Chronic Stress and Steatosis of Muscles, Bones, Liver, and Pancreas: A Review

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Keywords

Stress · Myosteatosis · Osteosarcopenic obesity · Nonalcoholic fatty liver disease · Nonalcoholic fatty pancreas disease · Nonalcoholic steatohepatitis

Abstract

Background: Chronic stress is a recognized risk factor for poor health, body composition disequilibrium, impaired mental health, and deterioration of quality of life. Chronic stress-related cortisol oversecretion and circadian dysregulation and associated systemic low grade, injurious inflammation (“para-inflammation”) contribute to steatosis in various metabolically active solid organs, affecting both their structure and function. The aim of this review was to summarize current knowledge on the impact of chronic stress and associated para-inflammation on skeletal muscle, bone, liver, and pancreas, leading to their steatosis. Current management of these maladaptive conditions is also included and underscored in this review. **Summary:** Steatosis of metabolically active solid organs is involved in various metabolic processes and considered a risk factor for chronic noncommunicable diseases, yet its role in chronic stress physiology and pathophysiology has been overlooked. **Key Messages:**

Chronic stress-associated steatosis of several solid organs is generally disregarded in current clinical practice. Physicians should be alert for these steatoses and should address them adequately so as to provide appropriate medical care. New guidelines generated by learned societies are needed, along with large observational studies, to offer novel solutions to this old problem.

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Introduction

Chronic stress is defined as a protracted “dyshomeostatic,” or “cacostatic,” state due to real or perceived threats, the stressors; in this state, normal homeostasis cannot be reestablished via the multifaceted behavioral and physiological adaptive responses of the human organism [1]. These responses are effected via discrete biochemical processes, acting as compensatory mechanisms, which may have a pathophysiologic “cost” for the human organism (allostatic or cacostatic load). Frequent activation of these maladaptive compensatory systems, failure to switch off the stress response after the cessation of the stressor, bringing about altered activities of parts of the

Fig. 1. Summary of the review.

stress response potentially lead to the onset and progression of a number of chronic noncommunicable diseases [2].

Consequently, chronic stress is an established risk factor of chronic noncommunicable diseases [3]. Chronic mental or physical stressors induce various stress responses and apply cacistatic loads on the organism [4]. The chronic stress-related dysregulation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system influence, mostly negatively, various functions of the immune system [5, 6]. Thus, many studies have demonstrated deterioration of cell-mediated immunity during chronic stress [7, 8], while others have shown that chronic stress is associated with a smoldering, low grade systemic inflammation, which is injurious rather than beneficial to the organism and has, hence, been called “para-inflammation.”

A significant epidemiologic transition has been observed during the last 50 years; thus, the leading causes of death are no longer infectious diseases, but rather chronic, noncommunicable diseases, such as cardiometabolic, allergic/autoimmune, and mental/behavioral disorders, closely associated with the epidemic of obesity. As a result, one substantial controlling factor of overall health, wellness, quality of life, and life expectancy, seems to be the body composition. Body composition disorders affected by poor quality and excessive quantity of nutrition and lack of physical exercise are also induced by chronic stress and associated behavioral and physical changes. Thus, negative behavioral reactions, associated with “comfort eating,” overeating, or binge-eating, are quite

common in chronically stressed individuals [9], while increased concentrations of pro-oxidation factors are observed in all metabolic tissues. The cumulative deleterious effects of chronic stress on body composition have been repeatedly shown in different types of analyses [10–13].

Complex metabolic disorders, such as osteosarcopenic obesity (OSO), prediabetes, metabolic syndrome (MetS), diabetes type 1 and 2, polycystic ovaries syndrome, non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and nonalcoholic fatty pancreas disease (NAFPD), are all products of the damaging actions of chronic stress and associated para-inflammation. Their pathogenesis is mediated by the sustained, excessive secretion and actions of the major mediators of the “stress” and “sickness” (“inflammation”) syndromes, which influence the activities of multiple homeostatic systems. “Steatorsis” refers to the phenomenon of fat infiltration of and/or collection in various tissues in body composition disorders. “Myosteatorsis” frequently accompanies sarcopenia, osteopenia or osteoporosis, OSO, central/visceral adiposity, NAFLD, NASH, and NAFPD. These disorders represent chronic, maladaptive effects of the above two physiological programs, those of stress and inflammation, whose mediators are meant to be secreted in a quantity- and time-limited fashion, but whose actual secretions have been protractedly deranged and damaging [14].

Concomitance of chronic stress and para-inflammation and disordered body composition is frequent in the general population, and usually underreported in epide-

miologic studies. The aim of this review was to summarize the current knowledge on the role of chronic stress on skeletal muscle, bone, liver, and pancreatic steatosis (Fig. 1). Emphasis is also given on the current treatments of these disorders.

Methods

A search strategy was developed for PubMed; the algorithmic procedure resulted from the combination of the following MESH words: stress OR oxidative stress OR inflammation OR stress-derived cytokines AND sarcopenia OR frailty OR osteosarcopenic obesity OR osteoporosis OR bone marrow fat OR bone marrow reconversion OR bone marrow steatosis OR NAFLD OR NAFLP OR obesity. No restrictions were applied to publication language or study design. “Snowball” procedure was employed; reference lists of relevant articles were hand-searched for potentially eligible studies to maximize the amount of evidence. Interventional, prospective, and retrospective studies, in vitro and animal studies, narrative, systematic reviews, and meta-analyses were included. SANRA scale was used to improve the general quality of this review [15].

Stress and Skeletal Muscle Steatosis

Fat infiltration of the skeletal muscle mass (myosteosis), and when not prevented, reversed, or halted, results in myopenia/sarcopenia and may possibly lead to cachexia [16]. Myosteosis presents as intermuscular or intramuscular adipose tissue, and as intramyocellular lipids. These deposits comprise different risk factors of metabolic muscle health [17]. Intermuscular adipose tissue includes fat content between muscle groups and found beneath the muscle fascia, but outside the muscle *per se*. Intermuscular fat is, thus, considered an “ectopic” fat depot. Intramuscular fat, on the other hand, is the fat found within the cells of a muscle.

Intermuscular adipose tissue is an active element in the skeletal muscle mass, capable of secreting pro-inflammatory cytokines and other mediators of inflammation, and contributing to the process of para-inflammation, decline of muscle cell proliferation and differentiation, and catabolism. Intermuscular and intramuscular fat has been associated with decreased insulin sensitivity of the skeletal muscle contributing, thus, to the MetS. Indeed, the accumulation of fatty acids, long chain-CoA esters, diacyl-glycerol, and ceramides decreases insulin action by inhibiting the insulin PI3K/Akt/mTOR signaling pathway [18]. Intramuscular fatty infiltration in the form of intramyocellular lipids, on the other hand, alters muscle fiber orientation and decreases muscle strength, increas-

ing the risk of dynapenia [19]. Several studies have shown deteriorated mitochondrial function in myosteosis [20].

Myosteosis is common in wasting disorders, such as cancer, malnutrition, advanced age, and several genetic diseases, and not a synonym for sarcopenia/myopenia [21]. There are many contributing factors, such as defective leptin signaling, deficient function of skeletal muscle stem cells, impaired mitochondrial function, decreased blood flow, and impaired neuronal signaling in the skeletal muscles, leading to skeletal muscle function deficit [22]. When combined with increased concentrations of inflammation markers, myosteosis is associated with an unfavorable course in several groups of patients [23–25]. Chronic stress and accompanying para-inflammation create a pro-oxidant microenvironment that promotes adipogenic signaling, causing progenitor mesenchymal stem cells of the skeletal muscles to dysfunction and to be diverted towards adipogenesis, ultimately creating a hypertrophic and hyperplastic ectopic fat mass [12, 23].

To summarize, chronic stress and the associated para-inflammation exacerbate the steatosis of the skeletal muscles and promote the onset and progression of chronic noncommunicable disorders. The causes of myopenia and myosteosis are multifactorial and the two states may share a common pathogenesis. Many underlying factors contribute to a decline in muscle health, including catabolic and anti-anabolic humoral mediators, such as cortisol and interleukin-6, and activation of proteolytic processes, such as those caused by glucocorticoids and pro-inflammatory cytokines, adipokines, and myokines [24]. The genetic background of the human organism and the epigenetically active environment, such as a sedentary lifestyle, poor nutrition, etc., act together in the aforementioned detrimental pathologic phenomenon [25]. Involvement of other tissues in alterations in quantity and/or quality of skeletal muscle adds complexity to the problems of myosteosis, myopenia, and dynapenia [26].

Stress and Bone Steatosis (Osteopenia/Osteoporosis, OSO, and Bone Marrow Reconversion)

Pathophysiologic connections between chronic oxidative stress and osteopenia/osteoporosis have been already established [27, 28]. Also, abdominal obesity, hypertension, dyslipidemia, and insulin resistance (all components of the MetS) are closely related to osteopenia/osteoporosis [29]. In addition, fat mass has been inversely correlated to bone mineral content in adult males and

females, while abdominal obesity, measured by waist circumference, has been negatively associated with bone mineral density, independently of total fat mass.

Of note, a strong relation between major depression and osteoporosis has been established, granted that increased secretion of stress hormones and pro-inflammatory cytokines takes place in depression (chronic stress and para-inflammation), which contributes to sarcopenia/myosteatosis progression. On the other hand, sarcopenia/myosteatosis progression-related chronic pain and impaired mobility in osteoporosis patients may disturb daily activities and, thus, contribute to the pathogenesis of depression [30]. Female populations are the main subjects in studies of depression and osteoporosis, as both entities are more prevalent in females than males. Osteoporosis has been documented as a major cause of morbidity in males as well, while unipolar depression, not as common as in females, still affects one in ten males [31].

OSO is another facet of chronic stress-related steatosis. In this entity, stress leads to an inapparent “cachectic” phenotype, consisting of reduced muscle mass, reduced bone mass, increased fat in the bone marrow and liver, and visceral and/or subcutaneous fat adiposity. It seems to be a phenotype that not only pertains to the elderly, or patients with chronic stress-related disorders [10, 32], but also young populations [11, 13, 33]. Recent studies demonstrated that chronic stress and its related pro-inflammatory mediators contribute to osteopenia/osteoporosis, sarcopenia, and excess adiposity, ultimately leading to OSO, via disturbances of differentiation in the mesenchymal cell lineage [34]. OSO has been associated with increased fracture risk, impaired functional status – with multiple psychologic and physical complaints (“medically unexplained symptoms”), which may include daily living activities, physical disability, increased risk of infections, increased length of hospital stays, and reduced survival rates [26].

Hematopoiesis occurs in the bone marrow microenvironment. The bone marrow is a complex tissue containing cells of different embryologic origin with different functions, important for maintenance of homeostasis. Negative influences, such as chronic stress and the associated para-inflammation, may disturb homeostasis and affect normal hemopoiesis and other bone marrow functions. The microenvironment of the bone marrow, in fact, has a central role in mediating, balancing, and integrating stressful stimuli, representing a key tissue to fully understand the physiology and pathophysiology of inflammation, lipogenesis, osteogenesis, and myogenesis [35].

Yellow bone marrow is a chief source of pro-inflammatory mediators [36], exhibiting distinct immune regulatory properties [37]. Interestingly, patients with anorexia nervosa had, as expected, reduced subcutaneous and visceral fat, but an increased quantity of yellow bone marrow [38]. Increased yellow bone marrow is actually a risk factor of reduced bone density and integrity, as it is implicated in the regulation of bone turnover [29]. Conversion of red to yellow bone marrow, called “bone marrow reconversion,” results from the differentiation of mesenchymal stem cells of the bone to fat cells in response to chronically stressful stimuli [39]. Visceral adipose tissue and yellow bone marrow are potent risk factors of disturbed bone microarchitecture in obese persons, in contrast to muscle mass, which has been already defined as a positive predictor of bone and muscle health [40]. Bone marrow reconversion has been described in pediatric patients with trauma, infections, obesity, NAFLD, and in-born errors of metabolism [41–44], and in adults, who are smokers and/or obese, as well as in patients with sleep apnea [45].

Stress and Hepatic Steatosis

NAFLD serves as an umbrella term for several liver disorders, ranging from hepatic steatosis to NASH. Hepatic steatosis or fatty liver is described as increased accumulation of lipids in hepatocytes; it emanates from increased production or reduced clearance of hepatic triglycerides or fatty acids. NASH is the last stage of the disorder, with necro-inflammatory liver disease and hepatic fibrosis being typical findings in histologic images [46]. Presence of increased oxidation and dysfunction of the hepatocytes, along with dysregulation of lipid metabolism, have been demonstrated in progressively deteriorating fatty liver stages. NAFLD is now deemed part of the MtS constellation, paralleling epidemiologically the obesity pandemic [47].

Although chronic stress has been implicated as a contributing factor in the severity and progression of several disorders, the role of stress in liver disease, in general, and hepatic inflammation specifically, has not gained substantial scientific attention, apart from the observation of decreased hepatic blood flow and the accompanying hypoxic vasospasm. In acute hepatic inflammation, the hypothalamic-pituitary-adrenal axis is activated, while patients with chronic liver disease have delayed cortisol clearance and altered cortisol binding to the cortisol-binding globulin in plasma.

The activation of the sympathetic nervous system, i.e., the central sympathetic nerve pathways and the peripheral sympathetic outflow, results in the release of catecholamines from postganglionic nerve terminals and from the adrenal medulla. The released catecholamines, which constitute the peripheral effector of this arm of the stress response, stimulate the secretion of hepatokines, such as FGF21, hepcidin, fetuin A and B, and selenoprotein P, further aggravating impairments in glucose and lipid metabolism [48]. In patients with either acute liver failure or hepatic cirrhosis, concentrations of plasma catecholamines are elevated. Thus, up-regulation of the sympathetic arm of the stress system occurs in these patients. Moreover, plasma norepinephrine concentrations increase in acute toxin-induced hepatic inflammation in rats. Sympathetic activation drives the Th1/Th2 balance toward more Th2 expression, due to increases of IL-4, IL-5, and IL-10 and beta-adrenoreceptor-induced inhibition of IL-12 production [5]. A catecholamine-induced increase in IL-10 release from monocytes also appears to occur in vivo. This sequence of events promotes an adipogenic environment in the hepatic tissue [49]. NASH progresses in a continuing mode as follows: steatosis of liver cells, activated cascade of inflammation, fibrosis, and cirrhosis. The lipotoxicity of hepatic fat further induces inflammatory and oxidative stress [50].

Chronic stress affects the immune system, eliciting an imbalance between pro-inflammatory and anti-inflammatory cytokines. The upregulated biochemical pathways activated during stress initiate and exacerbate the formation and activity of the inflammasome and might lead to hepatocyte death by apoptosis and liver damage. Inflammatory stress pathways initiate and aggravate the progression of NAFLD by increasing the influx and reducing the efflux of lipids, especially during the second-hit stage of NAFLD. The activators of IL-1, NLRP6 and NLRP3 inflammasomes accelerate the rate of NAFLD and NASH progression, as well as multiple components of the MetS. A recent study extended the aforementioned findings by demonstrating that maternal obesity may be linked to NAFLD in the offspring [51].

Last, but not least, there are multiple reports on the positive association between the bone marrow fat mass and the hepatic fat content in children and adults with known or suspected NAFLD [52]. An interesting positive association was also found between epicardial adipose tissue and NAFLD, rendering the former a risk factor for NAFLD and vice versa [53].

Stress and NAFLD

Fat accumulation in the pancreas associated with obesity and the MetS has been defined as NAFPD. Other terms have also been used, including fatty pancreas, pancreatic steatosis, lipomatous atrophy of the pancreas, pancreatic lipomatosis, pancreatic adiposity, fatty replacement of the pancreas, and fatty infiltration of the pancreas [54].

An association of NAFPD with adipocyte-derived inflammatory factors has been suggested, especially those induced by free fatty acids. The expression of IL-6, tumor necrosis factor- α , and monocyte chemoattractant protein-1 in rats with free fatty acid hyperlipidemia, the percentage of body fat, and the amount of visceral fat were significantly increased [55].

Obesity and MetS have been recognized as risk factors for NAFPD. The latter initiates a vicious cycle of pancreatic islet beta-cell deterioration of function and further organ fat accumulation. Latest evidence indicated a correlation between NAFPD and atherosclerosis markers, such as carotid intima-media thickness. A recent meta-analysis reported that NAFPD was significantly associated with an increased risk for MetS and its components [56]. NAFPD seems to be more common in the general adult population and to better reflect dysmetabolic status, perhaps because it is more easily detectable than NAFLD. NAFLD, diabetes mellitus, HOMA-IR, increased circulating total cholesterol, triglyceride, lipoprotein, and adiponectin concentrations, and decreased glucagon-like peptide 1 (GLP-1) concentrations were independent risk factors for the onset of the NAFPD. It has been suggested that NAFLD presence and increased circulating triglyceride, lipoprotein, and adiponectin concentrations, were independent risk factors of NAFPD progression. Epidemiologic data are scant due to the lack of standardized methods of detection of this entity [57], however, NAFPD prevalence was reported in between 11%–35% of Chinese adults [58]. Severe NAFPD, in terms of the extent of fat deposition, was associated with NAFLD and dyslipidemia [58]. A large meta-analysis demonstrated a high prevalence of NAFPD and suggested a normal cutoff point of 6.2% for ectopic pancreatic fat [59].

NAFPD is, hence, a marker of local fat accumulation, islet beta-cell dysfunction, carbohydrate intolerance, atherosclerosis, acute and chronic pancreatitis, and exocrine pancreatic insufficiency, or even a pancreatic fistula [60]. NAFPD has been significantly and positively correlated to NAFLD, possibly due to a similar pathophysiologic

process; of note, pancreas and liver are both derived from the same embryonic endoderm, which may explain, to some extent, the similarities and relations of fat accumulation in both conditions. In approximately half of pediatric patients, NAFLD is comorbid with NAFLD, corresponding to presence of NAFLD in 80% of NASH patients, while NAFLD children with comorbid NAFLD had more severe insulin resistance and liver disease than those with NAFLD alone [61].

Current Therapeutic Interventions

For the time being, no specific therapeutic or interventional guidelines exist for the steatosis of muscles, bones, liver, and/or pancreas beyond proper lifestyle changes. The Hippocratic suggestion of daily exercise and moderate consumption of good quality food remains the mainstay of treatment, along with all treatment modalities of obesity.

Exercise

Health-related physical fitness includes cardiorespiratory fitness, a good body composition, and muscular fitness. All these should be considered when exercise is recommended. Evaluation of exercise regimens and their effects remains controversial. The weekly recommended duration of aerobic conditioning is 150 min, as it serves as a minimum for the treatment of obesity. Resistance training is advised as part of an overall fitness program, as it does not increase VO_{2max} significantly, consumes only moderate amounts of calories, and slightly alters the resting metabolic rate [62]. Resistance and combined aerobic exercises are recommended to protect against bone loss during body weight loss therapy of older adults with obesity [63]. Resistance exercise may improve muscular strength and affect favorably various functional tasks of the muscle. Resistance training may also stimulate an increase in fat free mass, although it does not contribute to body weight loss [62].

Dietary Regimens

Numerous guidelines recommend that energy intake should be diminished or controlled. Many types of diets have been proposed, such as very low-carbohydrate or ketogenic diets, Mediterranean diet, intermittent fasting, protein-sparing modified fasts, and many other calorie-restriction regimens, such as formula-based regimens, preprepared foods, or detailed meal plans for the adults. In children and adolescents, body weight loss for specific

groups of patients with obesity and associated comorbidities or severe obesity, should be based on age, growth, pubertal status and/or BMI percentile. A personalized dietary intervention approach to dietary change, rather than the traditional focus on energy restriction alone, may provide additional benefit for young people with obesity and severe obesity, who are likely to present with comorbidities. Also, in children and adolescents, family involvement in the implementation of dietary regimens is indispensable for success [64].

Stress Management Programs

Mindfulness stress management programs seem to be the center of attention for the complementary medicine obesity management for adults [65], but, also, for children and adolescents [66]. There is a growing number of studies supporting the benefit of implementing stress management and emotional control training in obesity management. Mindfulness stress management programs, implementing the “here and now” mentality, are promising therapeutic options for improving body weight loss, food awareness, self-acceptance of body image, and limiting food cravings and emotional eating. Large studies of various ages are needed to determine whether these strategies are effective in the long-term and whether they can be consistently introduced into the clinical practice.

Pharmacological Modalities and Bariatric Surgery

Myosteatosis and bone steatosis reduction via the use of pharmacological treatments has not been evaluated as yet. Nevertheless, studies evaluating treatment of osteoporotic patients have reported a concomitant increase of skeletal muscle mass [67]. Troglitazone and orlistat administered to mouse models significantly prevented or reversed pancreatic fat infiltration and reduced organ failure and mortality via body weight loss [60]. Combination of sitagliptin and telmisartan demonstrated efficacy in controlling NAFLD progression in mice. Other pharmacological modalities are under investigation [68]. Given the similarities with NAFLD, early treatment of NAFLD should be emphasized with the goal of minimizing pancreatic fat accumulation through a healthy diet, body weight loss, and physical exercise [60]. Body weight loss and bariatric surgery decrease pancreatic triglyceride content, but pharmacological treatments of NAFLD have not been evaluated. Evidence for the reversibility of NAFLD has been found in both animal and human studies.

Conclusions

Chronic stress-induced multi-organ steatosis is common, preventable, and when detected early, reversible in the general population, irrespectively of any concurrent disease. Due to the morbidity and mortality associated with solid organ steatosis, clinicians should be on guard and should employ preventive measures against the steatosis of the muscles, bones, liver, and pancreas. For the time being, only healthy routine measures of lifestyle may be implemented, such as moderate consumption of good quality food, regular physical exercise, healthy sleep, and sustained regularity of daily meals, activity, and sleep on-set, and sleep hygiene. Experts should develop guidelines about the steatosis of solid organs, preventing its onset and progression, decreasing their prevalence and incidence. Future studies should be performed to discover novel pharmaceutical agents, aiming at the skeletal mus-

cles and their mitochondria, the yellow bone marrow, and the immune cells of the liver and the pancreas, among other targets.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed equally and according to ICMJE criteria for authorship.

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