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Association between sarcopenia and hypertension, ways of mutual influence on clinical course in the elderly (literature review)

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Abstract. Population aging remains one of the most important demographic processes in recent decades. Representatives of the older age groups make up a significant proportion of various patient profiles. Among the specific features of these patients there is not only comorbidity, but also age-related changes in the peripheral tissues. Although formally they remain physiological, such changes may significantly burden the patient's condition. One of the processes accompanying aging is the loss of muscle tissue – sarcopenia. At the same time, hypertension is the most common cardiovascular disease, which develops in people over 40 years of age, and among the elderly its prevalence is 30–40%. The development of hypertension-associated complications, comorbidity in the elderly is directly related to disability, loss of self-care capacities and loss of physical independence. Reducing physical activity may contribute to the progression of muscle tissue involution, which negatively affects the quality of life, as well as life span prognosis. Taking into account the above mentioned facts, the review deals with the pathogenetic mechanisms of communication of arterial hypertension and sarcopenia, their mutual influence on the clinical course in people of the older age groups. The emphasis lies on the negative effects of potentiating synergism of sarcopenia, sarcopenic obesity, disorders of the hemostasis system and autonomic regulation on the development of hemodynamic disorders associated with hypertension, especially in the elderly. This article is of interest to a wide range of internists, which care for the older patient groups.

Keywords: sarcopenia; hypertension; cardiovascular risk; comorbidity; older age

One of the principal epidemiological tendencies characterizing our generation is population's ageing [1]. As of January 1, 2010, people of 50 years and above number 17,3 million (32 % of total number of men and 42 % of total number of women) in Ukraine. Presently, one in more than four Ukrainians is 50 years and older; the group characterized by a worsened health condition and increased morbidity rate [2]. The share of people of 60 years and older is predicted to double by 2050, amounting to 2 billions [3].

Age-related changes of the human body result in a gradual decrease of adaptation capacities, and frailty syndrome, i.e. increased physical vulnerability of human body exposed to various factors. Frailty develops due to a reduced physical activeness and mobility, and is characterized by a slowed walking and low stamina [4]. One of the key determinants of this syndrome is a sarcopenia, i.e.

gradual age-related degenerative atrophic loss of weight, force and functional abilities of skeletal muscles, which belongs to five principal factors of grave morbidity and mortality of those over 65 [5]. Average annual muscle loss amounts to 1 % in people over 35–40 years, 1,4–2,5 % in those over 60 years, and may reach 50 % at the age of 80 years and older [6].

Sarcopenia prevalence evaluations vary to a significant extent reflecting difference of clinical and diagnostic approaches. Thus, sarcopenia frequency range of 1–29 % was registered in people of preserved working capacity and in 14–33 % of those requiring long-term care [7].

The term of 'sarcopenia' was suggested by I. Rozenberg in 1998, who wrote that no other ageing-related feature is more prominent or damaging than reduced body weight, affecting general mobility, moving capacity, energy consumption, nutrient absorption, self-sustaining ability and

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breathing function [8]. Taking into account sarcopenia's connection with an increased risk of falls and fractures, cognitive and muscle disorders, frailty, disorders of everyday activity, loss of independence and early mortality risk [9], this condition causes an increasing public concern as to the possible ageing preventive options.

In addition, as of today, one of the most topical problems across the world is a high mortality rate attributed to the cardio-vascular diseases, their principal trigger being arterial hypertension (AH). AH afflicts most frequently those aged 40-60 years, while the AH's rate among the elderly reaches 30-40 % [10]. Polymorbidity among the older age groups, affected target organs, namely AH-caused left ventricle hypertrophy, may result in a progressive muscle tissue involution [11]. On the other hand, the level of involutive sarcopenia's development promotes development and progress of myocardial dysfunction [12].

There are a number of studies showing a clear connection between sarcopenia and cardiovascular diseases in the elderly. For instance, M. Ochi et al. observe that the older subjects with a confirmed smaller lower thigh muscle cross cut have an increased number of cardiovascular risk factors, namely thickened intima-media complex and accelerated pulse wave [13]. Moreover, P. Srikanthan and A. S. Karlamangla report that a sarcopenia index had a negative correlation with carotid artery's intima-media thickness, revealing a probable correlation with atherosclerotic plaque formation [14]. Similarly, A. M. Abbatecola et al. describe a higher pulse wave acceleration in the elderly Americans with a low appendicular lean mass (ALM) index [15]. Studies by K. Sanada et al. (2010) attribute an increase in sarcopenia rate to an increase of humeral pulse wave acceleration in the Japanese elderly [16]. Following these studies, the others also reveal a connection between sarcopenia's stage and arterial stiffness. T. N. Kim and K. M. Choi prove a close relation of sarcopenia and arterial stiffness, especially in women [1], promoting hypertension and other cardio- and cerebrovascular diseases. Examination of 130 Brazilian women showed that elderly women with a higher (ALM) index had a lower pulse pressure and three times as low a cardiovascular complication risk as older women with sarcopenia [9, 17]. J. C. Helio Junior et al. found that a low muscle mass is related to cardiovascular risks, such as AH and arterial stiffness. Authors revealed a risk of cardiovascular diseases in the elderly women with sarcopenia to be three times as high as the one characteristic of their peers without sarcopenia [9]. The above mentioned data prove an additive effect of low muscle mass on the arterial blood pressure (BP).

Considering the above mentioned data, we need to describe the pathogenetic mechanisms of arterial hypertension's connection to sarcopenia in the elderly group, their mutual effect on the clinical course of both patholo-

gies, in order to generalize the obtained results and create a platform for the further development of prophylaxis and treatment strategies.

It is some universal knowledge that human body is ageing as a whole; however, its tissues, organs and systems are affected by ageing to a varying degree. The total body mass has two components with a totally opposing biological effect – fat and muscle tissue. While the fat tissue is associated with adverse health consequences, the developed muscle one positively correlates with physical training, higher calorie loss and overall resistance to physical stress, resulting in an improved life span prediction [18].

About 40 % of human body mass is attributed to skeletal muscle, while 10 % is made up by smooth and cardiac muscles. Thus, skeletal muscle tissue is a key component of body composition, having a high correlation with physical activity and health [19].

The role and functioning of muscles is well-known. They are coordinated and regulated by numerous systems; however, the muscles themselves, as a broad receptor field, affect all the organs and systems' functioning [20]. Muscle tissue ageing, under the modern conditions of reduced mobility and poor muscle development through lack of training, starts too early. It is caused by the lack of myocyte mitochondria adequate biogenesis. Under the increased exposure to oxidative stress, muscle tissue's mitochondrial dysfunction grows exponentially, turning from functional into morphological. In its turn, this transformation results in a compromised metabolism and clinical manifestations of deficit and worsening of muscle tissue quality [21].

The recent studies show that skeletal muscles together with cardiomyocytes and fat tissue belong to the endocrine organs and create bioregulators, acting not only in a paracrine or juxtacrine manner, but in an endocrine one as well. While contracting, the skeletal muscles release a number of autacoids (signal organic molecules of a short-distance no-conduit action). Among them there are cytokines, as well as other peptides also known as 'myokines'. They have an antagonistic action towards the pro-inflammatory fat tissue autacoids – adipokines [20]. Myokines induce glucose absorption and fat cell β -oxidation in the muscles, stimulate the liver gluconeogenesis and lipolysis in the fat tissue. Moreover, the myokines under physical strain promote and increased capillarisation of skeletal muscles [1]. In case of obesity, cytokine imbalance will result in metabolic shifts and increased risk of cardiovascular diseases.

There is an hypothesis that myokines are principal regulators of skeletal muscle, liver, pancreatic cell and fat tissue interaction [9]. While studying the newly-discovered CXCL1 myokine's action, it was established that its excessive expression intensifies the muscle fat cell oxidation, simultaneously reducing the fat deposit in the

subcutaneous hypoderm [22]. It's worth mentioning the connection found between regular physical exercising and reduction of development and progressing of malignant tumors, namely breast cancers [23, 24]. With tumor cells incubated in the serum sample taken right after the intense physical exertion, with an increased myokine rate, cancer cells proliferation was suspended through apoptosis activation by caspasis. Myokine, having the anti-proliferative effect, was identified as oncostatin M [25].

Myokine promoting the muscle tissue growth and differentiation is a myostatin; besides the muscle growth activation, it is also likely to have other metabolic effects. Reduced myostatin rate in response to physical strain may be considered as one of positive metabolic effects of regular exercises on obesity and diabetes mellitus [26]. Myostatin is recently viewed as a promising target for therapeutic intervention with patients having sarcopenia, namely secondary one, resulting from endocrine diseases, hypercorticism in particular [27].

Another myokine is irisin, which, according to many researchers, is able through its own receptors to transform the white fat tissue properties, turning it into brown one. This effect ensures positive metabolic changes and also extends telomere length. Owing to it, some researchers regard irisin as 'myokine of youth and life' [28].

Moreover, another well-known cytokine, IL-6 interleukin, whose active release during intense physical exercises was formerly associated with muscle damage, now is viewed as myokine secreted as a response to physical exertion. According to the researchers, rapid IL-6 production and its short circulation under physical strain has a positive effect on muscle growth [29].

Myokine concept was suggested by Bente Klarlund Pedersen, head of the Centre of Inflammation and Metabolism (CIM) by the University of Copenhagen. She refers to such diseases as Type II diabetes, cardiovascular diseases, breast cancer, dementia and depression as 'hypodynamia diseases' cluster, while myokines serve as protective substances against the diseases [30].

Considering the antagonistic 'myokines versus adipokines' action, the so-called sarcopenic obesity (SO), involving complex metabolic disorders, high comorbidity rate, cardiovascular risk, mortality etc., is especially worthy of mentioning [31]. The French EPIDOS study revealed that in those younger than 70 years old had SO in 10-12 % of cases, while those over 80 – in 15-27 % [32].

Reduction of muscle (lean) mass is not an isolated process; rather, it occurs together with fat mass accumulation [33]. Imbalance between muscle and fat tissues results in a lowered resistance to physical strain, while hypodynamia promotes sarcopenia and SO. Obesity, as well as sarcopenia, is known to be associated with such cardiovascular risks as a decreased glucose tolerance and metabolic syndrome [34, 35], diabetes mellitus, cardiovascular diseases (ischemic heart disease, myocardial infarction) [36], po-

tentially leading to compromised vital functions and disability [8, 37]. SO increases the cardiovascular diseases risk by 23 %, and congestive heart failure (CHF) risk – by 42 %, compared to people without obesity or sarcopenia [38]. Other researchers demonstrated an 8-fold increase in metabolic syndrome, AH and dyslipidemia risk in patients with SO [31].

Sarcopenia and obesity have a mutually aggravating effect: sarcopenia leads to physical activity reduction and, as a result, to fat mass accumulation, while obesity is accompanied by an increased pro-inflammatory cytokine production, leptin and adiponectin secretion disorders, decreased muscle sensitivity to insulin, ever increasing the sarcopenia severity [39].

Obesity promotes increased adipokine secretion from fat tissue due to its preponderance over muscle tissue [40]. Besides, lack of adequate protein and calorie consumption, increased muscle loss and function are key sarcopenia-provoking factors in the elderly [41]. Ageing and disability are associated with visceral fat tissue accumulation, aggravating functional limitations and cardiovascular risk [42].

T. N. Kim et al. report that subjects with SO diagnosed according to the ALM index had metabolic syndrome more frequently [43]. Recent study by S. Lim et al. revealed a closer connection between SO and metabolic syndrome than in case of sarcopenia and obesity on their own [35]. Thus, sarcopenia and obesity may have a synergistic influence on metabolic and functional disorders in the elderly [40, 44], which is probably associated with an increased risk of falls, depreciated life quality and functional capacities [45].

Having analyzed the SO's underlying pathogenic mechanisms, A. Kalinkovich and G. Livshits found adipocyte hypertrophy and hyperplasia, leading to pro-inflammatory macrophages and other immune cells accumulating, as well as to the deregulated production of various adipokines, which, together with other ageing cells, immune-competent cytokines and chemokines, produce a local pro-inflammatory state [46]. Furthermore, obesity is characterized by an excessive production and failed lipid utilization, the latter being accumulated ectopically in the skeletal muscle. Those intermuscular lipids and their derivatives induce mitochondrial dysfunction, characterized by β -oxidation disorders and increased production of active oxygen forms [21]. As a result, lipotoxic environment is created, insulin resistance occurs, and certain pro-inflammatory cytokines are secreted in larger amounts, resulting in muscle dysfunction by auto- and paracrine pathways [46]. Using an endocrine pathway, the myokines are able to intensify inflammatory processes in the fat tissue, while maintaining sub-clinical chronic systemic inflammation [21]. In this way a vicious circle occurs, with inflammation occurring both in the fat tissue and skeletal muscles, inducing and promoting SO [46].

M. Hamer et al. (2015) described SO as a risk factor for depression symptoms [47]. As a result of 6-year observation of a large sample of the elderly, they found that reduction of dynamometric parameters, one of muscle loss indicators, was associated with depression symptoms, especially if the subjects had obesity. However, reduction of hand grip force over 4 years was associated with a higher risk of depression symptoms only in subjects with excess weight. Anxiety and depression occurring as a result of heightened psycho-emotional strain promoted hypertension. Thus, SO's tangential effect on hypertension through adverse influence on psycho-emotional state should also be monitored.

Ageing process is closely related to the age-associated hormonal status changes, such as decreased sex hormone synthesis, insulin, insulin-like growth factor 1 (IGF-1) and increased cortisol synthesis, stimulating both sarcopenia and AH [48].

One of the powerful hormones with a pronounced anabolic effect as to the muscle mass is a somatotropin, also known as growth hormone [49]. Ageing brings about lowering of somatotropin secretion. Reduction in growth hormone's synthesis results in decreased secretion and level of IGF-1 [21]. Thus, IGF-1 somatotropin blood secretion may slow down due to the age-related hypothyroidism and melatonin secretion drop [49], hyperglycemia and increase of free fat acid rate in blood [50].

Correlation between the men's hormonal status and sarcopenia was analyzed in a number of recent studies [37, 49]. Testosterone was found to suppress IL-1 and IL-6 production, both having catabolic muscle effect. By contrast, estrogen affects the renin-angiotensin system, suppressing angiotensin I conversion into angiotensin II and reducing receptors' sensitivity to angiotensin II [51]. Renin's activeness in blood plasma is lower for women than it is for men; however, it intensifies during post-menopause due to sympathetic nervous system's activation and resulting neuroautonomic disorders [52]. Sympathicoadrenal system's increased tone leads to increased platelet aggregation, heart rate, development of left ventricle hypertrophy. On the other hand, estrogens stimulate regenerative processes in the muscles, though their mechanisms are not yet fully ascertained [51]. It is suggested that in this case estrogens act as antioxidants, restricting the oxidative damage and providing membrane-stabilizing effect [19]. Thus, a reduced androgen and estrogen concentration depreciates muscle force and mass [53], at the same time creating favorable conditions for the AH development. With ageing, women tend to accumulate and lose fat and lean tissue at a consistent rate, while men are first losing muscle mass, then accumulating and later on losing fat mass [45].

It is known that a relative increase of free cortisol level together with its age-related circadian rhythm disruption is one of the adverse hypertension factors [54].

Increased AH occurs due to an increased angiotensin production, reduced prostaglandin production due to phospholipase A inhibition and increased insulin resistance, all in its turn leading to a sympathicoadrenal activation. Excess concentration of glucocorticoids (GCs) also affects renal mineralocorticoid receptors due to 11β -Hydroxysteroid dehydrogenase hyperactivation. 11β -Hydroxysteroid dehydrogenase is an enzyme catalyzing cortisol being converted into cortisone, leading to an increased sodium and water re-absorption. There are data on vasodepressor mechanism weakening, namely of the endothelial nitrogen oxide [55]. Furthermore, with hypercorticism, due to cortisol's catabolic effects, there occurs an increased visceral fat accumulation, muscle mass and bone density loss. Increased exposure of visceral adipose cells to GC as a result of ageing, together with a reduced lipolytic effect and growth hormone level, promotes an age-related tendency towards visceral fat accumulation [1, 56].

The Korean NHANES study held in 2008-2010 also involved the elderly people. Its findings show a connection between sarcopenia and AH [57]. Patients with sarcopenia were found to have an increased prevalence of hypertension than patients without one, irrespective of the fact whether they belonged to the obesity group or not. Researchers suggest four possible mechanisms explaining the effect of ageing muscle on hypertension. First of all, the loss of muscle fibers leads to a reduction of insulin-sensitive target organ mass and promotes insulin resistance, and with it – obesity, metabolic syndrome and hypertension [57, 58]. Insulin resistance index is much higher in sarcopenia patients than in subjects free of it [57].

Secondly, inflammatory process may have a low intensity and systemic character, which probably explains sarcopenia's association with hypertension. It is confirmed by a significantly higher rate of leucocytes in sarcopenia patients than in subjects free of it [57].

Thirdly, myokines produced due to muscle contraction and having anti-inflammatory effect [59] are at a deficit in sarcopenia patients [57]. The relative myokine deficiency may increase the risk of cardiovascular diseases, namely AH [57, 60].

Fourthly, renin-angiotensin-aldosterone (RAA) system changes may promote sarcopenia and hypertension. Mineralocorticoid receptor activation associated with heart failure promotes a progressive loss of heart myocytes due to apoptosis [57, 61]. Myocytes' apoptosis develops in the skeletal muscles of CHF patients, and is referred to as 'heart cachexia', potentially resulting in muscle loss, weakness, reduced tolerance to physical strain, a process resembling sarcopenia [57]. Aldosterone's concentration in the blood plasma of patients with cachexia is three times as high as a similar parameter of non-cachexia patients with no CHF.

Considering the fact that involutive changes in muscle tissue, together with excessive weight, perform an additive effect on the AH's development/course, efforts to reduce the risk and mortality rate should be focused not only on the obesity prevention, but on muscle mass and force increase.

To sum up, it's possible to conclude that a combination of pathological factors, such as sarcopenia, sarcopenic obesity, disorders of homeostasis and autonomic regulation, is a range of negative factors promoting AH-associated hemodynamic disorders, especially in the elderly. Sarcopenia is a key factor of physiological ageing, together with a number of pathological conditions. It depreciates the clinical condition of patients with various diseases, having a negative effect on their life quality.

In this connection, it's advisable to continue studying the fundamental aspects of this topical problem, introduce methods of intervention, prophylaxis and treatment of sarcopenia into the broad clinical practice both for the elderly patients and those with arterial hypertension. Further studies are required to ascertain whether muscle quality maintenance measures would reduce the risk of cardiovascular diseases in the obese adults. The ultimate aim is to determine the behavioral change strategies and methods of treatment preventing and restricting sarcopenia onset.

Conflicts of interests. Authors declare the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

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Асоціація саркопенії й артеріальної гіпертензії, шляхи взаємного впливу на клінічний перебіг в осіб старших вікових груп (огляд літератури)

Резюме. Одним з найбільш важливих демографічних процесів протягом останніх десятиліть залишається постаріння населення. Представники старших вікових груп становлять ва-

гому частку пацієнтів різного профілю. Особливістю цих хворих є не тільки коморбідна патологія, а й вікові зміни периферичних тканин. Формально залишаючись фізіологічними,

такі зміни можуть суттєво обтяжувати стан хворого. Одним із процесів, що супроводжує старіння, є втрата м'язової тканини — саркопенія. Разом з тим найбільш поширеним захворюванням серцево-судинної системи є артеріальна гіпертензія, що розвивається в осіб віком від 40 років, а серед людей літнього віку її поширеність сягає 30–40 %. Розвиток ускладнень артеріальної гіпертензії, коморбідність в осіб старших вікових груп безпосередньо пов'язані з інвалідизацією, втратою здатності до самообслуговування й фізичної незалежності. Зниження фізичної активності може сприяти прогресуванню інволюції м'язової тканини, що погіршує якість життя, а також прогноз. З огляду на вищевикладене в огляді розглянуто па-

тогенетичні механізми зв'язку артеріальної гіпертензії й саркопенії, їх взаємний вплив на клінічний перебіг у людей старших вікових груп. Наголошено на негативному впливі потенціального синергізму саркопенії, саркопенічного ожиріння, порушень системи гемостазу й вегетативної регуляції на розвиток гемодинамічних порушень при артеріальній гіпертензії, особливо в осіб літнього віку. Дана стаття становить інтерес для широкого кола лікарів-інтерністів, що стикаються у своїй практичній діяльності з пацієнтами літнього й старшого віку.

Ключові слова: саркопенія; артеріальна гіпертензія; кардіо-васкулярний ризик; коморбідність; літній вік

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Ассоциация саркопении и артериальной гипертензии, пути взаимного влияния на клиническое течение у лиц старших возрастных групп (обзор литературы)

Резюме. Одним из наиболее важных демографических процессов в течение последних десятилетий остается старение населения. Представители старших возрастных групп составляют весомую долю пациентов различного профиля. Особенностью этих пациентов является не только сопутствующая патология, но и возрастные изменения в периферических тканях. Формально сохраняя физиологический характер, такие изменения могут существенно ослабить состояние пациента. Одним из процессов, который сопровождает старение, является потеря мышечной ткани — саркопения. Вместе с тем наиболее распространенным заболеванием сердечно-сосудистой системы является артериальная гипертензия (АГ), которая развивается у лиц в возрасте от 40 лет, а среди пожилых людей ее распространенность достигает 30–40 %. Развитие осложнений АГ, коморбидность у лиц старших возрастных групп напрямую связаны с инвалидизацией, утратой

способности к самообслуживанию и потерей физической независимости. Снижение физической активности может способствовать прогрессированию инволюции мышечной ткани, что ухудшает качество жизни, а также прогноз. С учетом вышеизложенного в обзоре рассмотрены патогенетические механизмы связи АГ и саркопении, их взаимное влияние на клиническое течение у лиц старшего возраста. Сделан акцент на негативное влияние потенцированного синергизма саркопении, саркопеничного ожирения, нарушений системы гемостаза и вегетативной регуляции на развитие гемодинамических нарушений при АГ, особенно у пожилых людей. Данная статья представляет интерес для широкого круга врачей-интернистов, которые сталкиваются в своей практической деятельности с пациентами старших возрастных групп.

Ключевые слова: саркопения; гипертоническая болезнь; сердечно-сосудистый риск; коморбидность; пожилой возраст