid [43]. Vitamin E, when used in combination with omega-3 fatty acids, prolongs survival. Additionally, the inclusion of vitamin C improves multiple aspects of quality of life [28]. Furthermore, vitamins C and E, together with β-carotene, act as antioxidants and may exert protective effects on vascular walls [12].

It is well established that most researchers recognize obesity as a chronic inflammatory process. Adipose tissue is considered an important endocrine organ that produces numerous factors, including cytokines (tumor necrosis factor-α, interleukin-6, interleukin-1, interleukin-10, and others) and adipokines. These factors, in turn, are involved not only in essential inflammatory processes but also in the pathogenesis of cachexia [7]. In chronic heart failure and cachexia, an increase in tumor necrosis factor-α is observed. This leads to suppression of bone marrow activity, reduced sensitivity to erythropoietin-induced production, and the release of iron [49]. Intestinal malabsorption is also associated with cardiac cachexia, developing as a consequence of intestinal wall edema and reduced perfusion [5]. The absorption of fats is a complex process that begins with the hydrolysis of dietary glycerides by pancreatic lipase [46]. The resulting fatty acids and monoglycerides combine with bile salts synthesized in the liver to form micelles. Subsequently, dietary fats are absorbed into intestinal mucosal cells, where triglycerides are resynthesized. They are then incorporated into chylomicrons and transported into the lymphatic system. Any disruption at one of these stages may lead to impaired fat absorption. It is well known that chronic heart failure is often accompanied by impaired liver function. From a theoretical perspective, this may reduce bile salt production, thereby disturbing fat absorption in the intestines. Additionally, bacterial colonization of the small intestine may also contribute to fat malabsorption.

In cachexia, energy losses observed in the liver lead to a reduction in oxidative phosphorylation activity. As a result, mitochondrial cardiolipins accumulate excessively. This, in turn, is accompanied by an increase in tumor necrosis factor-α [23].

Unlike the traditional view that attributes the loss of exercise capacity in chronic heart failure solely to impaired cardiac function, over the past two decades increasing attention has been given to the importance of myopathy. In 1994, the so-called 'muscle hypothesis' was proposed, emphasizing the role of skeletal muscle hypoxia in the development and progression of chronic heart failure. According to this hypothesis, changes in skeletal striated muscles are accompanied by other pathological alterations and symptoms of the disease. The theory suggests that the reduced exercise tolerance observed in patients with chronic heart failure is associated with muscle fiber atrophy, an increased proportion of type II fibers, and diminished oxidative capacity [3].

Skeletal muscles regulate cardiovascular and respiratory system activity through ergoreflex mechanisms. These changes arise as a consequence of the accumulation of metabolites within muscle fibers, aimed at promoting their elimination and enhancing aerobic oxidation. The development of skeletal muscle myopathy in chronic heart failure is linked to the predominance of anaerobic processes over aerobic ones within muscle fibers under hypoxic conditions [50].

According to the observations of several researchers, muscle atrophy, a reduction in the proportion of type I oxidative muscle fibers, decreased capillary density, impaired mitochondrial respiration, and consequently reduced oxygen utilization capacity are characteristic findings in chronic heart failure. Importantly, these alterations apply equally to both phenotypes of chronic heart failure: those with preserved and those with reduced left ventricular ejection fraction [42].

In addition to its primary function, muscle tissue also exhibits hormonal activity. Myokines represent a broad spectrum of biologically active molecules secreted by skeletal muscles and cardiomyocytes.

Their profile corresponds to the progression of chronic heart failure, the development of sarcopenia, and cachexia. At the early stages of chronic heart failure, myokines regulate energy homeostasis through autocrine and paracrine pathways. The functional activity and structure of skeletal muscles are modulated by adaptive metabolic and hormonal changes during the early stages of chronicheart failure. At different stages, alterations in the profile of myokines are observed, and they may be considered as potential therapeutic targets. Certain myokines, particularly myostatin, irisin, brain-derived neurotrophic factor, and fibroblast growth factor-21, play roles in regulating the pathogenesis of myopathy associated with chronic heart failure. They are detectable in peripheral blood, and their levels in the early stages of chronic heart failure provide prognostic information regarding adverse outcomes [4].

Myostatin levels in patients with chronic heart failure are higher compared to healthy individuals, with the highest concentrations recorded in patients with New York Heart Association (NYHA) functional class IV. Elevated myostatin levels are associated with the lowest survival rates and the highest frequency of hospital readmissions. Moreover, a positive correlation has been demonstrated between atrial natriuretic peptide and myostatin concentrations [11]. The analysis suggests that circulating myostatin levels reflect the severity of chronic heart failure and serve as predictors of adverse clinical outcomes.

The analysis of the reviewed literature confirms that the development of cachexia in chronic heart failure is a complex, multifactorial process. In addition to the hemodynamic changes that occur in this severe complication, disruptions in protein metabolism, hormonal balance, vitamin D metabolism, and alterations in myokine synthesis play a leading role. However, certain links in the pathological chain underlying the development of cachexia in chronic heart failure remain insufficiently studied.

In our Republic, no scientific research specifically dedicated to this topic has been conducted. From this perspective, studying the mechanisms of cachexia development in chronic heart failure among patients living in the Ferghana Valley holds not only scientific but also important practical significance.

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