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ABSTRACT

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AGE-RELATED FEATURES OF LIVER CHANGES DURING INTERMITTENT FASTING (LITERATURE REVIEW)

The increase in average life expectancy in the world and the corresponding increase in the prevalence of age-related diseases make it necessary for modern medicine to seek new approaches to their prevention and treatment. Intermittent fasting (IF) can be proposed as an effective method not only for weight loss and treatment of metabolic diseases, but also for maintaining the healthy state of internal organs, particularly the liver, during aging.

Materials and methods. An analysis of literary sources was conducted to investigate modern ideas about the role of various IF methods in maintaining a healthy liver in people of different age groups.

Results. Aging of liver tissue is accompanied by the gradual development of steatosis and fibrosis, which, under certain living conditions, nutrition, and the presence of metabolic disorders, leads to the development of chronic liver diseases.

Intermittent fasting is based on various schemes of alternating fasting and meal times, which lead to the following changes in liver metabolism: activation of signaling pathways of the adaptive cellular response to stress, which improve mitochondrial function; glucose regulation, DNA repair, increased stress resistance, activation of lipophagy in hepatocytes, suppression of inflammation, and increased regulation of autophagy. IF has protective and rejuvenating effects and improves the functionality and composition of biomolecules, which are responsible for homeostatic, energetic, and remodeling processes in liver cells.

Conclusions. IF is an effective and affordable method of non-drug treatment of metabolic diseases through the restoration and rejuvenation of the main metabolic organ of the body – the liver. The positive effect of IF on liver metabolic processes is to reduce body weight, decrease blood pressure and the level of inflammatory markers in the body, improve insulin resistance and lipid profile, and slow down aging processes.

IF helps reduce the risk of developing diseases such as type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular disease, and certain types of cancer, and improves the body's metabolic health. IF is a promising and relevant direction in combating the effects of liver aging, which opens up new opportunities for maintaining health in elderly people.

Keywords: intermittent fasting, liver aging, age-related liver diseases, steatosis, fibrosis, autophagy, inflammation.

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ВІКОВІ ОСОБЛИВОСТІ ЗМІН ПЕЧІНКИ ПІД ЧАС ІНТЕРВАЛЬНОГО ГОЛОДУВАННЯ (ОГЛЯД ЛІТЕРАТУРИ)

Зростання середньої тривалості життя у світі та відповідне збільшення поширеності вікових захворювань спонукає сучасну медицину шукати нові підходи до їх профілактики й лікування. Інтервальне голодування (ІГ) може бути запропоноване як ефективний спосіб не тільки для зниження ваги та лікування метаболічних захворювань, але й для підтримки здоров'я внутрішніх органів, зокрема печінки, при старінні організму.

Матеріали і методи. Проведений аналіз літературних джерел щодо сучасних уявлень про роль різних методів ІГ у підтримці здорового стану печінки у людей різних вікових груп.

Результати. Старіння тканин печінки супроводжується поступовим розвитком ознак стеатозу та фіброзу, що за певних умов життя, харчування та наявності метаболічних розладів призводить до розвитку хронічних захворювань печінки.

В основі інтервального голодування лежать різні схеми чергування часу голодування та прийому їжі, що призводять до наступних змін метаболізму печінки: активації сигнальних шляхів адаптивної клітинної відповіді на стрес, які покращують функції мітохондрій, регуляцію рівня глюкози, відновлюють ДНК, підвищення стійкості до стресу, активації ліпофагії в гепатоцитах, пригнічення запалення та посилення регуляції аутофагії. ІГ має захисні і омолоджувальні ефекти, покращуючи функціональність та склад біомолекул, які відповідають за гомеостатичні, енергетичні та ремоделюючі процеси в клітинах печінки.

Висновки. ІГ є ефективним і доступним методом немедикаментозного лікування метаболічних захворювань через відновлення та омолодження головного метаболічного органу організму - печінки. Позитивний вплив ІГ на метаболічні процеси печінки полягає у зниженні ваги тіла, артеріального тиску, рівня запальних маркерів в організмі, покращенні інсулінорезистентності та ліпідного профілю, уповільнені процесів старіння.

ІГ допомагає знизити ризик розвитку таких захворювань, як цукровий діабет 2 типу, неалкогольної жирової хвороби печінки, серцево-судинних захворювань, деяких видів раку, покращує метаболічне здоров'я організму. ІГ є перспективним та актуальним напрямком боротьби з наслідками старіння печінки, що відкриває нові можливості для збереження здоров’я в людей старшого віку.

Ключові слова: інтервальне голодування, старіння печінки, вікові захворювання печінки, стеатоз, фіброз, аутофагія, запалення.

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ABBREVIATIONS

IF – Intermittent Fasting
NAFLD – nonalcoholic fatty liver disease
SASP – senescence-associated secretory phenotype
AMPK – adenosine monophosphate-activated protein kinase
mTOR – mechanistic target of rapamycin
LD – lipid droplets
ROS – reactive oxygen species

INTRODUCTION

Physiological aging of the body is accompanied by irreversible functional and organic restructuring of all systems and organs. As a central organ involved in metabolic, detoxification, and synthetic processes, the liver is particularly sensitive to age-related changes, leading to fibrosis, steatosis, and decreased regenerative capacity. Aging contributes to the risk of developing liver diseases, which cause increased mortality rates and become an important public health problem. A decrease in the reparative and regenerative potential of the liver leads to diseases such as nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis, acute and chronic liver damage, and others [1]. Thus, the prevalence of NAFLD increases in the elderly: it is reported in less than 30% of people under 40 years of age and in more than 50% of people over 60 years of age [2, 3].

The liver is a complex metabolic organ essential for maintaining whole-body homeostasis by regulating energy metabolism, clearance of xenobiotics and endobiotics, and molecular biosynthesis; therefore, age-related changes in liver function increase susceptibility to age-related diseases [4]. For example, the liver regulates systemic energy metabolism through hepatic glucose and lipid homeostasis, steroid biosynthesis and degradation, and insulin signaling. Thus, the liver plays a key role in mediating the beneficial effects of nutritional interventions on aging and age-related diseases, such as calorie restriction and protein restriction. On the other hand, dysregulation of energy metabolism in the liver contributes to common age-related pathologies and diseases, such as insulin resistance, diabetes mellitus, and NAFLD [5].

It should be noted that hepatocytes retain high regenerative activity for a long time; therefore, the liver is considered a slowly aging organ. Even in adulthood, hepatocytes undergo structural changes that are a compensatory reaction and allow the organ to function satisfactorily. However, the prevalence of systemic diseases in older people provokes the development of structural pathological changes in the liver. Metabolic syndrome is a powerful risk factor for the development of steatohepatitis, which leads to fibrosis. Thus, diabetes mellitus has a biological association with the progression of NAFLD: up to 75% of individuals with type 2 diabetes have NAFLD [6]. As a method of modulating metabolic processes in the body, IF is a promising and relevant direction in combating the consequences of liver aging.

Objective. To analyze modern literary sources regarding age-related changes in the liver and to investigate the prospects of IF as a method of liver disease prevention and treatment.

MATERIALS AND METHODS

The results of studies published in the scientific metric databases "PubMed", "Scopus", and "EMBASE" on age-related features of liver structural reorganization and intermittent fasting, mainly over the last 10 years, were analyzed.

RESULTS AND DISCUSSION

Liver disease incidence increases in the elderly, but the cellular and subcellular abnormalities that underlie this predisposition to pathology remain poorly understood. Aging causes several structural changes in the liver that can affect its function: these include a decrease in liver volume, a slowing of blood circulation slowing, a moderate decrease in metabolism, and changes in the expression of various proteins. Other changes, such as a poor response to oxidative stress, reduced expression of growth-regulating genes, and reduced DNA repair rates, contribute to a decrease in the liver's regenerative capacity, an increased risk of developing liver disease in the elderly, and reduced survival after liver transplantation. With age, liver volume decreases by 20–40% [5]. In people under 50 years of age, there is a decrease in the total number of hepatocytes, on average per cell in the field of view, and in liver volume – up to 600 grams on average [6]. By the age of 80, liver atrophy develops. These changes are caused by decreased regenerative processes, reduced intensity of blood flow in the liver, and the progression of fibrosis [7].

In 2013, Lopez-Otin et al. identified 9 cellular hallmarks of aging: genomic instability, epigenetic changes, loss of proteostasis, telomere attrition, mitochondrial dysfunction, deregulated nutrient uptake, cellular senescence, stem cell exhaustion, and altered intercellular communication [8]. Thus, changes in liver aging occur at the genomic, epigenetic, molecular, cellular, and subcellular levels, occurring in various liver cells and the extracellular matrix, ultimately leading to impaired liver function [9, 10]. In recent years, there has been a surge of interest in long non-coding RNAs and microRNAs. They are thought to be involved in the aging process, especially in metabolic modulation and intercellular interaction [11, 12]. In 2018, Barbosa et al. highlighted the role of decreased autophagy activity in characteristic signs of aging [13].

Signs of aging directly affect different types of liver cells: hepatocytes, hepatic sinusoidal endothelial cells, hepatic stellate cells, and Kupffer cells [4]. In the young liver, lipoproteins, insulin, and carbohydrates can pass between the blood and hepatocytes through the fenestrations of the liver sinusoidal endothelial cells. The homeostatic phenotype of liver cells is maintained through intercellular interactions with vascular endothelial growth factor, nitric oxide, and hepatocyte growth factor. With age, numerous changes occur in each cell type, impairing their dynamics.

Unique organ-specific macrophages of the liver are Kupffer cells (sinusoidal macrophages or Kupffer–Browicz cells), which constitute 20-40% of the non-parenchymal elements of the liver and about 70% of the entire macrophage population of the body. These are star-shaped liver endothelial cells that are capable of transforming into specialized macrophages. They are key factors of inflammation; they also actively participate in liver regeneration and, exfoliating into the lumen of the sinusoids, perform the role of free organ-specific macrophages. Notably, the colony-stimulating activity of hepatic macrophages is 10 times higher than that of pulmonary and peritoneal macrophages.

The largest number of these cells is located in the peripheral parts of the hepatic lobules (near the portal tracts), which comprise a sinusoidal lining together with endothelial cells. Kupffer cells are capable of local proliferation, which allows the population of these cells to self-renew.

Hepatic stellate cells in the adult liver reduce fenestrations, cause disruption of angiocrine factor release and cellular autophagy, and increase expression of cell adhesion markers. Kupffer cells in aging liver exhibit phenotypic changes such as increased lipid load and collagen production, leading to basement membrane deposition and impaired vitamin A metabolism. Kupffer cells accumulate in the liver with age and attach to adhesion markers expressed on stellate cells; they also contribute to liver inflammation, stimulate the release of interleukin-6, and demonstrate impaired phagocytosis.

Hepatic stellate cells (Ito cells) make up 5% of liver cells and are located in the space of Disse (between sinusoidal endothelial cells and the surface of hepatocytes). In a normal healthy liver, stellate cells are quiescent and store most of the body's vitamin A in characteristic lipid droplets. These versatile cells are known to play a crucial role in liver development, regeneration, and modulation of immunological responses within the liver. When the liver is damaged by toxins or viral infection, hepatocytes and immune cells release factors that activate stellate cells [8].

Activated cells transform into proliferative, contractile, and fibrogenic myofibroblasts, which are capable of secreting a protein complex that includes collagens, glycoproteins, and proteoglycans. This process is necessary to ensure the healing of a damaged liver. However, under prolonged exposure to a pathogenic factor, stellate cells remain activated and secrete excessive amounts of collagen, leading to liver fibrosis. The latter, over time, can transform into cirrhosis, with further development of chronic liver failure.

Cellular senescence is characterized by a prolonged, irreversible arrest of the cell cycle, which has a direct impact on the microenvironment. Thus, senescent cells can interact through direct intercellular contact [17], cell fusion [18], formation of cytoplasmic bridges [19], extracellular vesicles [20], and through SASP [16].

The process of liver aging is accompanied by important changes in hepatocytes in the form of polyploidy and DNA damage, which can lead to genetic instability and cell cycle disorders [10]. There is also an accumulation of lipofuscin – a pigment formed due to incomplete lysosomal digestion of molecules, particularly proteins and lipids, which is a marker of cellular aging [14]. A decrease in the oxidative capacity of mitochondria leads to an increased level of oxidative stress and reactive oxygen species (ROS), which damage cellular components and contribute to the progression of pathological processes [15]. In addition, cells with a secretory phenotype (SASP) accumulate in the liver as the body ages and secrete molecules that increase the risk of developing chronic diseases, including fibrosis and cirrhosis. It is known that SASP includes pro-inflammatory cytokines (interleukins IL-1b, IL-6, IL-8), chemokines (monocyte chemoattractant protein 1), growth factors (human growth factor, fibroblast growth factor), proteases (matrix metalloproteinases), fibronectin, reactive oxygen species, and nitric oxide. In liver aging, SASP is indirectly involved in a variety of biological processes, including regeneration, tissue remodeling, embryogenesis, inflammation, and tumorigenesis [16]. As cells age, they appear enlarged and flattened with enlarged nuclei under a light microscope. Increased activity of acidic lysosomal β-galactosidase is the “gold standard” among markers of cellular aging. It is associated with cell cycle arrest through suppression of gene expression. The enzyme is determined by cytochemical analysis or bioluminescent imaging (this test can only be applied to fresh biopsy materials) [1].

Thus, in the process of liver aging, there is an increase in structural and functional disorders, which causes the appearance of the following clinical and morphological changes: steatosis, steatohepatitis, fibrosis, cirrhosis, and progression of chronic liver diseases in the elderly. Age-related changes in the structure of the liver are inevitable, but their intensity may vary depending on lifestyle and proper nutrition, the presence of chronic diseases, and the influence of harmful factors.

Recently, IF has attracted great attention from the medical community as an approach to weight loss and as a treatment strategy against metabolic diseases, primarily. Clinical studies demonstrated the benefits of IF in many diseases, including obesity, diabetes, and cardiovascular disease, through weight loss and improved metabolic parameters [21].

Several IF protocols have been proposed and are currently used in practice. Some of them include alternate-day fasting, which involves fasting for 24 hours every other day, and the 5:2 diet, which involves fasting for 24 hours twice a week and a very low-calorie diet consumed for the other 2 days of the week. In the latter method, fasting can be consistent or inconsistent. Time-restricted feeding is another popular approach, in which fasting occurs daily at varying times, but typically it involves a 6-h eating window with breakfast in the morning and dinner by 3:00 PM, resulting in a fasting duration of 14–18 h [22, 23].

These IF regimens have a beneficial metabolic effect, periodically inducing the metabolism of fatty acids to ketones. The use of IF methods generally leads to weight loss, improved lipid profile, and reduced blood pressure, which has a positive effect on type II diabetes and NAFLD [24, 25, 26]. There are currently no approved treatments for NAFLD, and the recommended treatment strategy is weight loss, including IF patterns [27].

In 1963, Randle P. J. and co-authors proposed a theory of energy metabolism during meals and fasting, known as the “glucose-fatty acid cycle,” in which glucose and fatty acids compete for oxidation [28]. Glucose is the primary energy source for most tissues throughout the day. During prolonged periods of fasting, triglycerides from adipose tissue are converted to fatty acids and glycerol, which are subsequently metabolized for energy. The liver converts fatty acids into ketone bodies, which during fasting become the main source of energy for many tissues, especially the brain. Insulin is the main driving hormone during eating, when the body uses glucose as fuel, while in the fasting state, glucagon is the main hormone, and the body uses glycogen stores in the liver for energy. The onset of the metabolic switch is the point of negative energy balance, when glycogen stores in the liver are depleted and fatty acids are metabolized. This usually occurs 12 hours after stopping eating. The metabolic switch from glucose to fatty acid-derived ketones is a stimulus that shifts metabolism from lipid/cholesterol synthesis and fat storage to fat mobilization through fatty acid oxidation and fatty acid-derived ketones, preserving both muscle mass and function [23].

Thus, this unique dietary strategy works through altered liver metabolism, called a metabolic switch, stimulating adaptive cellular responses, including improved glucose regulation, increased stress resistance, suppression of inflammation, and upregulation of autophagy, where damaged molecules are removed or repaired to protect against oxidative and metabolic stress.

IF correlates with the natural circadian rhythm, meaning it is a more adaptive and physiological way of eating, and has significant metabolic benefits over other restrictive eating regimens such as the ketogenic diet, vegan diet, or daily calorie restriction. However, the influence of various factors (environment, social influence, peculiarities of the physiology in different ages and health conditions, etc.) creates limitations on the use of fasting as a method of treating diseases and requires further research. There is a possibility that fasting may be dangerous, so it is not recommended for people with hormonal imbalances, pregnant and breastfeeding women, young children, the elderly with chronic diseases, and immunocompromised individuals, including those with a history of cancer [24].

IF can affect the liver of older people both positively and negatively, depending on their overall health and comorbidities. Given the increase in metabolic disorders with age, a particularly important positive effect on the liver cells of older people is the loss of fatty liver accumulation, which reduces the risk of NAFLD. It is a progressive liver disease manifested by the development of steatosis, fibrosis, and cirrhosis, and is characterized by excessive accumulation of triglycerides and cholesterol in lipid droplets in hepatocytes. Excessive lipid accumulation in the liver causes hepatocellular lipotoxicity by inducing endoplasmic reticulum stress and mitochondrial dysfunction, leading to hepatocyte apoptosis [29]. Several studies highlighted the therapeutic potential of IF in NAFLD [30, 21, 31]. Current evidence suggests that ketogenesis eliminates two-thirds of the lipids entering the liver, and its dysregulation significantly contributes to the pathogenesis of NAFLD [72]. It is important to note that simple steatosis is a completely reversible process if patients are on an appropriate diet and weight loss regimen [32].

Lipid catabolism in hepatocytes was previously thought to be similar to that of adipocytes, that is, using a series of cytoplasmic lipases. In 2009, Singh et al. provided the first concrete evidence for a link between autophagy and lipid metabolism in the liver [33]. With age, there is a decrease in lipophagy activity in the liver. During fasting, autophagy is activated – this is the natural cleansing of cells from cellular components, which promotes cell renewal and can slow down aging. Cellular energy levels can be increased through the utilization of free fatty acids derived from the selective breakdown of lipid droplets (LDs) by lipophagy (or macrolipophagy) [34].

Among the mechanisms of liver lipophagy stimulation, the following processes can be mentioned: activation of adenosine monophosphate-activated protein kinase (AMPK), inhibition of the mechanistic target of rapamycin (mTOR), accumulation of proteins LC3 (a protein associated with the membrane of autophagosomes) and p62/SQSTM1 (an adapter protein that binds LD to autophagosomes), decreased insulin levels, leptin activity, oxidative stress, and others. All of these processes are important for energy balance in the cell, especially during aging and fasting.

Studies by Li D. et al. suggest that the enhancement of hepatic lipid metabolism is due to the ability of IF to activate macrophage migration inhibitory factor signaling, which, in turn, promotes AMPK-mediated autophagy and reduces liver cell apoptosis [35].

The mTOR complex is a master switch for the most energy-dependent processes in the cell; it stimulates their growth and biomass accumulation in cases of sufficient nutrients and, conversely, allows autophagic recycling of cellular components after nutrient restriction. mTOR and autophagy control additional adaptations to nutrient restriction, namely maintaining fasting glucose homeostasis [36]. Mice with increased mTOR signaling activity in the liver demonstrate resistance to age- and diet-dependent hepatic steatosis. Over the past decade, there has been growing interest in rapamycin as a life-extending agent. Interestingly, its effects are compared to the effects of dietary measures on the body (in particular, this was shown in experiments with food restriction in animals) [37, 38, 39].

Lipophagy is the selective degradation of lipid droplets by autophagy, which removes excess lipids from the liver. The LD-resident perilipin proteins PLIN2 and PLIN3 function as barriers against unregulated lipolysis; removal of the perilipin shell surrounding LDs during autophagy is a prerequisite for lipolysis or classical lipophagy. PLIN2 expression leads to lipid accumulation in the liver (triglycerides and LD cholesterol esters) [40]. Its expression was found to be associated with age-related diseases: insulin resistance, type 2 diabetes, atherosclerosis, and cardiovascular diseases [41]. Interestingly, the authors consider athletes who engage in endurance sports to be an exception. PLIN2 expression can be significantly increased when liver cells are exposed to fatty acids, as was demonstrated in hepatocytes from fasted mice [42].

Many potential regulatory factors can modulate the lipophagy process indirectly or directly. Glycine-N-methyltransferase is an example of the enzymes that can indirectly affect hepatic lipophagy; the lack of its expression leads to increased levels of circulating methionine and decreased autophagy. Thus, high levels of LD in individuals with fatty liver disease and glycine-N-methyltransferase deficiency may exacerbate hepatic steatosis due to the inability to mobilize LD through lipophagy [43].

The effect of sirtuins, a family of nicotinamide adenine dinucleotide (NAD+)-dependent deacetylases, on lifespan extension was first discovered when studying a mutation in the Sir4 gene that extends the replicative lifespan of yeast [44]. Sirtuins are linked to IF metabolism through the need for NAD+, so dietary supplements with NAD+ or NAD+ precursors are being actively investigated as a way to promote healthy aging and intervene in diseases by activating sirtuins [45, 46, 47].

LDs were demonstrated to have an important physiological function, as they provide storage of non-esterified fatty acids in the form of inert triacylglycerides. An excess of fatty acids in the cytoplasm was found to trigger the formation of harmful bioactive lipids, causing lipotoxicity. LDs also participate in the biosynthesis of cell membranes and other types of lipids, and are a source of metabolic energy through fatty acids β-oxidation when nutrients are not enough in the body, i.e., autophagy can be called an adaptive mechanism [48]. LDs also play an important role in the removal of damaged organelles, protein aggregates, and exogenous pathogens, in the assembly of viruses such as the hepatitis C virus, protein sequestration, and in transmembrane signaling [49]. At the same time, metabolic processes in hepatocytes undergo significant changes with age, and the accumulation of neutral lipids in lipid droplets becomes a sign of liver aging and a cause of disease. Recent studies have shown that fasting activates autophagic degradation of LD in various cell types, including hepatocytes, neurons, enterocytes, and cancer cells [50].

The protective and rejuvenating effects of IF may be partly mediated by changes in the composition and functionality of circulating biomolecules, such as increased levels of sirtuins and decreased rates of protein carbonylation, thus promoting cellular health and stability. Recent evidence also suggests that IF may also promote rejuvenation by increasing the formation of new cells in various tissues, primarily the liver [51].

Thus, hepatic lipophagy can be regulated in various ways. Identifying the factors that can mediate targeted control of this process is important from a therapeutic perspective, including through IF patterns. However, the process of autophagy itself is quite complex and requires the coordinated action of more than 30 genes and corresponding proteins [67]. Such a complex system is difficult to correct if necessary.

In addition to specific lipophagy, it is worth noting equally important types of autophagy that target membrane cellular compartments (damaged mitochondria, endoplasmic reticulum, and nuclei [52, 53, 54]) and non-membrane compartments (protein aggregates, peroxisomes, P granules, and ferritin) [55]. Time-dependent loss of autophagy skills was found to critically affect the aging phenotype [56]. Furthermore, some lifestyle changes that have a positive role in regulating longevity (including IF and exercise) are usually due to their ability to stimulate autophagy.

One of the major changes that occur during cellular aging is dysregulation of the immune response, leading to a chronic systemic inflammatory state. The important role of the transcription factor NF-κB in maintaining the immune response during age-related inflammation involves the activation of proinflammatory cells, which enhances the expression of various cytokines and chemokines [57]. Abnormal increases in migration of macrophages, T cells, B cells, natural killer cells, and neutrophils, as well as infiltration in the liver during aging, seem to trigger a pro-inflammatory process at the tissue level. Senescent macrophages (M2-like phenotype) are known to demonstrate decreased secretion of pro-inflammatory cytokines, impaired phagocytosis and chemotaxis, and proliferation [58]. Macrophages are preprogrammed to clear SAPS-associated senescent cells; thus, insufficient clearance of senescent cells by senescent macrophages prolongs inflammatory processes, i.e., chronic inflammation. Japanese scientists, who studied physiological system functioning in unique groups of centenarians and elderly (85–99 years old) people, concluded that it was the “suppression” of inflammation, and not the length of telomeres, that was the most important factor in “successful” longevity [59].

One of the hypotheses of chronic inflammation in the liver during aging is the high sensitivity of the transcription factor NF-κB to oxidative stress and changes in redox balance [57]. Constant oxidative stress and disruption of antioxidant defense systems during aging cause an increase in the number of reactive species, including reactive oxygen species, reactive nitrogen species, and reactive lipid aldehydes. Although young organisms have a well-functioning antioxidant system to maintain redox balance, age-related decline in the antioxidant defense system does not maintain redox homeostasis of liver cells, leading to the activation of various pro-inflammatory signaling pathways. In addition to other factors that provoke inflammatory processes in liver cells, a decrease in autophagy processes plays an important role in the aging process [60].

One of the most important mechanisms leading to impaired energy metabolism and aging of the body is the increase in mitochondrial dysfunction. Aging is associated with decreased mitochondrial capacity and increased oxidative stress in the liver, potentially affecting metabolic function. Scientists have found that in rats, the content of hepatic superoxide dismutase and catalase decreases with aging, while there is an increase in mitochondrial DNA damage [61, 62, 63]. As a result, mitochondria produce reactive oxygen species (ROS), which cause oxidative damage to mitochondria. ROS can contribute to mitochondrial DNA damage, oxidation of mitochondrial proteins, a less efficient electron transport chain, and poor quality control in mitophagy. However, antioxidants do not extend lifespan in model organisms through ROS scavenging, suggesting that ROS generation and oxidative stress alone do not cause aging [40]. Instead, ROS are described as important signaling molecules in the cell that induce the expression of protective genes beneficial for longevity. However, a review of current scientific sources has not found a positive effect of antioxidant supplements on the health of patients with various diseases [64].

According to the latest literature, ROS protect the body through the mechanism of the so-called “mitochondrial stress”, in which moderate and temporary stress in mitochondria causes positive reactions at the cellular and tissue levels [65]. This phenomenon can be observed in the context of exercise, calorie restriction, intermittent fasting, or exposure to phytochemicals that stimulate the production of reactive oxygen species (ROS) through the respiratory chain.

Along with the obesity epidemic, up to 10% of the global population has type 2 diabetes, more than one-third of these individuals have NAFLD, and approximately 1 in 6 people have progressive liver fibrosis [68]. By reducing the load on the liver during IF, glucose regulation and insulin sensitivity improve. A study by Wegman M.P. et al. found that IF positively affected glucose metabolism by reducing insulin levels and had an antidiabetic effect [62]. The authors investigated the decrease in insulin levels in IF and found that it was due to the activation of oxidative stress and inflammation in various tissues, including the liver [21]. The effects of IF on metabolic processes are also explained by the regulation of circadian rhythms and lifestyle modification [66].

Allahverdi H. conducted studies on rats subjected to periodic starvation and found that IF had a protective effect against microvesicular steatosis and liver fibrosis in the form of decreased density of collagen and lipid droplets, significantly reduced age-related inflammation in the liver, and inhibited the modeling of the Notch and Hedgehog signaling pathways, which contributed to phenotypic changes in hepatic stellate cells and controlled the transitions between epithelial and mesenchymal states.

Thus, IF can activate hepatic autophagy, which is important for maintaining cellular homeostasis and energy balance, cell and tissue remodeling, and protection against extracellular damage and pathogens. FG affects hepatic autophagy through many interacting pathways and molecular mechanisms, including AMPK, mTOR, sirtuin, peroxisome proliferator-activated receptor alpha (PPARα), as well as signaling pathways and molecular mechanisms such as glucagon and fibroblast growth factor 21 (FGF21). These pathways can modulate the pro-inflammatory cytokines, interleukin-6 and tumor necrosis factor α (TNF-α), play a cytoprotective role, reduce the expression of aging-related molecules, and prevent the development of steatosis-associated liver tumors. Ketone bodies (acetone, acetoacetate, β-hydroxybutyrate) produced in the liver during fasting regulate the expression of several genes involved in antioxidant and anti-inflammatory responses through an epigenetic mechanism [70]. In particular, β-hydroxybutyrate functions as a stress response molecule by inhibiting mitochondrial ROS production in stressed cells due to facilitating NADH oxidation and orchestrating an antioxidant defense program to maintain redox homeostasis in response to environmental and metabolic challenges. β-hydroxybutyrate also leads to lifespan extension [71].

IF protects hepatocytes from genetic and environmental factors by influencing the metabolism of energy and oxygen radicals and cellular stress response systems. By activating hepatic autophagy, IF has a potential role in the treatment of a variety of liver diseases, including nonalcoholic fatty liver disease, drug-induced liver injury, viral hepatitis, liver fibrosis, and hepatocellular carcinoma. A better understanding of IF effects on liver autophagy may lead to new approaches to preventing and treating liver diseases. Overall, various IF patterns, including time-restricted feeding, alternate-day fasting, 5:2 fasting, and fasting-mimicking diet, have been shown to be effective in NAFLD [30].

Characteristic signs of liver aging are the development of steatosis and fibrosis. Raja G. R. and co-authors investigated that activation of ketogenesis in the liver attenuated ROS-mediated progression of steatohepatosis [72]. Cotter et al. found that mice with hepatic ketogenic failure (overfeeding) developed severe hepatocellular injury, characterized by increased numbers of sinusoidal macrophages, infiltration of inflammatory cells, and accumulation of dead hepatocytes. There is also clinical evidence of the effectiveness of some IF patterns in steatohepatitis [73].

A crucial step in the process of hepatic fibrogenesis is the activation of hepatic stellate cells into myofibroblasts. Myofibroblasts have the ability not only to synthesize extracellular matrix components but also to express and secrete many pro- and anti-inflammatory cytokines and growth factors. In particular, transforming growth factor β plays an important role in the development of fibrogenesis. It enhances the expression of matrix genes, reduces the production of matrix metalloproteinases, and increases the production of their tissue inhibitors. Impaired ketogenesis increases lipid accumulation in hepatocytes, leading to lipotoxicity and cell apoptosis [74].

Sanyal A. J. et al. found that NAFLD patients with advanced fibrosis (stage 3–4) were at increased risk of liver complications and death in the elderly, which highlighted the need to identify and prevent fibrosis progression [69]. Fibrosis, for which steatohepatitis is the main progression factor, is a confirmed cause of the development of portal hypertension, which is associated with manifestations of liver decompensation in the form of ascites, bleeding from esophageal varices, and encephalopathy.

However, in cirrhosis, especially in the later stages, the liver already has significant damage; therefore, its ability to regenerate is limited. In such cases, fasting can be dangerous: it can disrupt hormone synthesis and reduce brain function due to insufficient nutrient intake. Also, long gaps between meals can lead to bile stagnation in the gallbladder, which increases the risk of gallstone formation.

CONCLUSIONS

The body's aging process is accompanied by changes in all tissues and organs, including the liver, where signs of aging are represented by the following metabolic disorders: steatosis, fibrosis, and cirrhosis. Under certain conditions, age-related changes transform into pathological processes and lead to liver diseases. The most studied are biochemical, physiological, and morphological transformations in the liver in nonalcoholic fatty liver disease, which is most often observed in elderly patients. However, there are no effective medical treatment regimens for this disease.

Intermittent fasting (IF) has recently been shown to have numerous health benefits and is now being considered as a strategy for the treatment of obesity and other metabolic disorders. A lot of data has appeared in the scientific literature on the positive effect of IF on metabolic processes in the liver, which contributes to functional and structural changes in the organ, enhancing its adaptive potential during the aging process. IF with different feeding–fasting alternating patterns activates autophagic processes in the liver, in particular lipophagy and mitophagy, which are important for maintaining cellular homeostasis, energy balance, cell and tissue remodeling, and protection against extracellular damage. Studies have shown that IF has protective and rejuvenating effects and improves the functionality and composition of biomolecules, which are responsible for homeostatic, energetic, and remodeling processes in liver cells. In addition, IF helps improve metabolic processes and activate oxidative stress and inflammation in various tissues, which helps prevent the development of pathological changes in the liver with age. An important aspect is the physiological nature of this diet, which corresponds to the body's circadian rhythms, which is especially important for the liver, a metabolically active organ.

Intermittent fasting may benefit older adults, but its use requires an individualized approach, considering age-related physiological changes, health status, and nutritional needs. However, there is a lack of evidence regarding the effectiveness of IF in age-related liver disease, including clinical trials that could be used to develop treatment and prevention recommendations. Most of the scientific evidence on the health benefits of exercise in older adults comes from rodent studies, while the effects on humans are largely limited to observational and cross-sectional studies, as well as experiments with small numbers of participants. Because rodents' eating habits differ from those of humans, especially due to nocturnal circadian rhythms, not all results obtained in animals can be directly applied to humans.

Thus, the results of this analysis may serve as an incentive for further IF research as a cost-effective, effective, and safe way to counteract age-related changes in the liver, as well as prevent and treat chronic diseases.

PROSPECTS FOR FUTURE RESEARCH

Prospects for further research: study of clinical and morphological features of liver changes in rats of different age groups under conditions of interval fasting.

AUTHOR CONTRIBUTIONS

Kryvozub D.: concept of the work and research design; data collection and analysis; writing.
Ryabenko T.: critical review; final approval of the article.
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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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The authors declare that no artificial intelligence (AI) technologies were used during the writing or editing of the manuscript.

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