Chronic stress and body composition disorders: implications for health and disease

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Abstract

Recent studies have suggested that body composition is key to health and disease. First, fat tissue is a complex, essential, and highly active metabolic and endocrine organ that responds to afferent signals from traditional hormone systems and the central nervous system but also expresses and secretes factors with important endocrine, metabolic, and immune functions. Second, skeletal muscle mass is an important predictor of health in adult life, while severe mass loss has been associated with the frailty of old age. Studies have shown that skeletal muscle is also an important endocrine organ that secretes factors with autocrine, paracrine, or endocrine actions, which have been associated with inflammatory processes. Third, the bone is also a systemic endocrine regulator playing a pivotal role in health and disease. Finally, proper hydration in humans has been neglected as a health factor, especially in adults. Chronic stress and stress hormone hypersecretion alone or associated with distinct disorders, such as anxiety, depression, obesity, metabolic syndrome, autoimmune disorders, type 2 diabetes mellitus, and polycystic ovary syndrome (PCOS), have been associated with psychological and somatic manifestations, typically, increased fat mass, osteosarcopenia/frailty, cellular dehydration, and chronic systemic inflammation. This review aims to provide new insights into the newly developed concept of stress-related osteosarcopenic obesity and its prevention.

Keywords Body composition · Stress hormones · Stress physiology · Muscle · Fat · Bone

Introduction

Body composition is defined as the percentages of adipose and lean body masses as well as of body water volume [1]. Body composition has been included in all textbooks of medical physiology, primarily with reference to water and electrolyte imbalance disorders. Generally, however, water homeostasis has been overlooked, despite the widespread epidemic

of our time, obesity [2–4]. In everyday clinical practice, fat mass is evaluated mainly by using common methods of anthropometry, such as body weight, height, and fat measurements using common scales, stadiometers, measuring tapes, and skinfold calipers [5]. A series of mathematic formulas, also known as anthropometric indicators, such as body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), and waist-to-height ratio (WtHR), has been used to identify obesity, abnormal patterns of fat distribution, and extent of abdominal adiposity [6].

BMI alone does not distinguish between lean and fat masses and does not incorporate assessment of the distribution of fat mass. WC, HC, WHR, and WtHR are useful markers of fat distribution and abdominal adiposity but do not provide information on water volume and muscle or bone mass. More advanced methods, such as computed tomography (CT), nuclear magnetic resonance (NMR), dual-energy X ray absorptiometry (DXA), ultrasound (US), or bio-impedance (BIA) methods, have been employed. The DXA accurately estimates bone, fat, and muscle masses but not water volume compartments. BIA devices, via the application of electrical currents sent through the body, estimate water volume and lean and fat

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masses, while U/S devices evaluate organ-specific fat content in semi-quantitative ways [7]. The provision of such methods in the evaluation of body composition is justified by the major effects that body composition exerts on human health. Obesity, a modern-day epidemic, is just one aspect of the several kinds of body composition disorders [8].

Obesity is the condition of abnormal or excessive fat accumulation to the extent that body health is impaired. It is caused by an imbalance between the energy input of the diet and the body's energy demands [9–11]. Fat accumulation in various tissues has been implicated in many metabolic disorders, such as non-alcoholic fatty liver disease (NAFLD) or hepatosteatosis [12] and myosteatosis [13]. Both entities may co-exist not just in obese or overweight patients but also in lean subjects. Recently, a combined entity was identified: osteosarcopenic obesity, i.e., obesity associated with both sarcopenia and osteopenia. This may result from chronic stress system hyperactivity [14, 15]. This non-systematic review aims at clarifying the role of chronic stress in the onset and natural history of disorders of human body composition.

Methods

A search strategy was employed for PubMed site using the following key words: obesity, OR body composition, OR water imbalance, OR osteopenia, OR sarcopenia, OR overweight, OR fat mass, OF muscle mass, OR bone mass, AND stress, OR stress hormones. No restrictions related to publication language, date, or study design were implemented. Reference lists of relevant articles were hand-searched for potentially eligible studies (“snowball” procedure) to maximize the amount of synthesized data. Interventional, prospective, and retrospective studies, in vitro and animal studies, narrative and systematic reviews, and meta-analyses were included.

Body composition disorders and stress

Water volume: dehydration

Water, as a key component of life, is a pivotal constituent of the human body. It is a principal factor in metabolism and thermoregulation, plays an essential role in metabolism, and acts as a solution medium, a reactant, and a reaction product of metabolism [16]. In addition, it is a lubricant and a shock absorber. Over half of the mass of the human body in adults is constituted of water (about 60%). This ratio is high in infants (75–80%), toddlers, and children (75–65%), reaches lower percentages in adolescents (60–65%), and may fall to a nadir of 40% in aged humans. In a human of average weight

and height, water volume is distributed in the extracellular (40%) and the intracellular (60%) water compartments [17].

Hydration status is regulated by homeostatic mechanisms residing in the brain, the cardiovascular system, and the kidneys. A homeostatic balance is maintained by the amount of water uptake, the proportion of water included in food, and the water that is produced during metabolism vs. the water consumed or excreted [18]. The primary mechanism of water homeostasis lies in the brain. When water balance is disrupted, the osmotic pressure of the extracellular fluid compartment (ECF) increases. By activation of hypothalamic osmoreceptors, antidiuretic hormone (ADH) is released from the posterior pituitary gland. Both the increased ECF osmotic pressure and ADH elicit the feeling of thirst, while ADH acts on the kidneys to increase water reabsorption even before thirst is elicited. Thirst is often blunted in elderly subjects, who are at risk of having an insufficient water intake in conditions of elevated temperature and humidity.

Both deficient and excessive water intakes are counterbalanced by subtle hormonal changes (renin-angiotensin-aldosterone system—RAAS—ADH, and atrial natriuretic peptide—ANP) that contribute to buffering the deleterious effects of these abnormal conditions [19, 20]. The kidneys are the main sites and regulators of water losses, their unique property being the ability to modify the osmotic pressure of urine within a large range in response to minute changes in plasma osmotic pressure. Aldosterone stimulates sodium and water reabsorption from the gut and the salivary and sweat glands in exchange for potassium. It further stimulates the secretion of potassium into the tubular lumen, thereby upregulating epithelial sodium channels, in the collecting duct and the colon, increasing apical membrane permeability for sodium and thus absorption [21].

Induction of the HPA axis during stress interacts with the activated RAAS to sensitize subsequent behavioral and autonomic responses to hydromineral imbalance; however, central angiotensinergic circuits activated by subsequent exposure to a psychogenic stressor may also be primed for heightened stimulation [22, 23]. Real threats to water homeostasis and perceived threats derived from psychogenic stress activate the RAAS. Blood-borne angiotensin-II (Ang-II) stimulates angiotensin type 1 receptors (AT1) expressed on neurons residing in circumventricular organs (CVOs). These neurons have direct connections to hypothalamic and limbic nuclei controlling physiologic and behavioral responses to systemic and psychogenic stressors. In addition, AT1 receptors are present on neurons within the confines of the blood-brain barrier and their expression is regulated by the hydration state and stress exposure. These AT1 receptors most likely bind brain-derived Ang-II and influence the function of neurons mediating hydromineral balance and cardiovascular function, as well as affect and mood [24]. Several studies have also demonstrated that aldosterone concentrations are higher in depressed

subjects than in healthy controls, eliciting more prominently the aforementioned responses [25, 26].

The RAAS occasionally fails to maintain water homeostasis, resulting in dehydration. Apart from water losses, dehydration may also result from shifts in water compartment redistribution; these water shifts are exaggerated by the actions of cortisol [27, 28]. ANP increases glomerular filtration rate and the sodium filtration fraction, reduces cardiac output, and inhibits both renin secretion and the aldosterone response to angiotensin [29]. As mentioned above, during stress, water tends to shift from the intracellular to the extracellular water compartment to maintain homeostasis of blood pressure and plasma volume. Non-osmotic release of ADH activates the sympathetic nervous system and the RAAS. Moreover, the sympathetic nervous system is involved in the non-osmotic release of ADH (carotid and aortic baroreceptors) and in the activation of RAAS primarily through renal beta-adrenergic receptors [30].

All in all, in terms of physiology, stress is equal to dehydration for the average human, whether this is due to behavioral changes or to physiologic mechanisms (Fig. 1).

Muscle mass: myosteatosis and sarcopenia

Skeletal muscle is a key organ exhibiting plasticity by adapting its mass to environmental cues, while it affects pathways of carbohydrate, lipid, and protein turnover. Skeletal muscle, the target of numerous hormones, is itself a secretory organ of cytokines and other polypeptides, termed myokines. These myokines have autocrine, paracrine, and endocrine actions and are involved in inflammatory processes. The health of the skeletal muscle is largely dependent on the optimal function of its mitochondria. Muscle mass functionality also depends on the turnover of contractible muscle fibers. Therefore, the health of skeletal muscle mass depends on the production and degradation of protein fibers, a delicate and dynamic balance. Another important aspect of skeletal muscle physiology is its dense vasculature. Muscle contraction depends on an active consumption of energy substrates, provided by an extensive net of muscle microcirculation [31].

The endomysium, perimysium, and epimysium of skeletal muscles, formed of layers of extracellular matrix, provide essential structural and mechanical support to contractile proteins. For proper function, the skeletal muscle requires adequate elasticity and protein contractility and relies heavily on sufficient cell-matrix interactions. A compound system of collagen, non-fibrillar collagens, proteoglycans, matricellular proteins, matrix metalloproteinases, adhesion receptors, and signaling molecules maintain the physical structure for force transmission within motor units, entrench cellular structures, such as capillaries, and motor neurons, and enable essential sarcolemma-matrix adhesion processes and molecular signaling. Recent proteomic studies confirm that the extracellular

matrix readily influences the integrity of the muscles and their cellular functions. Thus, changes in the organization of the extracellular matrix play a crucial role during muscle protein regeneration following injury, extensive neuromuscular activity, or pathologic insults.

Exercise training, which is perceived as a stress event by the human organism, causes elevations of the circulating concentrations of catecholamines and cortisol. Catecholamines stimulate local production of IGF-I and IGF-II by the skeletal muscle. Activation of beta-adrenergic receptors increases intracellular cAMP levels and activates protein kinase A (PKA), which may also stimulate the AKT pathway and the transcription factor CREB, a pathway that should be investigated in contracting muscle. The increase in skeletal muscle glucose uptake during exercise results from a coordinated increase in rates of higher capillary perfusion, surface membrane glucose transport, and intracellular substrate flux through glycolysis. During exercise, skeletal muscle satellite cells are activated, these constituting a distinct muscle precursor cell subtype responsible for postnatal adaptation, growth, and repair. To conclude, since the balance between protein production and degradation is very delicate, every factor affecting this cascade may influence the health of skeletal muscle, contributing to disease [32, 33].

Classic proinflammatory cytokine release, such as that of IL-6, in response to exercise seems to exert pleiotropic effects in skeletal muscle by increasing glucose uptake and fatty acid oxidation locally. Simultaneously, hepatic glucose output and fatty acid release from adipose tissue are stimulated to provide energy substrates for the exercising muscle. Other proinflammatory cytokines may act as anabolic factors in skeletal muscles [34].

Paradoxically, muscle-originating IL-6, i.e., a myokine, increases during exercise training and provides important autocrine and paracrine benefits by regulating energy metabolism. In persistent inflammatory conditions, such as those experienced during chronic stress, IL-6 secretion and action are coupled with increased muscle wasting, very often acting in combination with cortisol and other molecules to promote atrophy. The direct action of IL-6 as a regulator of atrophy has not as yet been definitively corroborated by experimental findings [35–37]. Hyperactivation of the HPA axis associated with hypercortisolemia and subclinical systemic inflammation disrupts the metabolism of muscle mass. Chronic stress and the stress hormones also affect skeletal muscle mitochondrial functions, rendering significant numbers of mitochondria inactive, resulting in their inability to cover their metabolic needs [38–41]. Hypercortisolemia, on the other hand, induces accumulation of fat within the muscle as well as a dramatic decrease of skeletal muscle mass called, respectively, myosteatosis and sarcopenia [32].

Thus, chronic stress and associated hypercortisolism together with systematic low-grade inflammation negatively

Fig. 1 The impact of stress on hydration

impact on muscle mass, resulting in mitochondrial dysfunction. This dysfunction, in the form of either dysregulated exchange between mitochondria and endoplasmic reticulum [42] or reduced mitochondrial biogenesis and quality control [43], may lead to sarcopenia, myosteatosis, osteosarcopenic obesity, and, ultimately, cardiometabolic diseases (Fig. 2) [44].

Fat mass: obesity and non-alcoholic fatty liver disease

Fat mass, also known as adipose tissue, acts like a thermal insulator and as an energy deposit in the form of triacylglycerols. Adipose tissue is also an active endocrine organ synthesizing and releasing adipokines, i.e., fat-derived cytokines, complement components, growth factors, extracellular matrix proteins, and vasoactive agents. There are three types of adipose tissue, white, beige, and brown. A stem cell type of preadipocytes grows into mature adipocytes according to the energy needs of the human organism.

White adipose tissue includes the subcutaneous abdominal, visceral, retroperitoneal, inguinal, and gonadal fat depots. In contrast to white adipocytes that play a role in energy storage, brown and beige fat cells display energy-dissipating capacity and generation of heat in the process of thermogenesis. Brown adipose tissue contains a large quantity of mitochondria with laminar cristae. It is abundant in neonates and, because of its biological function of thermogenesis, is critical at this age. Thermogenesis is possible because of the presence of uncoupling protein-1 (UCP1), a mitochondrial protein that induces heat production by uncoupling respiration from ATP synthesis [45].

Positron tomography studies have revealed that adults have active brown fat in their neck, supraclavicular fat, mediastinum, and paravertebral and suprarenal region [46, 47]. The presence of brown-like cells within adipose tissue is termed beige fat. Beige adipocytes, which appear to originate from endothelial and perivascular cells within white adipose tissue, have a unique gene signature, different from that of white and

brown adipocytes. Under normal conditions, beige adipose tissue expresses low levels of UCP1, but upon β -adrenergic stimulation induced by exposure to cold or by exercise, beige adipocytes exhibit thermogenic properties [48].

When hyperplasia or hypertrophy of adipose tissue occurs, obesity begins. Obesity is merely part of the phenotype of a “diseasome” that is not restricted by age, body weight, or BMI [8, 49–52]. Thus, individually, BMI cannot be solely attributed to excess of fat or skeletal muscle masses [8]. Body phenotypes with relatively normal BMI may exist with accompanying increased fat mass, and/or visceral obesity, that cannot be defined by BMI calculations. Frequently, there are nonlinear relations between structure and function and the various component masses of living organisms. Allometric scaling of body mass provides a theory-based method for predictions of mass-related biological characteristics [53]. Thus, in “lean” obese subjects (with a lean BMI), there is a relatively high visceral fat content and low skeletal muscle mass [54].

Obesity is associated with adipose tissue dysfunction leading to the development of several pathologies, including carbohydrate intolerance, insulin resistance, type 2 diabetes mellitus, dyslipidemia, non-alcoholic fatty liver, or hypertension [55, 56]. The mechanisms underlying the development of obesity and its associated comorbidities include hypertrophy and hyperplasia of primarily visceral adipocytes, adipose tissue inflammation, impaired extracellular matrix remodeling, and fibrosis, together with altered secretion of adipokines [11, 57, 58]. Chronically stressful conditions cause hypertrophy and hyperplasia of the adipocytes, alter the secretion of adipokines, and cause attraction and activation of stromal fat immune cells [59–61]. More specifically, glucocorticoids cause insulin resistance and have a stimulatory effect on the maturation of both omental, subcutaneous abdominal, and other preadipocytes [62, 63]. Glucocorticoid-induced insulin resistance is dependent on 11β -HSD1, the enzyme that converts cortisone into cortisol and results in the critical activation of JNK signaling in adipocytes [64, 65]. Hyperactivation of the HPA axis not only affects adipose tissue directly but also

Fig. 2 Stress and myosteatosis

causes changes in eating behavior [2, 66, 67]. When perceived or real chronic stressors are present, eating control is lost due to the hedonic reward of eating as a counter-maladaptation to the dysphoria of stress [66, 68].

Non-alcoholic fatty liver disease (NAFLD), which is characterized by the accumulation of large droplets of triglyceride within hepatocytes in the absence of chronic alcohol consumption, is a leading cause of hepatic dysfunction worldwide. NAFLD represents a wide spectrum of diseases, ranging from simple steatosis to steatosis with inflammation to cirrhosis. Although simple hepatic steatosis is a slowly developing asymptomatic disease, the next stage, non-alcoholic steatohepatitis (NASH), is more likely to cause progressive cirrhosis and hepatocellular carcinoma, resulting in increased mortality [69]. It seems that chronic stress is directly linked to NAFLD and chronic inflammation in visceral fat [70]. Under normal dietary conditions, chronic stress induces noticeable hepatic oxidative stress and inflammation without causing manifest hepatocellular injury. Irrefutably, chronic stress leads to a chronic inflammatory state, including high concentrations of inflammatory cytokines, such as TNF- α and IL-6, both in the systemic and, mainly, in the hepatic circulation, causing NAFLD [71].

In summary, chronic stress provides a conducive environment for increased inflammation and reactive oxygen species (ROS) generation and hence oxidative stress (OS) in adipose tissue, dysregulating UCP1 expression and activation in both white and brown adipocytes, ultimately promoting lipotoxicity (Fig. 3) [42, 43, 72].

Bone mass: osteopenia and osteoporosis

Bone tissue consists of osteocytes, osteoblasts, osteoclasts, stem cells, and lining cells. Osteocytes represent the most abundant cell type of bone. They are formed by the incorporation of osteoblasts into the bone matrix. Osteocytes remain in contact with each other and with cells on the bone surface via gap junction-coupled cell processes passing through the matrix through small channels, the canaliculi, which connect the cell body-containing lacunae with each other and with the external environment. Osteoblasts and osteoclasts participate in bone remodeling, a highly crucial function of the bones. In bone remodeling, osteoclasts dissolve/resorb old bone tissue and osteoblasts produce osteocytes, actively renewing bone tissue. Bone tissue participates in numerous functions: it maintains blood pH levels, acts as calcium and phosphate storage, provides protection of vital organs and support for muscles, organs, and soft tissues, helps with leverage and movement, and, lastly, participates indirectly in the formation of blood cells in the bone marrow interspersed within the spongy bones [73].

Bone quality (bone turnover, geometry, and microarchitecture), accomplished via bone remodeling, plays a major role in bone health. This balance between bone resorption and bone formation, a homeostatic function, is responsible for proper bone architecture and thus for its function. Recently, a large number of studies have demonstrated that bone tissue participates actively in most metabolic pathways. Indeed, bone metabolism has been implicated in energy homeostasis through uncarboxylated osteocalcin,

Fig. 3 The impact of inflammatory stress on the adipose tissue

a hormonal product of osteoblasts, suggesting a connection between osteocalcin and insulin signaling through bone remodeling. Leptin, a classic adiponectin, is connected to bone remodeling. Thus, circulating leptin acts on bone cells directly to increase bone formation; however, because it stimulates the sympathetic system, it may inhibit bone formation through increased catecholamine effects [74, 75].

Many studies have linked bone health to reproductive function and immunity. Gonadal sex steroids contribute to maintaining peak bone density until menopause, including during the transient changes in skeletal mineral content associated with pregnancy and lactation. At menopause, decreased gonadal sex steroid production normally leads to rapid bone loss. The most rapid bone loss, due to decreased estrogen concentrations, occurs within the first post-menopausal decade, while age-related bone loss occurs at a slower pace during later life. Age-related bone loss in women is caused by ongoing gonadal sex steroid deficiency and, also, by vitamin D deficiency and secondary hyperparathyroidism [76].

Additional studies have found that there is intimate interplay between the immune system and bone metabolism. Among the cells of the immune system that regulate bone turnover and the responsiveness of bone cells to calciotropic hormones are bone marrow T lymphocytes [77]. T cells secrete osteoclastogenic cytokines, such as RANKL and TNF- α , as well as factors that stimulate bone formation, one of which is Wnt10b [78]. A significant study demonstrated that the metabolic syndrome and atherosclerosis are linked, since oxidized lipids decrease bone mass by increasing anti-osteoblastogenic inflammatory cytokines and decreasing pro-osteoblastogenic Wnt ligands [79].

Stress-related inflammation markers have proven to be efficient in predicting change in bone mineral density, i.e., either osteopenia or osteoporosis [80]. In depression, a prototype disease of stress system imbalance, it has been shown that biological factors include the inflammatory-mood pathway, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, metabolic dysfunction, and serotonin's direct and indirect effects on bone cells causing osteopenia and/or osteoporosis.

The pathophysiology lies within the vicious cycle of constant subclinical inflammation, increased proinflammatory cytokines, and disruption of bone remodeling balance [81]. Other molecules, such as IGFBP1 and FGF21, are implicated in bone remodeling. These molecules derive from the liver, though recently they were also characterized as bone hepatokines [82]. IGFBP1, an FGF21-induced pro-osteoclastogenic liver hormone functioning through integrin β 1 receptor in the osteoclast lineage, is stimulated by glucocorticoids and promotes excessive bone resorption [83].

To conclude, stress prevents bone remodeling directly via chronic hypercortisolemia and indirectly via the activated inflammasome (Fig. 4).

Combined disorders associated with imbalance of the stress system

Osteosarcopenic obesity

When there is a combination of impaired bone, muscle, and adipose tissue functions, a new clinical phenotypic entity arises, termed osteosarcopenic obesity, comprising the interrelation and consequent dyshomeostasis between the three tissues [84, 85]. Currently, there is a lack of consensus regarding this clinical entity. Some claim that it is strictly a condition affecting only the aged population [86], while others have demonstrated that elements of this entity exist even at a young age, implying that it may actually be a lifelong process, as is atherosclerosis [52].

Osteosarcopenic obesity syndrome is the coexistence of osteopenia/osteoporosis, sarcopenia, and obesity. All three entities are indisputably related to the cacostasis caused by chronic stress system imbalance at any age. Bone, muscle, and adipose tissues derive from the mesenchymal stem cells. The latter generally favor adipogenic differentiation over transdifferentiation to bone or muscle lineage, a tendency that is aggravated during low-grade, subclinical inflammation

Fig. 4 The impact of inflammatory stress on the physiology of the bones

[52]. Low-grade, subclinical inflammation exists in stress system disorder, a condition exacerbated by the Western, sedentary lifestyle [87–89].

Several studies have shown that high fat or high glycemic load diets are associated with decreased bone mineral density; as bone strength diminishes, adverse microstructure and inflammatory changes occur in the cancellous bone compartment, which is involved in both lipid metabolism and the bone marrow microenvironment [90]. In obesity, GLP-1 and other protective gut molecules decrease and the process of osteopenia and/or osteoporosis intensifies progression to osteosarcopenia [91]. Insulin resistance increases, advanced glycation end-products are produced, and reactive oxygen species are formed, and these negatively affect the skeletal muscle causing sarcopenia [92–94].

Cachexia: frailty and aging

Frailty is a clinical geriatric syndrome of generalized cachexia involving adipose tissue, skeletal muscle, and bone tissues. Physical inactivity, disability, dementia, and metabolic disorders characterized mainly by catabolism are observed in frail aged individuals [95]. Even when adequately nourished, frail aged humans are in a dyshomeostatic state with decrements in body water volume, increased systemic inflammation, decreased anabolism, mitochondrial dysfunction, and DNA disrepair associated with demethylation [96, 97]. Glucocorticoids further increase lean tissue catabolism, resulting in thinning of the skin and muscle and bone loss. Testosterone concentrations that normally prevent muscle and bone loss are diminished during the male aging process and are quite low in frail aged men. Loss of motor neuron end plates causes muscle

fiber loss and remodeling, which replaces high tension type II fibers by type I fibers. Muscle inflammation and loss of peripheral nerve functions cause muscle atrophy, replacement of skeletal muscle with adipose and fibrotic tissue, and a decrease of regenerative muscle capacity, or sarcopenia. The above constellation of the manifestations of frailty in the elderly is frequently accompanied by other chronic disorders characteristic of old age, such as anxiety depression, heart failure, chronic obstructive pulmonary disorder, and cancer. To conclude, all the latter, together with stress, which promotes DNA oxidation causing shortening of the telomeres cumulatively throughout the lifespan [98, 99], are in fact observed not only in the elderly but also in younger-aged populations [52, 100, 101].

DNA undergoes profound alterations in aging, including global hypomethylation, hypermethylation at specific loci, an increase in interindividual variation, and changes in stochastic DNA methylation. Pre-frailty and frailty are associated with higher oxidative stress and diminished antioxidant capacity [102]. Circulating oxidative damage biomarkers, such as MDA, protein carbonylation, reduced glutathione (GSH), oxidized glutathione (GSSG), tumor necrosis factor- α , malonaldehyde (MDA), and 4-hydroxy-2,3-nonenal (HNE) protein plasma adducts, are also related to frailty [103].

Conclusions

The aim of this non-systematic review was to clarify the close relationship between chronic stress and body composition disorders. First, we reviewed the main functions and components of each tissue, then we enumerated body

composition disorders, and lastly, we described their relation to chronic stress system hyperactivity. Dynamic variations in functional body composition arise from a dyshomeostatic state between the energy obtained from the diet and the body's energy demands. More specifically, changes in body composition at the chemical level result from imbalances between the macronutrients absorbed through the diet and the metabolic fuels oxidized to meet energy demands, these regulated by significant hormonal messages [104]. As energy expenditure and metabolic fuel utilization are both strongly influenced by body composition, there is a complex dynamic interplay between these variables.

Quite recently, a study by Tsigos et al. demonstrated the relations between the presence of chronic stress and the components of body composition, measured by means of an advanced bio-impedance device BIA-ACC. This cross-sectional study included a very large number of participants but failed to demonstrate any direct causation, although it exhibited their strong connection [104]. Chronic stress and its consequences are evident in ways that are ubiquitous, reflecting a disruption of the central stress system in the brain. Chronic stress affects every component of the body given that stress hormones readily stimulate their receptors, which are present in every tissue of the human body. As neither the levels of chronic stress nor body composition is static throughout the lifespan, assessment of functional body composition should become an essential component of evaluation of overall well-being throughout an individual's lifetime [105].

Given that stress and body composition concern not only the adult population but also younger ages, a very big challenge is the determination of the impact of stress on the developing muscle system and skeleton of children and adolescents, since it has been shown that features of osteosarcopenic obesity also exist in younger populations [52, 106]. Another aspect that needs to be addressed is the modern-day lifestyle characterized by sedentary behaviors and physical inactivity. This is inevitably associated with overweight and obesity and the development of a systemic proinflammatory state, inducing early onset of cardiovascular diseases, type 2 diabetes mellitus, anxiety, depression, dementia, and cancer, the sum total today being termed "the diseasome of physical inactivity" [50, 107]. In conclusion, given that stress and body composition disorders have been proven to be strongly interrelated, screening for body composition dyshomeostasis should be regularly carried out through such present-day medical devices as DXA and BIA, thereby enabling prevention or early treatment, which are critical for health and well-being. More studies with sophisticated designs are needed to elucidate the prevention and treatment options of obesity, osteosarcopenic obesity, and metabolic, cardiovascular, and other noncommunicable stress-related diseases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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