REVIEW ARTICLE

Sarcopenic Obesity: The Underlying Molecular Pathophysiology and Prospect Therapies

Anna Meiliana[1,2,*], Nurrani Mustika Dewi[3,4], Irma Ruslina Defi[5], Aziiz Mardanarian Rosdianto[6], Adziqa Ammara Qiantori[7], Andi Wijaya[2,3]

[1]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjajaran, Jl. Raya Bandung, Sumedang Km. 21, Jatinangor 45363, Indonesia
[2]Prodia Clinical Laboratory, Jl. Supratman No 43, Bandung 40114, Indonesia
[3]Prodia Education and Research Institute, Jl. Kramat Raya No. 150, Jakarta, 10430, Indonesia
[4]Doctoral Program of Pharmacy, Faculty of Pharmacy, Universitas Padjajaran, Jl. Raya Bandung, Sumedang Km. 21, Jatinangor 45363, Indonesia
[5]Department of Physical Medicine and Rehabilitation, Hasan Sadikin General Hospital/Faculty of Medicine, Universitas Padjadjaran, Jl. Pasteur No.38, Bandung 40161, Indonesia
[6]Cell Communication Pillar, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Jl. Raya Bandung, Sumedang Km. 21, Jatinangor 45363, Indonesia
[7]Faculty of Medicine, Universitas Padjadjaran, Jl. Raya Bandung, Sumedang Km. 21, Jatinangor 45363, Indonesia

*Corresponding author. E-mail: anna.meiliana@unpad.ac.id

Received date: Jul 1, 2024; Revised date: Aug 1, 2024; Accepted date: Aug 8, 2024

Abstract

BACKGROUND: Age contributes to body composition alteration, rises a common disorder in elderly known as sarcopenic obesity (SO), which is characterized by the combination of obesity (excess fat mass) and sarcopenia (reduced skeletal muscle mass) clinical form and function.

CONTENT: The primary cause of SO is insulin resistance. Glucose transporter 4 (GLUT4) dysfunction results in impaired fatty acids oxidation. Decreased muscle mass results in lower mitochondria number and volume. Both will increase oxidative stress. Together with altered myokines in SO, oxidative stress was promoted and lead to higher M1 macrophages and failure in autophagy. The pro-inflammatory condition and dysbiosis links SO to a variety of cardiometabolic conditions, including non-alcoholic fatty liver disease, type 2 diabetes, and cardiovascular disease. The mortality, comorbidities, cardiometabolic diseases, and disability or impairment of SO is higher compare to obesity or sarcopenia alone. Some treatments have been developed for SO including adequate dietary intake, vitamin D and antioxidant supplementation, and exercises.

SUMMARY: SO is more prevalent among the elderly and has a significant negative impact on their quality of life. Therefore, maintaining muscle mass and strength as well as preventing obesity should be the key goals of initiatives to support healthy aging.

KEYWORDS: aging, body composition, obesity, sarcopenia, skeletal muscle, metabolic syndrome

Indones Biomed J. 2024; 16(4): 292-308

Introduction

The prevalence of obesity keeps increasing globally and become a major health issue (1,2) with high comorbidities and poor health-related quality of life (HRQoL) (3), and mortality risk (4). A new phenotype of obesity has gained attention over the past 20 years known as sarcopenic obesity (SO), characterized by the obesity (5) and sarcopenia (6), an increase in body fat mass deposition, a decrease in lean mass, and a decrease in muscle strength (7). Aging process have a significant contribution in SO pathophysiology. The exact prevalence of SO is hard to determine regarding the fact of insufficient diagnostic standards and definition.(8,9)

Skeletal muscle is the largest tissue in human body, count for almost 50% with essential numerous physiological

processes. It produces energy, which controls human movement, and it takes role in preserving homeostasis by carrying out metabolic processes. Human health is significantly impacted by any decline in the skeletal muscle's contractile tissue and metabolic characteristics. (10) Thus, we also need a regular assessment of muscle mass and function.(11)

Since the average life span has increased recently, age-related loss of skeletal muscle mass and function have been extensively examined and represent a significant current and future public health concern. Less research has been done on its connection to cardiometabolic disorders, though. Sarcopenia is characterized by both muscular atrophy and dysfunction, which lead to problems in metabolism and endocrine function as well as contractile impairment. It contains measures pertaining to force, functional capacity, and body fat percentage, and it impacts immune system and inflammatory response as well as whole-body metabolism. (11,12) Genetic predisposition has a significant influence in the development of sarcopenia, which is a complex process. Some studies demonstrated the relationship between SO and weight-related comorbidities, (such as type 2 diabetes (T2DM), hypertension, etc.); and it is not yet understood how SO contributes to the development or worsening of these conditions.(8) Furthermore, few studies have been conducted in this field on SO, psychosocial comorbidities (such as depression and eating disorders), HRQoL, and harsh long-term outcomes like mortality. Ultimately, while some studies argue that it is necessary to address this trait, there is no validated strategies have been provided to prevent or cure it. Because of this, SO has been deemed a scientific and clinical priority by the European Society for Clinical Nutrition and Metabolism and the European Association for the Study of Obesity.(13,14) In this review article, recent insights to increase public awareness on SO characteristics, mechanisms, comorbidities, and therapeutic opportunity would be discussed.

Sarcopenic Obesity and Diagnostic Criteria

Sarcopenia, the decreased skeletal muscle mass combined with poor muscular function (15), and obesity, or a high body fat percentage, are the two main characteristics of SO. It is necessary to view SO as a distinct clinical condition that goes beyond simple sarcopenia or obesity. This is because there are two factors at play: 1) a pathogenic, bidirectional interaction between the accumulation of body fat mass and the loss of skeletal muscle mass and function; and 2) negative clinical interactions between obesity and sarcopenia that work together to increase the risk of metabolic disease and functional impairment more than the cumulative risk from each condition alone.(16,17)

The current criteria for sarcopenia and obesity should not be used to define SO. Sarcopenia is specifically defined as reduced skeletal muscle mass and function (appendicular lean mass in age-related primary sarcopenia); nevertheless, alterations in muscle mass should be taken into account in relation to obesity. Due to motor or cardiorespiratory issues, excess body fat may also significantly contribute to functional impairment and disability in and of itself. This suggests that components of skeletal muscle and fat have a synergistic detrimental effect on the clinical consequences of SO. Due to the changes in body composition that are often associated with aging, SO is more common in older persons.(18)

Due of the increased likelihood of developing age-related sarcopenia, it is therefore suggested that all individuals with obesity and overweight who are over 70 should be seen as being at risk of getting SO. It is suggested that this population be routinely evaluated under the guidance of muscle functional testing. The screening for SO can be carried out by a variety of health care professionals (HCPs), including nurses and general practitioners, who may or may not be experts in the fields of obesity and sarcopenia. Somehow, due to the absence of data, it has been difficult to determine the reference ranges for each race or ethnic group.

A number of chronic illnesses that are known to increase the risk of losing muscle mass and function, as well as dietary imbalances or catabolic processes that may result in muscle loss, are additional risk factors. Thus, SO is not exclusive to elderly. A number of risk factors, including inflammation, insulin resistance, and clustering systemic and muscle oxidative stress, which can arise in obesity, especially in the presence of metabolic problems and other comorbidities, might hasten the formation of sarcopenia in obese persons. Therefore, SO can also be seen in middle-aged and younger people who are obese, frequently as a result of acute and chronic illnesses, as well as in people who rapidly increase or decrease their body weight after receiving weight loss treatment.(19)

Following diagnosis, SO staging can be determined based on how far the altered skeletal muscle and body composition parameter contribute to the comorbidities. Functional impairment might be viewed as an exacerbating or perpetuating component as well, as it may have a

negative independent impact on maintaining or recovering an appropriate body composition and function, even if it is primarily a consequence of SO with a strong negative prognostic value.

The goal of the suggested staging is to stratify the patients according to their clinical severity and increased likelihood of unfavorable outcomes, necessitating more intensive care and monitoring. SO definition and diagnostic criteria, including the staging currently solely dependent on the advice of clinical experts such as The European Society for Clinical Nutrition and Metabolism (ESPEN) and The European Association for the Study of Obesity (EASO) to determine the impact of functional measures on clinical outcomes in SO patients.(20) The modifications in the diagnostic criteria for obesity and sarcopenia affect the criteria for SO. Based on ESPEN and EASO consensus statement 2022, SO can be diagnosed in two steps: 1) Skeletal muscle functional parameters: assessed from muscle strength, knee extensor strength, or chair-stand test. The cut-off points need to be validated according to sex, ethnicity and age stratum. When low skeletal muscle functional parameters are detected, the diagnostic algorithm will continue to step two, the assessment of body composition; 2) Body composition: assessed using dual-energy X-ray absorptiometry (DXA), or bioelectrical impedance analysis (BIA) as the second choice. Computerized tomography (CT) should be used when possible (*e.g.*, when the patient have some condition that requires CT scan, then this can be perfoemed at once).(20) SO (stage 1) will be defined when both muscle functional and body compositions are out of normal range. When at least one complication detected, SO will be defined as stage 2.

Prior to 2010, the primary criterion for diagnosing SO was the combination of obesity and muscular mass. DXA and appendicular skeletal muscle divided by height in meters squared (ASM/ht^2) are used to diagnosis SO, defined when the relative skeletal muscle index is low, compared to the average value of young individuals, plus an increase in body fat percentage more than 60% compared to the population with same age.(21) The body fat and fat removal content of the human body were indirectly measured using anthropometric measures and bioimpedance analysis (BIA).(22) The body muscle mass and fat mass were then calculated to define SO, which is defined as having a body fat content that is 60% higher than the population level and a muscle mass that is 60% lower. However, the diagnosis of SO now includes the comprehensive evaluation of muscle mass, muscle strength, and muscle function, and is determined in combination with obesity, unlike when European Working Group on Sarcopenia in Older People (EWGSOP) first proposed the comprehensive diagnostic criteria and stages of sarcopenia in 2010.(23,24)

Overall, it can be concluded that SO defines as the co-existence of excess adiposity and low muscle mass/function, with reference value depend on the sex, ethnicity and age factor. Any comorbidities including metabolic and cardiovascular will regard as more advanced stage of SO.

Sarcopenic Obesity: Molecular Mechanisms

The primary causes of death globally are cardiometabolic diseases, which encompass cardiovascular disorders, T2DM, and non-alcoholic fatty liver disease (NAFLD). Insulin resistance (IR) is a common mechanism linked to the diseases (25), and obesity, high calorie consumption, and poor levels of physical exercise are the main contributors (26). IR together with the other factors are the main core of SO pathophysiological. The largest insulin-sensitive tissue, skeletal muscle also has the highest postprandial glucose need due to an insulin-dependent mechanism. As a result, poor insulin signaling is frequently seen in SO.(27)

A number of interrelated factors can affect SO pathogenesis, for example aging process (which impact on visceral and muscle fat accumulation as well as muscle mass decreasing), lifestyle, systemic chronic inflammation, and myokines dysregulation.(24) The muscular atrophy and an increase in body fat seen in subjects with SO lead to a lower mitochondrial number and volume, decreased baseline metabolic rate, and increased oxidative stress, which intensifies the vicious cycle. Compared to either sarcopenia or obesity alone, this complex condition carries a 2-3 times greater risk of functional impairment.(28)

When the fatty acid intake surpasses the skeletal muscle's oxidative capability, intramyocellular lipid (IMCL) is produced (29), majority from triacylglycerol (TAG); however, there are other lipid intermediates as well, including diacylglycerol (DAG), sterol esters, long-chain acetyl coenzyme A, and sphingolipids, which include ceramides.(30,31) These lipids interfere with PI3K activation and prevent glucose transporter 4 (GLUT4) translocation by activating protein kinase C (PKC) and phosphorylating the serine of insulin receptor substrate-1 (IRS-1).(32) When GLUT4, a membrane transporter that carries glucose from the blood into the myocytes, malfunctions, the mitochondria oxidize more fatty acids and use less glucose. Elevated intake of fatty acids causes the mitochondria's ATP/ADP ratio to

rise and the electron transport chain to shorten. Following this, there is a decrease in mitochondrial respiration, an increase in the production of reactive oxygen species (ROS) which is toxic to myocytes, and ultimately the fasten onset of sarcopenia. Intermyocellular adipose tissue (IMAT) and IMCL also secretes myostatin, chemokine ligand 2 (CCL2), tumor necrosis factor (TNF)-α, IL-1β, and IL-6 to induce IR and lipotoxicity.(33)

Perilipin (PLIN) is a family of proteins that is contained in lipid droplets and regulates mitochondrial oxidation and skeletal muscle lipid metabolism.(34,35) PLIN is made up of PLIN1 through PLIN5, with PLIN2 and PLIN 5 being mostly present in muscle tissue.(36,37) In skeletal muscle, overexpression of PLIN5 raises the expression of genes related to fatty acid oxidation, which mediates peroxisome proliferator-activated receptor (PPAR)α and PPARγ coactivator 1 alpha (PGC1α).(35) Reduced triacylglycerols (TAG) storage is the outcome of PLIN5 ablation, however sphingolipids such ceramide and sphingomyelin are elevated, which causes IR in the skeletal muscle.(38) Insulin-stimulated glucose uptake in cultured myocytes is reduced due to increased expression of the NLR family pyrin domain containing 3 (NLRP3) inflammasome, which is caused by the lipid droplet-associated protein PLIN2. These findings imply that increasing muscle fat deposition affects glucose homeostasis and energy metabolism, resulting in catabolic state and skeletal muscle atrophy.(39)

Adipocytes accumulate in different organs in addition to muscle tissue in SO, lead to the interconnected signaling between adipose tissue and skeletal muscle tissue as described in Figure 1. Proinflammatory cytokines including TNF-α, IL-6, and IL-1 are secreted by hypertrophied adipose tissue, which encourages the infiltration of inflammatory cells, including macrophages. Macrophages control inflammation in adipose tissue and perform autophagic tasks, such as transferring cytoplasmic contents to lysosomes for degradation and promoting homeostasis via mTOR activation, thereby preventing proinflammatory M1 macrophage-polarization.(40) About 10% of cells in lean participants' adipose tissue stained positive for macrophages; while in obese subjects, this number rose to as high as 50%.(41) Muscle tissue-infiltrating macrophages deliver antigens generated from adipocytes and stimulate $CD4^+$ T cells that are specific to those antigens. Additionally, M2 to M1 macrophage phenotypes emit proinflammatory molecules such TNF-α, IL-1β, IL-6, and monocyte chemoattractant protein-1 (MCP-1)/CCL2.(42,43) By promoting filament protein proteosomal degradation and upregulating apoptosis, these cytokines cause muscle atrophy.(44) Reduced physical activity, a low metabolic rate, and a myokine shortage brought on by sarcopenia all contribute to a proinflammatory response that worsens obesity.

In states of obesity, serine/threonine kinases such as PKC, C-Jun NH2-terminal kinase (JNK), and IκB kinase (IKK) become activated due to increased lipid metabolites like diacylglycerol (DAG) and ceramides. This leads to the phosphorylation of serine/threonine residues on the insulin receptor protein and its substrates, disrupting insulin signaling.(45) PKC is a family of serine/threonine kinases activated by phospholipase C through the hydrolysis of membrane phosphoinositides, which are classified into three

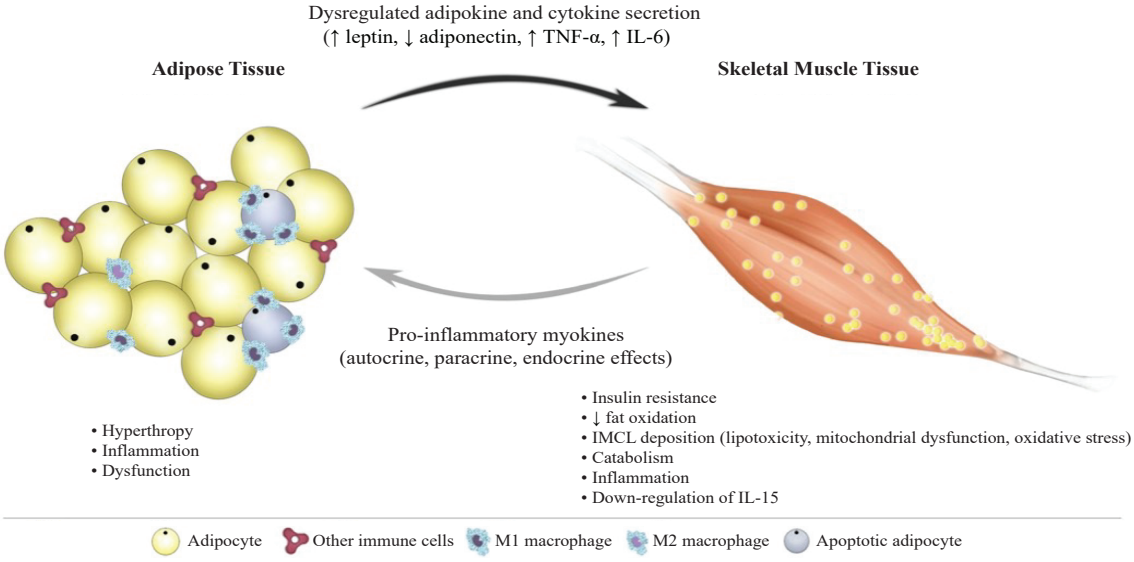

Figure 1. The core biological pathway mediating the pathophysiology of SO is the strong interconnection between adipose and skeletal muscle tissue.(16) (Adapted with permission from Bentham Science Publishers).

groups: classical PKCs (α, β1, β2, γ), novel PKCs (δ, ε, η, θ), and atypical PKCs (ζ, λ/ι). PKCθ is mainly expressed in skeletal muscle and endothelium and is activated by elevated DAG levels in muscles.(46) In lipid infusion experiments, an increase in muscle DAG concentration activates PKCθ, which subsequently impairs the phosphorylation of IRS-1, interfering the PI3K activation and blocking the uptake of glucose via GLUT4, thereby disrupting insulin signaling in muscle. These showed an association between IR and reduced mitochondrial lipid oxidation in SO.(47)

As we grow older, the build-up of fats and their metabolites, especially long-chain fatty acids, results in lipotoxicity, inflammation-induced ROS generation, and endoplasmic reticulum (ER) stress, all of which impair mitochondrial function.(47) Further intracellular fatty acid ambulation is the consequence of mitochondrial failure, which feeds a vicious cycle of lipotoxicity.(48) IκB kinase (IKK), c-Jun N-terminal Kinase (JNK), and p38-mitogen-activated protein kinase (MAPK) are among the stress pathways that are activated by an increase in oxidant chemicals.(49)

Numerous cell types, including leukocytes, adipocytes, and myocytes, generate the cytokine IL-6, which has two distinct impacts on inflammation.(50) IL-6 is released from the skeletal muscle as a myokine when there is an acute contraction of the muscles without causing injury.(51) Acute rise in IL-6 in healthy individuals correlated with enhanced glucose uptake, enhanced insulin sensitivity through classic signaling, and elevated fatty acid oxidation in myocytes. (52) IL-6 in the pancreas increases glucagon-like peptide-1 (GLP-1) in order to induce beta cells to secrete more insulin. (53) It also suppresses the TNF-α pathway's feedback and generates anti-inflammatory cytokines such IL-10.(49)

Through the MAPK and extracellular signal-regulated kinase (ERK) pathways, irisin, a PGCα-dependent myokine, reduces obesity and IR by inducing higher energy expenditure and browning in subcutaneous adipose tissues as described in Figure 2.(54-56) Irisin also prevents saturated fatty acid-induced apoptosis in pancreatic beta-cells and promotes beta-cell survival and glucose-stimulated insulin production via the PGA pathway.(57) In mice with constitutive Rho-associated protein kinase 1 (ROCK1) activation in the muscles, low levels of irisin inhibit the synthesis of irisin in the muscles, which reduces adipocyte browning and impairs insulin sensitivity.(58) The level of plasma irisin was found to be negatively correlated with fasting glucose levels and positively correlated with muscle mass and strength in human studies.(59)

One of the adipokines that is released from adipocytes that controls appetite and energy expenditure is called adiponectin. Adiponectin's serum level falls in obesity. As a result, it improves insulin sensitivity by boosting skeletal muscle's absorption of glucose and promoting fatty acid oxidation via activating the 5′-AMP-activated protein kinase (AMPK) signaling pathway.(60) By reducing the release of TNF-α and IL-6 and increasing the synthesis of IL-10 and IL-1 receptor antagonists by monocytes and macrophages, adiponectin also reduces inflammation.(50) On the other hand, TNF-α causes skeletal muscle dysfunction by compromising mitochondrial biogenesis, oxidative capability, and adiponectin signaling. To summarize, adiponectin has been found to have a negative correlation with obesity and to protect against inflammation and lipid accumulation in skeletal muscle. However, more study is required to fully understand its therapeutic implications, especially for those with SO.

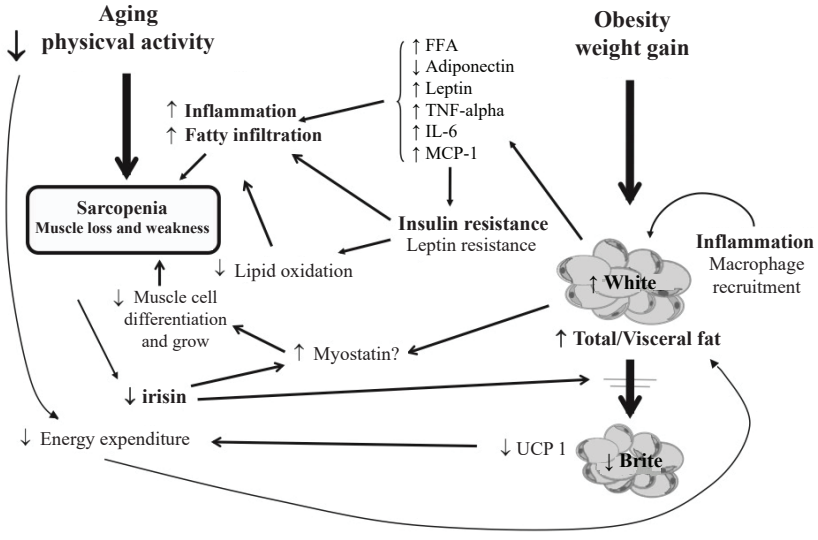

Figure 2. Cross talk between adipocyte and myocyte in older age: a mechanism leading to SO. The main steps are given in bold. (54) (Adapted with permission from Wolter Kluwer Health).

A number of clinical studies showed the correlation between SO and metabolic syndrome (MetS).(61-63) Nonetheless, SO was linked to MetS in an Australian study evaluating older men; with obesity alone to be more predictive of MetS than the sarcopenia assessed by appendicular lean mass (ALM), grip strength, or gait speed. (64) IR, the primary feature of NAFLD, is seen in the adipose tissue, skeletal muscle, and liver of SO.(65) Hepatocytes' insulin signaling appears to be compromised by SO, leading to a rise in *de novo* hepatic lipogenesis and a decrease in hepatic β-oxidation.(65) Additionally, obesity contributes to the buildup of lipids in the liver, which exacerbates hepatocyte insulin resistance.(65) Hepatic steatosis and obesity were elevated in genetic animal models of muscle-specific IR by deleting the insulin receptor tyrosine kinase (IRTK) or GLUT4 genes.(46,66.67)

Mechanisms Underlying Metabolic Syndrome-related Sarcopenia

Ageing initiate SO which increases the risks of metabolic impairment and death.(68) Elderly's quality of life (QoL) is negatively impacted by sarcopenia and the comorbidities, which can lead to frailty, dependency, and a rise in mortality rates.(68-72) Adipocytes in the adipose tissue increase due to hypertrophy and hyperplasia in obesity and MetS. Activated pro-inflammatory macrophages and other immune cells also penetrate the tissue. This modified adipose tissue's cells are characterized by a dysregulated production of leptin and adiponectin, two adipokines that cause detrimental effects on tissues like the pancreas, liver, hypothalamus, and skeletal muscle, as well as an increased production of circulating proinflammatory molecules. (73,74) Modifications in adipokine secretion can lead to increased food intake, a reduction in energy expenditure via hypothalamic effects, and a decrease in muscle insulin sensitivity. Adipose tissue can produce various substances, including TNF-α, MCP-1, IL-6, and C-reactive protein (CRP), which can affect insulin resistance and the release of anabolic hormones like growth hormone (GH) and insulin. These substances can cause SO.(75)

Increased levels of CRP and IL-6 are linked to a two-to three-fold increased risk of developing sarcopenia and losing more than 40% of grip strength. Moreover, lipocalin-2, a cytokine generated from adipose tissue that is essential for controlling lipid metabolism, may be a viable option for controlling the quantity of adipose tissue in the context of persistent inflammation and insulin resistance. It is unclear, nevertheless, if lipocalin-2 levels rise with aging normally and are enhanced even more in MetS-related sarcopenia.(76) Furthermore, the release of plasminogen activator inhibitor-1 (PAI-1), which is primarily obtained from visceral fat and derived from adipocytes, into the circulation occurs concurrently with an increase in fat mass. It is an essential adipokine that has detrimental effects on vascular biology and physiological metabolism. IR, osteoporosis, and excess glucocorticoid-induced sarcopenia have all been linked to PAI-1 in mouse models. The MetS is linked to the fibrinolisis abnormalities caused by PAI-1, which can result in dysregulated vascular clotting, endothelial dysfuction, and metabolic abnormalities that can cause cardiovascular disease. Other clinical conditions like cancer and non-alcoholic hepatic steatosis (NASH) are linked to PAI-1. As a result, it has been suggested that this could serve as a study target for potential therapeutic drugs or a biomarker of inflammatory activity in SO.(77)

Numerous proteins are produced when muscles contract because the skeletal tissue alters the pattern of protein release that is set during periods of inactivity. Myokines which is expresses, manufactures, and secretes from skeletal muscle are essential for physical activity, energy expenditure, and glucose elimination in autocrine, paracrine, or endocrine manner. They also aid in the adaptation to mechanical, neurological, and humoral stimuli.(78) Additionally, myokines increase inflammation in adipose tissue and/or cause long-term low-grade systemic inflammation. This creates a detrimental vicious cycle that maintains inflammation in skeletal muscle and adipose tissue, which in turn promotes and exacerbates the development of sarcopenia.(79) Obesity and IR have been linked to elevated production of myostatin (MSTN), a secreted anabolic inhibitor of muscle growth and development. In order to cause atrophy, MSTN enhances the activity of the ubiquitin–proteasome system and negatively controls the Akt pathway, which stimulates protein synthesis.(80) IL-6 levels rose in response to exercise. It affects the immune system, adipose tissue, and the liver, IL-6 is a significant factor in metabolism. Furthermore, IL-6 may promote lipolysis and IL-6 generated from adipocytes may cause insulin resistance in muscle.(81) Conversely, skeletal muscle produces the myokine IL-15, which has anabolic effects on muscle. It also contributes to the decrease in the mass of adipose tissue.(82-84) The co-occurrence of obesity and sarcopenia in older individuals may compound their impact on mortality and cardiovascular risk, potentially leading to poorer illness and mortality outcomes for older persons with an obese and sarcopenic body composition.(54,85-88)

Sarcopenic Obesity: A Gut Microbiota Perspective

Age-related systemic chronic inflammation, commonly known as inflammaging can result in decreased muscular function and elevated proinflammatory cytokines. Inflammaging usually accompanied with increasing level of reactive oxygen species (ROS) which triggers the nuclear factor kappaB (NF-κB) signaling pathway and initiate the release of IL-6 and TNF-α.(89) Obesity on the other side also contribute the similar mechanism, and SO indeed have a worse prognostic in term of oxidative stress and inflammation.

Dysbiosis of the gut microbiota is connected to the degree of inflammation (90), lifestyle, and antibiotics exposures. Non-obese elderly usually have a better metabolic health since their microbial diversity higher compare to obese population.(89) In addition, many studies indicate that dysbiosis plays a very important role in the metabolic pathogenesis, especially among the elderly, by demonstrating characteristic changes in gut microbiota.(91) Gut microbiota plays many roles not only in endocrine and immune, but also neuronal organs.(92) Higher inflammation in obese elderly can lead to increased intestinal permeability and loosen of the tight junction in the gut, which leads to bacterial translocation and endotoxemia, reduced beneficial bacterial diversity including species of *Bifidobacterium*, *Lactobacillus*, *Akkermansia*, *Fecalibacterium*, *Eubacterium*, *Roseburia*, *Ruminococcus*, and *Blautia* while increasing opportunistic bacterias including including *Ruminococcus*, *Enterobacter*, *Enterococcus*, and *Clostridium*.(93,94) The imbalance of gut population result in reduced short chain fatty acids (SCFA) mainly propionate, butyrate, and acetate production lead to higher pro-inflammatory cytokines production, insulin signaling impairment, and systemic inflammation.(91) A significant reduction in the proportion of *Lactobacilli*, *Bacteroides*/*Prevotella*, and *Faecalibacterium prausnitzii* and an increase in the proportion of *Ruminococcus*, *Atopobium*, and *Enterobacteriacae* was also observed in older persons with high frailty scores.(92)

Different macronutrients promote different features on the microbiome, nutrition may play a critical role in the regulation of the gut microbiota.(94) The gastrointestinal tract's bacterial fermentation is thought to be the primary mechanism via which the gut microbiota interacts with many gut–brain communication pathways to produce SCFAs from dietary fiber.(95,96) Furthermore, given that dietary protein has anabolic effects on skeletal muscle, increasing protein intake above the recommended dietary allowance (RDA) of 0.8 g/kg/day is thought to be a useful strategy to combat the progressive loss of muscle mass and supressing food appetite to prevent obesity.(97)

GPCRs, or G protein-coupled receptors, are found in the L- and G-cells of the colon and small intestine, respectively. These receptors use amino acid sensing to modulate the secretion of peptide YY (PYY) and GLP-1, which inhibits the regulation of food intake in the gut–brain axis.(98-100) Cholecystokinin (CCK) release, which is induced by protein ingestion, also contributes to increased satiety.(101) These effects, which have been demonstrated in studies in comparison to dietary fat and carbohydrate consumption (101), may be explained by the control of ghrelin and leptin secretion (102-105). It is noteworthy that amino acid composition and, in particular, essential amino acids (*i.e.*, leucine) may influence appetite-induced reactions triggered by communications between the gut microbiota and dietary protein.(106,107) Somehow, concerns have been expressed about how dietary proteins affect gut flora and about the potential health implications of their bioactive byproducts.(108)

The regulation of metabolic activities, such as the metabolism of nutrients and amino acids, is also significantly influenced by the gut microbiota.(109,110) Changes in dietary patterns can lead to alterations in microbial composition within 24 hours, although for significant changes will need a long-term adherence.(111) There is a correlation between higher medication use and a higher incidence of sarcopenia and physical frailty. This correlation may be partially accounted for by the possible influence of polypharmacy on the composition of the microbiota.(112) Indeed, through effects on the mTOR signaling pathway, a main proponent of muscle protein synthesis (MPS) (113), significant changes in the microbiota of healthy and frail older persons may help explain in part the emergence of frailty and sarcopenia (114). Proinflammatory responses in the microbiome have also been proposed as a modulator of dysfunctional musculoskeletal health.(115) Aging-related inflammatory reactions can lead to changes in microbiota that are impacted by infections, undernourishment, and a poorer standard of living, ultimately resulting in intestinal mucosa permeability.(116,117) Dysbiosis, or changed gut microbial composition, is triggered by intestinal permeability, which also raises the levels of proinflammatory cytokines including IL-6 and TNF-α.(118,119)

The majority of proteins are effectively broken down and absorbed in the small intestine by enterocyte-used

pancreatic enzymes and peptidases; nevertheless, about 10% of proteins that go through the small intestine could not be fully digested.(120)

Amino acids are not absorbed by colonocytes as effectively when they go to the large intestine for additional proteolysis by the colonic microbiota, and certain metabolites may be utilized for waste or metabolic products.(121,122) Bacterial proteases and peptidases hydrolyze endogenous and dietary proteins into peptides and amino acids, resulting in a longer transit time and a higher concentration of microbiota in the large intestine than in the small.(123) Large volumes of indigestible products are produced by the undigested proteins and peptides that enter the colon, which also affect the composition and production of the gut microbiota.(121,124,125) This is because an increase in protein consumption results in an increase in the amount of proteins that reach the colon. This leads to the production of a wide variety of bacterial metabolites in the gastrointestinal tract, such as hydrogen sulfide, branched-chain fatty acids (BCFAs), SCFAs, polyamines, ammonia, methane, aromatic compounds, nitric oxide, tyramine, tryptamine, phenethylamine, serotonin, and others.(122,126,127) Certain metabolic byproducts are harmful to metabolic health and have been linked to a number of disorders, including inflammatory bowel disease and colorectal cancer, as well as chronic inflammation. Nevertheless, considering the lack of long-term experimental trials on high-protein diets and the gut microbiome and their complex connections, there is currently no causal association in humans.(128,129)

It's been proposed that the balance of amino acids and the sources of protein could affect the diversity of gut microbes. For example, higher levels of *Bifidobacterium*, *Ruminococcus bromii*, *Lactobacillus*, and *Roseburia* have been linked to plant proteins (130), whereas animal proteins are largely home to *Bacteroides*, *Alistipes*, *Bilophila*, and *Clostridium perfrigens* (131). Soy protein intake has been linked to higher numbers of *Bacteroidetes* and *Bifidobacterium* as well as lower serum lipopolysaccharide (LPS) levels in comparison to consumption of meat, dairy, and casein protein.(131,132) Consuming soy protein has also been connected to higher levels of *Bifidobacteria* and *Lactobacilli*, which are associated with reduced diet-induced obesity and enhanced insulin sensitivity.(131,132) Similarly, after consuming soybean, mungbean, and buckwheat proteins, studies have shown increased bile-acid transformation, GLP-1 release, increased levels of *Lactobacillus* and *Bifidobacterium*, and decreased levels of *Firmicutes*.(133,134)

Additionally, mice treated with seafood protein showed lower *Proteobacteria* (*Helicobacter*) and higher SCFA content, which is associated with elevated taurine levels.(135,136) Elevated consumption of pea protein has been linked to increased synthesis of *Bifidobacterium*, *Lactobacillus*, and SCFA. Pea protein also has the effect of suppressing the secretion of inflammatory cytokines, such as TNF-α and IL-6, and enhancing the expression of IL-10 and glucose homeostasis.(137-140) On the other hand, because red meat contains higher concentrations of *Bacteroides* and *Fusobacterium* and lower levels of *Lactobacillus* and *Roseburia*, all of which are associated with a decreased ability to produce an anti-inflammatory response and a higher risk of T2DM, heterocyclic amines and glycan derived from red meat may, on the other hand, increase inflammation in the gut.(141-143) That being said, trimethylamine oxide (TMAO), which is produced during the metabolism of L-carnitine found in red meat, has been linked to a higher risk of atherosclerosis (144) and obesity (145). This may not be in line with research, though, which shows that eating seafood and fish products, which are believed to be cardio-protective, raises circulation TMAO levels in comparison to eggs and red meat proteins. (146,147) Furthermore, a high-mix whey-beef protein supplement administered to endurance athletes for 70 days resulted in an increase in *Bacteroidetes* species and a decrease in *Roseburia*, *Bifidobacterium longum*, and *Blautia* as compared to the control group that received maltodextrin. (136) Although there are known positive and negative effects of eating protein, it is still unclear how amino acids affect the gut microbiota, which is essential to the metabolic human phenotype and depends on protein digestion and absorption.(148)

During colonic bacterial fermentation, non-digestible carbohydrates (dietary fiber) are the main source of SCFA synthesis. These fermentation products are roughly divided into three categories: soluble (pectin, guar gum, psyllium, inulin) and insoluble (cellulose, hemicellulose, lignin) fiber.(149) The fermented products also contain butyrate, propionate, and acetate.(150) It is believed that the recommended daily allowance of dietary fiber varies by nation. For instance, the recommended daily allowance in the United Kingdom is 30 g, however in Australia, it is 28 g for women and 38 g for males. Nonetheless, the majority of people in both nations do not consume the recommended amounts of fiber.(151,152) Dietary fiber has been shown to have a variety of metabolic effects (153), such as increased fat oxidation, insulin sensitivity, and decreased systemic inflammation through the regulation of cytokine production,

particularly IL-18 (154-157). A recent review examined the growing impact of SCFAs on the metabolism and function of skeletal muscles.(158) Furthermore, pigs with higher leucine levels also had higher concentrations of butyrate and propionate, which show increased *Actinobacteria* species abundance and body-fat reduction. This suggests that the microbiome may have a favorable function in metabolic health by being essential for mTOR activation and leucine metabolism in intestinal epithelial cells. Likewise, through modulating GLP-1, PYY, and serotonin from the intestinal enteroendocrine L cells, amino acids including tryptophan, alanine, and phenylalanine may likewise affect satiety and gut motility.(159-165) In a number of tissues, SCFAs may function as GPCR substrates, promoting the release of GLP-1 and PYY, postponing stomach emptying, and lowering hunger and food intake.(161,166,167) Propionate, on the other hand, has been demonstrated to reduce reward-based eating through striatal pathways.(168) These pathways are connected to the ingestion of hyperpalatable foods, which are high in calories and associated with circumstances that promote obesity. Because increased adiposity and anabolic resistance are precursors to SO, the strong anabolic effects and partially appetite-induced responses of SCFAs and amino acids, especially BCAAs, may therefore lower the risk of anabolic resistance concurrent with increased adiposity.(169) The availability of complex carbohydrates may reduce protein fermentation and increase the amount of nitrogenous substrates meant to support muscle anabolism. Knowing this, a recommendation on protein, carbohydrate and fiber source as well as the ratio for skeletal-muscle and metabolic health to modulate an appropriate gut microbial population is needed.(170) Therefore, gut microbiota has been indicated as a prospect target to modulate lean tissue mass, and metabolic improvement.(92)

Sarcopenic Obesity: Treatment Strategy

The cornerstones of treating SO include lifestyle modifications including calorie restriction (CR) and exercise. Nonetheless, deliberate weight loss in older individuals improves morbidity and physical function (171); few treatment trials explicitly address SO (172). After doing a meta-analysis of randomized trials involving persons over 55 who were obese and had follow-up periods longer than four years, researchers found that there was a 16% decrease in mortality (95% CI: 0.71–0.99). Medicare does for weight reduction therapy in the United States of America (171), but no significant societies list targeted therapies for SO. The study of Dennis Villareal most closely matches those with SO who exhibit physical fragility along with obesity.(173,174) Exercise alone or weight loss alone both improved physical function in this patient group; however, regular exercise in addition to weight loss improved physical function and lessened frailty more than either intervention alone.(173) Furthermore, according to a different study, the best way to improve the functional status of obese persons 65 years of age and older was to lose weight and mix resistance and aerobic exercise.(173) In a study assessing four groups of SO patients based on various exercise interventions (aerobic, resistance, combined aerobic and resistance), as well as controls who were not allowed to exercise, and found that the resistance training group showed the biggest gains in strength.(175)

The only effective technique found to treat sarcopenia is exercise, nutritional and medicinal interventions. Through a complex exchange of myokines and osteokines signaling between muscle and bone, exercise was found to restore mitochondrial homeostasis and decrease inflammatory responses, in contrast to nutraceutical and pharmacological therapies that exhibited mixed outcomes in alleviating sarcopenia. Some studies tried the application of stem cells and the secretome, due to their capacity to modulate the immune system and restore mitochondria, as potential treatments that can treat a wider range of patients than exercise alone, as exercise has limited benefits for immobile patients.(176)

Training exercises are shown to be the most effective intervention for alleviating sarcopenia, based on the results of current and/or finished research investigations. Only trials incorporating physical activity interventions, regardless of whether the exercise was resistance, anaerobic, or aerobic, showed a statistically significant increase in muscular strength and performance out of the 34 total studies listed. Conversely, when used in conjunction with an exercise regimen, pharmaceuticals and nutraceuticals did not demonstrate a positive synergistic effect or prove to be as beneficial.(176)

Furthermore, it has been demonstrated that exercise-induced mechanical loading causes osteocyte cell line production of insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF), and hepatocyte growth factor, all of which may have functions in controlling muscle growth.(177,178) Crucially, exercise also stimulates the release of osteocalcin (OCN), a hormone derived from osteoblasts that has been demonstrated to help mice adapt to exercise.(179) Lastly, it was discovered that older adults who regularly exercised also showed increased expression of

genes involved in mitochondrial biogenesis, including PGC-1, nuclear respiratory factor 1 (NRF-1), and mitochondrial transcription factor A (TFAM), as well as increased activity of mitochondrial oxidative enzymes.(180) These findings suggest that physical training can improve and even restore mitochondrial function and homeostasis by directly or indirectly stimulating mitochondrial biogenesis.(181)

Sarcopenia and frailty may benefit from a variety of nutritional therapies.(182) The three primary dietary therapies for SO are protein consumption, CR, and micronutrient supplementation. It is mentioned that the main recommendations for dietary therapy for SO at this time are expert opinions because to the absence of appropriate randomized clinical studies (RCTs). A suitable weight loss objective should be less than 5–8% of the starting body weight. CR is intended to cause changes in body composition in addition to weight loss.(183) Acute CR is not advised since it may increase proteolysis and have a detrimental effect on the synthesis of muscle proteins, which would further reduce muscle mass. On the other hand, long-term CR may promote rather than inhibit muscle protein synthesis.(184)

Sarcopenia brought on by weight reduction can be avoided with a higher protein diet. Based on current research, a young, healthy person should consume 1 g/kg of protein on average per day. However, because of anabolic resistance, older individuals should consume more protein to support muscle protein synthesis. Thus, it is advised that older adults with SO or other conditions requiring a greater protein intake consume between 1 and 1.2 g/kg of protein daily. It is recommended that persons with acute or chronic disorders associated with an imbalanced body composition consume 1.2–1.5 g/kg of protein each day to preserve the lean mass and providing the essential amino acids for immune system like leucine in whey protein.(185,186) Combining high protein intake with exercise also have a positive impact on inflammatory markers, body weight, body fat trunk, and waist circumference although some data were still controversial.(183,187)

Major RCTs in obese non-sarcopenic women have indicated that CR (500 kcal deficit) combined with protein consumption can successfully reduce body fat and enhance physical function (188,189) and will deliver more benefit, since obese older adults tend to have a blunted anabolic response (183). Therefore, resistance training in conjunction with protein intake is still more advantageous for improving mobility and strength both for SO or healthy elderly.(190)

Although the effects of vitamin D supplements on patients with SO have not been well investigated, a number of studies have linked vitamin D insufficiency to decreased muscle strength, increased body instability, falls, and impairment in the elderly population.(191) Therefore, increasing vitamin D consumption may be important to minimize the negative effects of weight loss.(192,193) Furthermore, research has demonstrated that vitamin D can control bioactive metabolites, which enhances muscular function.(194) Because the free metabolite of 25-hydroxyvitamin D3 is more strongly correlated with body fat than with muscle gene expression, a study has confirmed that the vitamin may have an indirect effect on muscle function.(192)

Oxidative stress is one of the main mechanism underlying SO, which impact mitochondrial dysfunction resulting in increased ROS production. ER stress can be increased due to higher ROS, lead to anabolic/catabolic pathway imbalance in skeletal muscle. ROS can damage mitochondrial proteins, reduce ATP generation, block the mammalian target of rapamycin (mTOR) pathway and subsequent down-regulation of protein synthesis, finally induce muscle waste and sarcopenia. On the catabolic side, through multiple mechanisms ROS also activates autophagy, induce protein breakdown.(195) Consuming antioxidants may potentially counteract ROS action and may help to avoid sarcopenia.(196,197) Some data also showed that supplementing with fish oil may enhance athletic performance.(198)

Multimodal interventions, which incorporate physical exercise, nutritional support, and various other strategies, appear to be the most logical approach for preventing and reversing these conditions. Recent clinical trials are adopting these comprehensive methods (199,200). An ambitious multicenter European experiment called "Sarcopenia and Physical frailty IN older people: multi-component Treatment strategies" (SPRINTT) aims to demonstrate the effectiveness of multimodal therapies in frail, sarcopenic patients.(18) Figure 3 showed the summarized treatment strategies that might be able to eradicate SO.

Conclusion

The extreme phenotype of SO, which is the simultaneous existence of obesity and sarcopenia in the same person, is the result of two factors coming together: an aging population that is occurring at a rapid pace and an increase in obesity rates. Due to its correlation with a higher risk of death, hospitalization, cardiometabolic dysregulation, impairment of QoL, and disability, SO places a significant

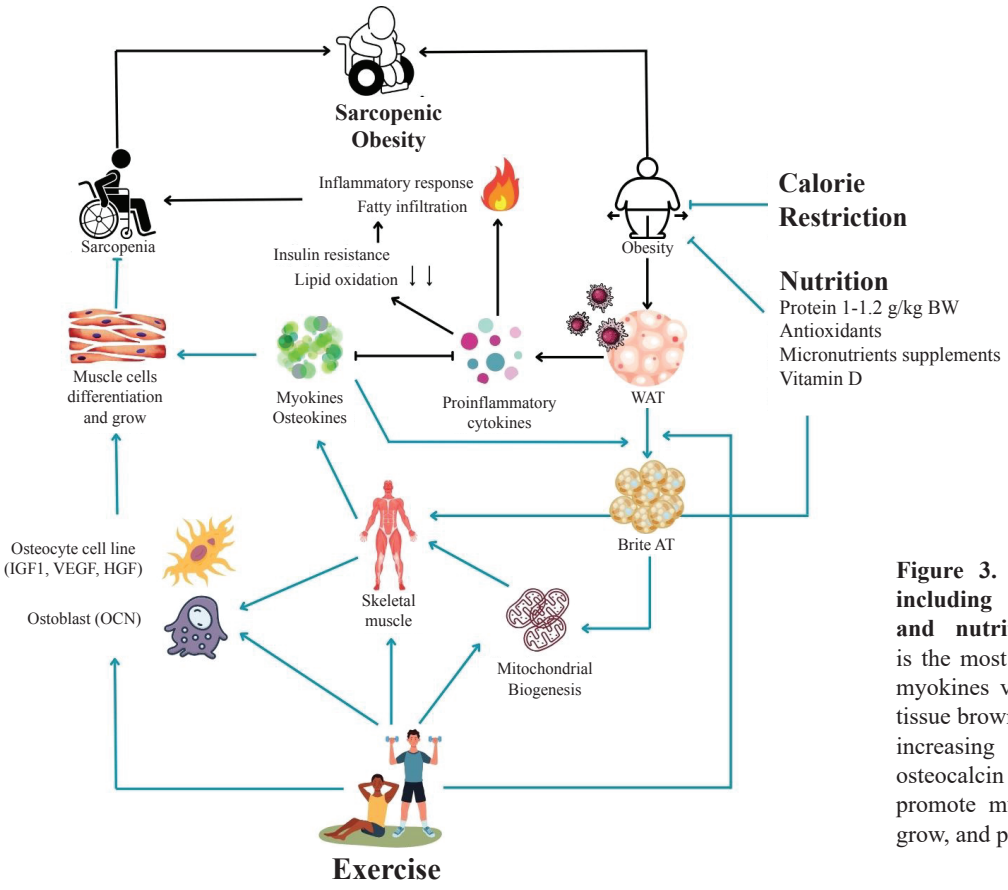

Figure 3. Treatment strategy for SO including exercise, calorie restriction and nutrition management. Exercise is the most impactful strategy to increase myokines via induction of white adipose tissue browning, mitochondrial biogenesis, increasing osteocytes cell line, and osteocalcin from osteoblast. Myokines will promote muscle cells differentiation and grow, and prevent sarcopenia.

burden on people, communities, and health care systems. Given the significant harm that SO causes, researchers and physicians find that timely diagnosis, efficient prevention, and effective treatment are of utmost importance. According on research on SO conducted thus far, older adults who fall into this body composition group are more likely to have greater levels of cardiovascular risk factors and to die younger than older adults who do not have sarcopenia or obesity. The pathophysiology of SO is multifactorial, primarily involving IR and chronic inflammation, but also including the interaction of these and other variables. The scientific community should work to develop a broadly applicable definition for this distinct phenotype, incorporate trustworthy body composition assessment methods into standard clinical practice, concentrate on patient-centered outcomes like physical function and quality of life, investigate the ideal features of dietary interventions, and ultimately ascertain the ideal frequency, intensity, and duration of aerobic and resistance training, the two main physical activity components of SO treatment together with adequate supplementation of vitamin D and antioxidant. Therefore, maintaining muscle mass and strength as well as preventing obesity should be the key goals of initiatives to support healthy aging.

Authors Contribution

AW proposed the topic of the manuscript. AM drafted the original manuscript. AM, NMD, and AAQ edited and revised the manuscript. IRD and AMR gave contextuaal feedbacks for the revised manuscript. AW supervised and gave critical correction to the manuscript. All author have agreed with the final revision of the manuscript.

Acknowledgments

This work was supported by *Layanan Direktorat Riset, Teknologi, dan Pengabdian Kepada Masyarakat* [Grant No. 3824/UN6.3.1/PT.00/2024].

References

1. Kreidieh D, Itani L, El Kassas G, El Masri D, Calugi S, Dalle Grave R, *et al.* Long-term lifestyle-modification programs for overweight and obesity management in the Arab States: Systematic review and meta-analysis. Curr Diabetes Rev. 2018; 14(6): 550–8.

2. Meiliana A, Wijaya A. Update on obesity: Induced inflammation to cause cardiometabolic diseases. Indones Biomed J. 2022; 14(2): 116–38.
3. Itani L, Calugi S, Dalle Grave R, Kreidieh D, El Kassas G, El Masri D, *et al.* The association between body mass index and health-related quality of life in treatment-seeking Arab adults with obesity. Med Sci. 2018; 6(1): 25. doi: 10.3390/medsci6010025.
4. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Ann Transl Med. 2017; 5(7): 161. doi: 10.21037/atm.2017.03.107.
5. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, *et al.* Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017; 377(1): 13–27.
6. Malafarina V, Úriz-Otano F, Iniesta R, Gil-Guerrero L. Sarcopenia in the elderly: Diagnosis, physiopathology and treatment. Maturitas. 2012; 71(2): 109–14.
7. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: A new category of obesity in the elderly. Nutr Metab Cardiovasc Dis. 2008; 18(5): 388–95.
8. El Ghoch M, Calugi S, Grave RD. Sarcopenic Obesity: Definition, Health Consequences and Clinical Management. Open Nutr J. 2018; 12(1): 70–3.
9. Batsis JA, Cook SB. Is the whole not greater than the sum of its parts? The case of sarcopenic obesity. Am J Clin Nutr. 2017; 106(1): 14–5.
10. Sakuma K, Yamaguchi A. Sarcopenic obesity and endocrinal adaptation with age. Int J Endocrinol. 2013; 2013: 204164. doi: 10.1155/2013/204164.
11. Biolo G, Cederholm T, Muscaritoli M. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: From sarcopenic obesity to cachexia. Clin Nutr. 2014; 33(5): 737–48.
12. Jensen GL, Hsiao PY. Obesity in older adults: Relationship to functional limitation. Curr Opin Clin Nutr Metab Care. 2010; 13(1): 46–51.
13. Barazzoni R, Bischoff SC, Boirie Y, Busetto L, Cederholm T, Dicker D, *et al.* Sarcopenic obesity: Time to meet the challenge. Clin Nutr. 2018; 37(6 Pt A): 1787–93.
14. Nezameddin R, Itani L, Kreidieh D, El Masri D, Tannir H, El Ghoch M. Understanding Sarcopenic Obesity in Terms of Definition and Health Consequences: A Clinical Review. Curr Diabetes Rev. 2020 Jan 9;16(9):957–61.
15. Aryana IGPS, Astika IN, Kuswardhani RAT, Putrawan IBP, Purnami NKR, Putra WG, *et al.* High myostatin serum related with high prevalence of sarcopenia among elderly population in Pedawa Village, Bali, Indonesia. Indones Biomed J. 2019; 11(3): 293–8.
16. Koliaki C, Liatis S, Dalamaga M, Kokkinos A. Sarcopenic obesity: Epidemiologic evidence, pathophysiology, and therapeutic perspectives. Curr Obes Rep. 2019; 8(4): 458–71.
17. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: Aetiology, epidemiology and treatment strategies. Nat Rev Endocrinol. 2018; 14(9): 513–37.
18. Batsis JA, Barre LK, Mackenzie TA, Pratt SI, Lopez-Jimenez F, Bartels SJ. Variation in the prevalence of sarcopenia and sarcopenic obesity in older adults associated with different research definitions: dual-energy X-ray absorptiometry data from the National Health and Nutrition Examination Survey 1999-2004. J Am Geriatr Soc. 2013; 61(6): 974–80.
19. Cruz-Jentoft AJ, Kiesswetter E, Drey M, Sieber CC. Nutrition, frailty, and sarcopenia. Aging Clin Exp Res. 2017; 29(1): 43–8.
20. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, *et al.* Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO Consensus Statement. Obes Facts. 2022; 15(3): 321–35.
21. Baumgartner RN. Body composition in healthy aging. Ann NY Acad Sci. 2000; 904(1): 437–48.
22. Davison KK, Ford ES, Cogswell ME, Dietz WH. Percentage of body fat and body mass index are associated with mobility limitations in people aged 70 and older from NHANES III. J Am Geriatr Soc. 2002; 50(11): 1802–9.
23. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, *et al*. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010; 39(4): 412–23.
24. Xie WQ, Xiao GL, Fan YB, He M, Lv S, Li YS. Sarcopenic obesity: Research advances in pathogenesis and diagnostic criteria. Aging Clin Exp Res. 2019; 33(2): 247–52.
25. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest. 2016; 126(1): 12–22.
26. Benziger CP, Roth GA, Moran AE. The global burden of disease study and the preventable burden of NCD. Glob Heart. 2016; 11(4): 393–7.
27. Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: The effect of diabetes, obesity, and other diseases. Lancet Diabetes Endocrinol. 2014; 2(10): 819–29.
28. Rolland Y, Lauwers-Cances V, Cristini C, Van Kan GA, Janssen I, Morley JE, *et al.* Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: the EPIDOS (EPIDemiologie de l'OSteoporose) Study. Am J Clin Nutr. 2009; 89(6): 1895–900.
29. Gemmink A, Goodpaster BH, Schrauwen P, Hesselink MKC. Intramyocellular lipid droplets and insulin sensitivity, the human perspective. Biochim Biophys Acta. 2017; 1862(10): 1242–9.
30. Brøns C, Grunnet LG. Mechanisms in Endocrinology: Skeletal muscle lipotoxicity in insulin resistance and type 2 diabetes: A causal mechanism or an innocent bystander? Eur J Endocrinol. 2017; 176(2): R67–78.
31. Pol A, Gross SP, Parton RG. Biogenesis of the multifunctional lipid droplet: Lipids, proteins, and sites. J Cell Biol. 2014; 204(5): 635–46.
32. Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest. 2000; 106(2): 171–6.
33. Rivas DA, McDonald DJ, Rice NP, Haran PH, Dolnikowski GG, Fielding RA. Diminished anabolic signaling response to insulin induced by intramuscular lipid accumulation is associated with inflammation in aging but not obesity. Am J Physiol Regul Integr Comp Physiol. 2016; 310(7): R561–9.
34. Peters SJ, Samjoo IA, Devries MC, Stevic I, Robertshaw HA, Tarnopolsky MA. Perilipin family (PLIN) proteins in human skeletal muscle: the effect of sex, obesity, and endurance training. Appl Physiol Nutr Metab. 2012; 37(4): 724–35.
35. Bosma M, Sparks LM, Hooiveld GJ, Jorgensen JA, Houten SM, Schrauwen P, *et al.* Overexpression of PLIN5 in skeletal muscle promotes oxidative gene expression and intramyocellular lipid content without compromising insulin sensitivity. Biochim Biophys Acta. 2013; 1831(4): 844–52.
36. Harris LALS, Skinner JR, Shew TM, Pietka TA, Abumrad NA, Wolins NE. Perilipin 5-driven lipid droplet accumulation in skeletal muscle stimulates the expression of fibroblast growth factor 21. Diabetes. 2015; 64(8): 2757–68.
37. Conte M, Vasuri F, Bertaggia E, Armani A, Santoro A, Bellavista E, *et al.* Differential expression of perilipin 2 and 5 in human skeletal muscle during aging and their association with atrophy-related

genes. Biogerontology. 2015; 16(3): 329–40.
38. Bosma M. Lipid droplet dynamics in skeletal muscle. Exp Cell Res. 2016; 340(2): 180–6.
39. Cho KA, Kang PB. PLIN2 inhibits insulin-induced glucose uptake in myoblasts through the activation of the NLRP3 inflammasome. Int J Mol Med. 2015; 36(3): 839–44.
40. Fitzgibbons TP, Czech MP. Emerging evidence for beneficial macrophage functions in atherosclerosis and obesity-induced insulin resistance. J Mol Med. 2016; 94(3): 267–75.
41. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003; 112(12): 1796–808.
42. Bing C. Is interleukin-1β a culprit in macrophage-adipocyte crosstalk in obesity? Adipocyte. 2015; 4(2): 149–52.
43. Castoldi A, De Souza CN, Saraiva Câmara NO, Moraes-Vieira PM. The macrophage switch in obesity development. Front Immunol. 2016: 6: 637. doi: 10.3389/fimmu.2015.00637.
44. Kob R, Bollheimer LC, Bertsch T, Fellner C, Djukic M, Sieber CC, *et al.* Sarcopenic obesity: Molecular clues to a better understanding of its pathogenesis? Biogerontology. 2015; 16(1): 15–29.
45. Boura-Halfon S, Zick Y. Phosphorylation of IRS proteins, insulin action, and insulin resistance. Am J Physiol Endocrinol Metab. 2009; 296(4): 581–91.
46. Hong SH, Choi KM. Sarcopenic obesity, insulin resistance, and their implications in cardiovascular and metabolic consequences. Int J Mol Sci. 2020; 21(2): 494. doi: 10.3390/ijms21020494.
47. Hafizi Abu Bakar M, Kian Kai C, Wan Hassan WN, Sarmidi MR, Yaakob H, Zaman Huri H. Mitochondrial dysfunction as a central event for mechanisms underlying insulin resistance: The roles of long chain fatty acids. Diabetes Metab Res Rev. 2015; 31(5): 453–75.
48. Stinkens R, Goossens GH, Jocken JWE, Blaak EE. Targeting fatty acid metabolism to improve glucose metabolism. Obes Rev. 2015; 16(9): 715–57.
49. Kalinkovich A, Livshits G. Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing Res Rev. 2017; 35: 200–21.
50. Chung HS, Choi KM. Adipokines and myokines: A pivotal role in metabolic and cardiovascular disorders. Curr Med Chem 2018; 25(20): 2401–15.
51. Fischer CP, Plomgaard P, Hansen AK, Pilegaard H, Saltin B, Pedersen BK. Endurance training reduces the contraction-induced interleukin-6 mRNA expression in human skeletal muscle. Am J Physiol Endocrinol Metab. 2004 ;287(6): E1189–94.
52. Wolsk E, Mygind H, Grøndahl TS, Pedersen BK, Van Hall G. IL-6 selectively stimulates fat metabolism in human skeletal muscle. Am J Physiol Endocrinol Metab. 2010; 299(5): E832–40.
53. Ellingsgaard H, Hauselmann I, Schuler B, Habib AM, Baggio LL, Meier DT, *et al.* Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. Nat Med. 2011; 17(11): 1481–9.
54. Zamboni M, Rubele S, Rossi AP. Sarcopenia and obesity. Curr Opin Clin Nutr Metab Care. 2019; 22(1):13–9.
55. Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, *et al.* A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012; 481(7382): 463–8.
56. Zhang Y, Li R, Meng Y, Li S, Donelan W, Zhao Y, *et al.* Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. Diabetes. 2014; 63(2): 514–25.
57. Natalicchio A, Marrano N, Biondi G, Spagnuolo R, Labarbuta R, Porreca I, *et al.* The myokine irisin is released in response to saturated fatty acids and promotes pancreatic β-cell survival and insulin secretion. Diabetes. 2017; 66(11): 2849–56.
58. Zhou X, Li R, Liu X, Wang L, Hui P, Chan L, *et al.* ROCK1 reduces mitochondrial content and irisin production in muscle suppressing adipocyte browning and impairing insulin sensitivity. 2016; 6: 29669. doi: 10.1038/srep29669.
59. Kurdiova T, Balaz M, Vician M, Maderova D, Vlcek M, Valkovic L, *et al.* Effects of obesity, diabetes and exercise on Fndc5 gene expression and irisin release in human skeletal muscle and adipose tissue: In vivo and in vitro studies. J Physiol. 2014; 592(5): 1091–107.
60. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, *et al.* Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med. 2002; 8(11): 1288–95.
61. Kang SY, Lim GE, Kim YK, Kim HW, Lee K, Park TJ, *et al.* Association between sarcopenic obesity and metabolic syndrome in postmenopausal women: A cross-sectional study based on the Korean National Health and Nutritional Examination Surveys from 2008 to 2011. J Bone Metab. 2017; 24(1): 9–14.
62. Lim S, Kim JH, Yoon JW, Kang SM, Choi SH, Park YJ, *et al.* Sarcopenic obesity: Prevalence and association with metabolic syndrome in the Korean Longitudinal Study on Health and Aging (KLoSHA). Diabetes Care. 2010; 33(7): 1652–4.
63. Lee J, Hong YP, Shin HJ, Lee W. Associations of sarcopenia and sarcopenic obesity with metabolic syndrome considering both muscle mass and muscle strength. J Prev Med Public Health. 2015; 49(1): 35–44.
64. Scott D, Cumming R, Naganathan V, Blyth F, Le Couteur DG, Handelsman DJ, *et al.* Associations of sarcopenic obesity with the metabolic syndrome and insulin resistance over five years in older men: The Concord Health and Ageing in Men Project. Exp Gerontol. 2018; 108: 99–105.
65. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest. 2005; 115(5): 1343–51.
66. Kim JK, Michael MD, Previs SF, Peroni OD, Mauvais-Jarvis F, Neschen S, *et al.* Redistribution of substrates to adipose tissue promotes obesity in mice with selective insulin resistance in muscle. J Clin Invest. 2000; 105(12): 1791–7.
67. Kim JK, Zisman A, Fillmore JJ, Peroni OD, Kotani K, Perret P, *et al.* Glucose toxicity and the development of diabetes in mice with muscle-specific inactivation of GLUT4. J Clin Invest; 108(1): 153–60.
68. Atkins JL, Wannamathee SG. Sarcopenic obesity in ageing: Cardiovascular outcomes and mortality. Br J Nutr. 2020; 124(10): 1102–13.
69. Semadhi MP, Barliana MI, Muliaty D, Wijaya A. Correlation of moderate-intensity physical exercise on irisin, oxidized-low-density lipoproteins and high-density lipoproteins cholesterol level in over 50 years old obese men. Indones Biomed J. 2019; 11(3): 257–61.
70. Walsh MC, Hunter GR, Livingstone MB. Sarcopenia in premenopausal and postmenopausal women with osteopenia, osteoporosis and normal bone mineral density. Osteoporos Int. 2006; 17(1): 61–7.
71. Griffiths RD. Muscle mass, survival, and the elderly ICU patient. Nutrition. 1996; 12(6): 456–8.
72. Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: mechanistic links between common co-morbidities. J Endocrinol. 2016; 229(2): R67–81.
73. Tilg H, Moschen AR. Adipocytokines: Mediators linking adipose

tissue, inflammation and immunity. Nat Rev Immunol. 2006; 6(10): 772–83.
74. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005; 115(5): 1111–9.
75. Lim JP, Leung BP, Ding YY, Tay L, Ismail NH, Yeo A, *et al.* Monocyte chemoattractant protein-1: A Proinflammatory cytokine elevated in sarcopenic obesity. Clin Interv Aging. 2015; 10: 605–9.
76. Yan QW, Yang Q, Mody N, Graham TE, Hsu CH, Xu Z, *et al.* The adipokine lipocalin 2 is regulated by obesity and promotes insulin resistance. Diabetes. 2007; 56(10): 2533–40.
77. Preissner KT. Adipose tissue-derived PAI-1: A molecular link for thrombo-inflammatory disease states? Thromb Haemost. 2012; 108(3): 415. doi: 10.1160/TH12-08-0540.
78. Das DK, Graham ZA, Cardozo CP. Myokines in skeletal muscle physiology and metabolism: Recent advances and future perspectives. Acta Physiol. 2020; 228(2): e13367. doi: 10.1111/apha.13367.
79. Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity: Definition, cause and consequences. Curr Opin Clin Nutr Metab Care. 2008; 11(6): 693–700.
80. Havekes B, Sauerwein HP. Adipocyte-myocyte crosstalk in skeletal muscle insulin resistance; is there a role for thyroid hormone? Curr Opin Clin Nutr Metab Care. 2010; 13(6): 641–6.
81. Trayhurn P, Drevon CA, Eckel J. Secreted proteins from adipose tissue and skeletal muscle - adipokines, myokines and adipose/muscle cross-talk. Arch Physiol Biochem. 2011; 117(2): 47–56.
82. Rubio-Ruiz ME, Guarner-Lans V, Pérez-Torres I, Soto ME. Mechanisms underlying metabolic syndrome-related sarcopenia and possible therapeutic measures. Int J Mol Sci. 2019; 20(3): 647. doi: 10.3390/ijms20030647.
83. Pedersen BK. Muscles and their myokines. J Exp Biol. 2011; 214(Pt 2): 337–46.
84. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: Skeletal muscle as a secretory organ. Nat Rev Endocrinol. 2012; 8(8): 457–65.
85. Aryana IGPS, Winangun IMA. Decreased follistatin levels as a risk of acute sarcopenia marker in elderly. Mol Cell Biomed Sci. 2023; 7(3): 147-54.
86. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic obesity and risk of cardiovascular disease and mortality: A population-based cohort study of older men. J Am Geriatr Soc. 2014; 62(2): 253–60.
87. Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity: Definition, cause and consequences. Curr Opin Clin Nutr Metab Care. 2008; 11(6): 693–700.
88. Kohara K. Sarcopenic obesity in aging population: Current status and future directions for research. Endocrine. 2014; 45(1): 15–25.
89. Sainsbury A, Zhang L. Role of the arcuate nucleus of the hypothalamus in regulation of body weight during energy deficit. Mol Cell Endocrinol. 2010; 316(2): 109–19.
90. Ticinesi A, Nouvenne A, Cerundolo N, Catania P, Prati B, Tana C, *et al.* Gut microbiota, muscle mass and function in aging: A focus on physical frailty and sarcopenia. Nutrients. 2019; 11(7): 1633. doi: 10.3390/nu11071633.
91. Livshits G, Kalinkovich A. Inflammaging as a common ground for the development and maintenance of sarcopenia, obesity, cardiomyopathy and dysbiosis. Ageing Res Rev. 2019; 56: 100980. doi: 10.1016/j.arr.2019.100980.
92. Picca A, Fanelli F, Calvani R, Mulè G, Pesce V, Sisto A, *et al.* Gut dysbiosis and muscle aging: Searching for novel targets against sarcopenia. Mediators Inflamm. 2018: 2018: 7026198. doi: 10.1155/2018/7026198.
93. Hiippala K, Jouhten H, Ronkainen A, Hartikainen A, Kainulainen V, Jalanka J, *et al.* The potential of gut commensals in reinforcing intestinal barrier function and alleviating inflammation. Nutrients. 2018; 10(8): 988. doi: 10.3390/nu10080988.
94. Cancello R, Turroni S, Rampelli S, Cattaldo S, Candela M, Cattani L, *et al.* Effect of short-term dietary intervention and probiotic mix supplementation on the gut microbiota of elderly obese women. Nutrients. 2019; 11(12): 3011. doi: 10.3390/nu11123011.
95. Oliphant K, Allen-Vercoe E. Macronutrient metabolism by the human gut microbiome: Major fermentation by-products and their impact on host health. Microbiome. 2019; 7(1): 91. doi: 10.1186/s40168-019-0704-8.
96. Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. Nat Rev Gastroenterol Hepatol. 2019; 16(8): 461–78.
97. Muscariello E, Nasti G, Siervo M, Di Maro M, Lapi D, D'Addio G, *et al.* Dietary protein intake in sarcopenic obese older women. Clin Interv Aging. 2016; 11: 133–40.
98. Fromentin G, Darcel N, Chaumontet C, Marsset-Baglieri A, Nadkarni N, Tomé D. Peripheral and central mechanisms involved in the control of food intake by dietary amino acids and proteins. Nutr Res Rev. 2012; 25(1): 29–39.
99. Van Der Klaauw AA, Keogh JM, Henning E, Trowse VM, Dhillo WS, Ghatei MA, *et al.* High protein intake stimulates postprandial GLP1 and PYY release. Obesity. 2013; 21(8): 1602–7.
100. Ojha U. Protein-induced satiation and the calcium-sensing receptor. Diabetes, Metabolic Syndrome and Obesity. 2018; 11: 45–51.
101. Bliss ES, Whiteside E. The gut-brain axis, the human gut microbiota and their integration in the development of obesity. Front Physiol. 2018; 9: 900. doi: 10.3389/fphys.2018.00900.
102. Erdmann J, Lippl F, Schusdziarra V. Differential effect of protein and fat on plasma ghrelin levels in man. Regul Pept. 2003; 116(1–3): 101–7.
103. Shrestha YB, Wickwire K, Giraudo SQ. Direct effects of nutrients, acetylcholine, CCK, and insulin on ghrelin release from the isolated stomachs of rats. Peptides. 2009; 30(6): 1187–91.
104. Al Massadi O, Pardo M, Roca-Rivada A, Castelao C, Casanueva FF, Seoane LM. Macronutrients act directly on the stomach to regulate gastric ghrelin release. J Endocrinol Invest. 2010; 33(9): 599–602.
105. Mignone LE, Wu T, Horowitz M, Rayner CK. Whey protein: The "whey" forward for treatment of type 2 diabetes? World J Diabetes. 2015; 6(14): 1274–84.
106. Blouet C, Jo YH, Li X, Schwartz GJ. Mediobasal hypothalamic leucine sensing regulates food intake through activation of a hypothalamus–brainstem circuit. J Neurosci. 2009; 29(26): 8302–11.
107. Leitão-Gonçalves R, Carvalho-Santos Z, Francisco AP, Fioreze GT, Anjos M, Baltazar C, *et al.* Commensal bacteria and essential amino acids control food choice behavior and reproduction. PLoS Biol. 2017; 15(4): e2000862. doi: 10.1371/journal.pbio.2000862.
108. Diether NE, Willing BP. Microbial fermentation of dietary protein: An important factor in diet−microbe−host interaction. Microorganisms. 2019; 7(1): 19. doi: 10.3390/microorganisms7010019.
109. Dai ZL, Wu G, Zhu WY. Amino acid metabolism in intestinal bacteria: Links between gut ecology and host health. Front Biosci. 2011; 16(5): 1768–86.
110. Neis EPJG, Dejong CHC, Rensen SS. The role of microbial amino acid metabolism in host metabolism. Nutrients. 2015; 7(4): 2930–46.
111. Faith JJ, Guruge JL, Charbonneau M, Subramanian S, Seedorf H, Goodman AL, *et al.* The long-term stability of the human gut microbiota. Science. 2013; 341(6141): 1237439. doi: 10.1126/

science.1237439.

112. Ticinesi A, Milani C, Lauretani F, Nouvenne A, Mancabelli L, Lugli GA, *et al.* Gut microbiota composition is associated with polypharmacy in elderly hospitalized patients. Sci Rep. 2017; 7(1): 11102. doi: 10.1038/s41598-017-10734-y.
113. Lustgarten MS. The role of the gut microbiome on skeletal muscle mass and physical eunction: 2019 update. Front Physiol. 2019; 10: 1435. doi: 10.3389/fphys.2019.01435.
114. Casati M, Ferri E, Azzolino D, Cesari M, Arosio B. Gut microbiota and physical frailty through the mediation of sarcopenia. Exp Gerontol. 2019; 124: 110639. doi: 10.1016/j.exger.2019.110639.
115. Steves CJ, Bird S, Williams FMK, Spector TD. The microbiome and musculoskeletal conditions of aging: A review of evidence for impact and potential therapeutics. J Bone Miner Res. 2016; 31(2): 261–9.
116. Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, *et al.* ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature. 2012; 487(7408): 477–81.
117. Ticinesi A, Lauretani F, Milani C, Nouvenne A, Tana C, Del Rio D, *et al.* Aging gut microbiota at the cross-road between nutrition, physical frailty, and sarcopenia: Is there a gut-muscle axis? Nutrients. 2017; 9(12): 1303. doi: 10.3390/nu9121303.
118. Qi YF, Goel R, Kim S, Richards EM, Carter CS, Pepine CJ, *et al.* Intestinal permeability biomarker zonulin is elevated in healthy aging. J Am Med Dir Assoc. 2017; 18(9): 810.e1–4.
119. Sovran B, Hugenholtz F, Elderman M, Van Beek AA, Graversen K, Huijskes M, *et al.* Age-associated impairment of the mucus barrier function is associated with profound changes in microbiota and immunity. Sci Rep. 2019; 9(1): 1437. doi: 10.1038/s41598-018-35228-3.
120. Portune KJ, Beaumont M, Davila AM, Tomé D, Blachier F, Sanz Y. Gut microbiota role in dietary protein metabolism and health-related outcomes: The two sides of the coin. Trends Food Sci Technol. 2016; 57: 213–32.
121. Blachier F, Beaumont M, Portune KJ, Steuer N, Lan A, Audebert M, *et al.* High-protein diets for weight management: Interactions with the intestinal microbiota and consequences for gut health. A position paper by the my new gut study group. Clin Nutr. 2019; 38(3): 1012–22.
122. Morowitz MJ, Carlisle EM, Alverdy JC. Contributions of intestinal bacteria to nutrition and metabolism in the critically ill. Surg Oncol Clin N. 2011; 91(4): 771–85.
123. Metges CC. Contribution of microbial amino acids to amino acid homeostasis of the host. J Nutr. 2000; 130(7): 1857S–64S.
124. Pesta DH, Samuel VT. A high-protein diet for reducing body fat: mechanisms and possible caveats. Nutr Metab. 2014; 11(1): 53. doi: 10.1186/1743-7075-11-53.
125. Westerterp-Plantenga MS, Lemmens SG, Westerterp KR. Dietary protein – its role in satiety, energetics, weight loss and health. Br J Nutr. 2012; 108(S2): S105–12.
126. Davila AM, Blachier F, Gotteland M, Andriamihaja M, Benetti PH, Sanz Y, *et al.* Intestinal luminal nitrogen metabolism: Role of the gut microbiota and consequences for the host. Pharmacol Res. 2013; 68(1): 95–107.
127. Windey K, de Preter V, Verbeke K. Relevance of protein fermentation to gut health. Mol Nutr Food Res. 2012; 56(1): 184–96.
128. Russell WR, Gratz SW, Duncan SH, Holtrop G, Ince J, Scobbie L, *et al.* High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. Am J Clin Nutr. 2011; 93(5): 1062–72.
129. Lan A, Andriamihaja M, Blouin JM, Liu X, Descatoire V, Desclée de Maredsous C, *et al.* High-protein diet differently modifies intestinal goblet cell characteristics and mucosal cytokine expression in ileum and colon. J Nutr Biochem. 2015; 26(1): 91–8.
130. Tomova A, Bukovsky I, Rembert E, Yonas W, Alwarith J, Barnard ND, *et al.* The effects of vegetarian and vegan diets on gut microbiota. Front Nutr. 2019; 6: 47. doi: 10.3389/fnut.2019.00047.
131. Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, *et al.* Dietary intervention impact on gut microbial gene richness. Nature. 2013; 500(7464): 585–8.
132. Reichardt N, Duncan SH, Young P, Belenguer A, Mcwilliam Leitch C, Scott KP, *et al.* Erratum: Phylogenetic distribution of three pathways for propionate production within the human gut microbiota. ISME J. 2014; 8(6): 1352. doi: 10.1038/ismej.2014.48.
133. Zhou XL, Yan BB, Xiao Y, Zhou YM, Liu TY. Tartary buckwheat protein prevented dyslipidemia in high-fat diet-fed mice associated with gut microbiota changes. Food Chem Toxicol. 2018; 119: 296–301.
134. Nakatani A, Li X, Miyamoto J, Igarashi M, Watanabe H, Sutou A, *et al.* Dietary mung bean protein reduces high-fat diet-induced weight gain by modulating host bile acid metabolism in a gut microbiota-dependent manner. Biochem Biophys Res Commun. 2018; 501(4): 955–61.
135. Yu H, Guo Z, Shen S, Shan W. Effects of taurine on gut microbiota and metabolism in mice. Amino Acids. 2016; 48(7): 1601–17.
136. Moreno-Pérez D, Bressa C, Bailén M, Hamed-Bousdar S, Naclerio F, Carmona M, *et al.* Effect of a protein supplement on the gut microbiota of endurance athletes: A randomized, controlled, double-blind pilot study. Nutrients. 2018; 10(3): 337. doi: 10.3390/nu10030337.
137. Kim CH, Park J, Kim M. Gut microbiota-derived short-chain fatty acids, T cells, and inflammation. Immune Netw. 2014; 14(6): 277–88.
138. Park JS, Lee EJ, Lee JC, Kim WK, Kim HS. Anti-inflammatory effects of short chain fatty acids in IFN-γ-stimulated RAW 264.7 murine macrophage cells: Involvement of NF-κB and ERK signaling pathways. Int Immunopharmacol. 2007; 7(1): 70–7.
139. Petropoulou K, Chambers ES, Morrison DJ, Preston T, Godsland IF, Wilde P, *et al.* Identifying crop variants with high resistant starch content to maintain healthy glucose homeostasis. Nutr Bull. 2016; 41(4): 372–7.
140. Chambers ES, Byrne CS, Morrison DJ, Murphy KG, Preston T, Tedford C, *et al.* Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma metabolome and systemic inflammatory responses: a randomised cross-over trial. Gut. 2019; 68(8): 1430–8.
141. Larsen N, Vogensen FK, Van Den Berg FWJ, Nielsen DS, Andreasen AS, Pedersen BK, *et al.* Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One. 2010; 5(2): e9085. doi: 10.1371/journal.pone.0009085.
142. Karlsson FH, Tremaroli V, Nookaew I, Bergström G, Behre CJ, Fagerberg B, *et al.* Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature. 2013; 498(7452): 99–103.
143. Shen Z, Zhu C, Quan Y, Yang J, Yuan W, Yang Z, *et al.* Insights into Roseburia intestinalis which alleviates experimental colitis pathology by inducing anti-inflammatory responses. J Gastroenterol Hepatol. 2018; 33(10): 1751–60.
144. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, *et al.* Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013; 19(5): 576–85.
145. Dumas ME, Rothwell AR, Hoyles L, Aranias T, Chilloux J, Calderari S, *et al.* Microbial-host co-metabolites are prodromal markers

predicting phenotypic heterogeneity in behavior, obesity, and impaired glucose tolerance. Cell Rep. 2017; 20(1): 136–48.
146. Cho CE, Taesuwan S, Malysheva OV, Bender E, Tulchinsky NF, Yan J, *et al.* Trimethylamine-N-oxide (TMAO) response to animal source foods varies among healthy young men and is influenced by their gut microbiota composition: A randomized controlled trial. Mol Nutr Food Res. 2017; 61(1): 1600324. doi: 10.1002/mnfr.201600324.
147. Landfald B, Valeur J, Berstad A, Raa J. Microbial trimethylamine-N-oxide as a disease marker: something fishy? Microb Ecol Health Dis. 2017; 28(1): 1327309. doi: 10.1080/16512235.2017.1327309.
148. Prokopidis K, Cervo MM, Gandham A, Scott D. Impact of protein intake in older adults with sarcopenia and obesity: A gut microbiota perspective. Nutrients. 2020; 12(8): 2285. doi: 10.3390/nu12082285.
149. Den Besten G, Van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013; 54(9): 2325–40.
150. Dhingra D, Michael M, Rajput H, Patil RT. Dietary fibre in foods: A review. J Food Sci Technol. 2012; 49(3): 255–66.
151. Gibson R, Eriksen R, Chambers E, Gao H, Aresu M, Heard A, *et al.* Intakes and food sources of dietary fibre and their associations with measures of body composition and inflammation in UK adults: Cross-sectional analysis of the airwave health monitoring study. Nutrients. 2019; 11(8): 1839. doi: 10.3390/nu11081839.
152. Fayet-Moore F, Cassettari T, Tuck K, McConnell A, Petocz P. Dietary fibre intake in Australia. Paper I: Associations with demographic, socio-economic, and anthropometric factors. Nutrients. 201; 10(5): 599. doi: 10.3390/nu10050599.
153. Harris HC, Edwards CA, Morrison DJ. Impact of glycosidic bond configuration on short chain fatty acid production from model fermentable carbohydrates by the human gut microbiota. Nutrients. 2017; 9(1): 26. doi: 10.3390/nu9010026.
154. Chambers ES, Preston T, Frost G, Morrison DJ. Role of gut microbiota-generated short-chain fatty acids in metabolic and cardiovascular health. Curr Nutr Rep. 2018; 7(4): 198–206.
155. Cox MA, Jackson J, Stanton M, Rojas-Triana A, Bober L, Laverty M, *et al.* Short-chain fatty acids act as antiinflammatory mediators by regulating prostaglandin E(2) and cytokines. World J Gastroenterol. 2009; 15(44): 5549–57.
156. Canfora EE, Meex RCR, Venema K, Blaak EE. Gut microbial metabolites in obesity, NAFLD and T2DM. Nat Rev Endocrinol. 2019; 15(5): 261–73.
157. Sukkar AH, Lett AM, Frost G, Chambers ES. Regulation of energy expenditure and substrate oxidation by short-chain fatty acids. J Endocrinol. 2019; 242(2): R1–8.
158. Frampton J, Murphy KG, Frost G, Chambers ES. Short-chain fatty acids as potential regulators of skeletal muscle metabolism and function. Nat Metab. 2020; 2(9): 840–8.
159. Alamshah A, Spreckley E, Norton M, Kinsey-Jones JS, Amin A, Ramgulam A, *et al*. L-phenylalanine modulates gut hormone release and glucose tolerance, and suppresses food intake through the calcium-sensing receptor in rodents. Int J Obes. 2017; 41(11): 1693–701.
160. Amin A, Neophytou C, Thein S, Martin NM, Alamshah A, Spreckley E, *et al.* L-arginine increases postprandial circulating GLP-1 and PYY levels in humans. Obesity. 2018; 26(11): 1721–6.
161. Chambers ES, Viardot A, Psichas A, Morrison DJ, Murphy KG, Zac-Varghese SEK, *et al.* Targeted delivery of propionate to the human colon prevents body weight and intra-abdominal adipose tissue gain in overweight adults. Proc Nutr Soc. 2014; 73: E22. doi: 10.1017/S0029665114000366.
162. Chimerel C, Emery E, Summers DK, Keyser U, Gribble FM, Reimann F. Bacterial metabolite indole modulates incretin secretion from intestinal enteroendocrine L cells. Cell Rep. 2014; 9(4): 1202–8.
163. Spreckley E, Murphy KG. The L-cell in nutritional sensing and the regulation of appetite. Front Nutr. 2015; 2: 23. doi: 10.3389/fnut.2015.00023.
164. Williams BB, Van Benschoten AH, Cimermancic P, Donia MS, Zimmermann M, Taketani M, *et al.* Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. Cell Host Microbe. 2014; 16(4): 495–503.
165. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, *et al.* Erratum: Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015; 163(1): 258.
166. Norton M, Murphy KG. Targeting gastrointestinal nutrient sensing mechanisms to treat obesity. Curr Opin Pharmacol. 2017; 37: 16–23.
167. Dagbasi A, Lett AM, Murphy K, Frost G. Understanding the interplay between food structure, intestinal bacterial fermentation and appetite control. Proc Nutr Soc. 2020; 79(4): 514–30.
168. Byrne CS, Chambers ES, Alhabeeb H, Chhina N, Morrison DJ, Preston T, *et al.* Increased colonic propionate reduces anticipatory reward responses in the human striatum to high-energy foods. Am J Clin Nutr. 2016; 104(1): 5–14.
169. Yau YHC, Potenza MN. Stress and eating behaviors. Minerva Endocrinol. 2013; 38(3): 255–67.
170. Beaumont M, Portune KJ, Steuer N, Lan A, Cerrudo V, Audebert M, *et al.* Quantity and source of dietary protein influence metabolite production by gut microbiota and rectal mucosa gene expression: a randomized, parallel, double-blind trial in overweight humans. Am J Clin Nutr. 2017; 106(4): 1005–19.
171. Kritchevsky SB, Beavers KM, Miller ME, Shea MK, Houston DK, Kitzman DW, *et al.* Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials. PLoS One. 2015; 10(3): e0121993. doi: 10.1371/journal.pone.0121993.
172. Villareal DT, Apovian CM, Kushner RF, Klein S. Obesity in older adults: Technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. Am J Clin Nutr. 2005; 82(5): 923–34.
173. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, *et al.* Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med. 2011; 364(13): 1218–29.
174. Villareal DT, Aguirre L, Gurney AB, Waters DL, Sinacore DR, Colombo E, *et al.* Aerobic or resistance exercise, or both, in dieting obese older adults. N Engl J Med. 2017; 376(20): 1943–55.
175. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: Aetiology, epidemiology and treatment strategies. Nat Rev Endocrinol. 2018; 14(9): 513–37.
176. Lo JH, U KP, Yiu T, Ong MT, Lee WY. Sarcopenia: Current treatments and new regenerative therapeutic approaches. J Orthop Translat. 2020; 23: 38–52.
177. Juffer P, Jaspers RT, Lips P, Bakker AD, Klein-Nulend J. Expression of muscle anabolic and metabolic factors in mechanically loaded MLO-Y4 osteocytes. Am J Physiol Endocrinol Metab. 2012; 302(4): 389–95.
178. Kaji H. Linkage between muscle and bone: Common catabolic signals resulting in osteoporosis and sarcopenia. Curr Opin Clin Nutr Metab Care. 2013; 16(3): 272–7.
179. Mera P, Laue K, Ferron M, Confavreux C, Wei J, Galán-Díez M, *et al.* Osteocalcin signaling in myofibers is necessary and sufficient for optimum adaptation to exercise. Cell Metab. 2016; 23(6):

1078–92.
180. Bori Z, Zhao Z, Koltai E, Fatouros IG, Jamurtas AZ, Douroudos II, *et al.* The effects of aging, physical training, and a single bout of exercise on mitochondrial protein expression in human skeletal muscle. Exp Gerontol. 2012; 47(6): 417–24.
181. Lanza IR, Nair KS. Muscle mitochondrial changes with aging and exercise. Am J Clin Nutr. 2009; 89(1): 467S–71S.
182. Barillaro C, Liperoti R, Martone AM, Onder G, Landi F. The new metabolic treatments for sarcopenia. Aging Clin Exp Res. 2013; 25(2): 119–27.
183. Trouwborst I, Verreijen A, Memelink R, Massanet P, Boirie Y, Weijs P, *et al.* Exercise and nutrition strategies to counteract sarcopenic obesity. Nutrients. 2018; 10(5): 605. doi: 10.3390/nu10050605.
184. Heymsfield SB, Gonzalez MCC, Shen W, Redman L, Thomas D. Weight loss composition is one-fourth fat-free mass: A critical review and critique of this widely cited rule. Obes Rev; 15(4): 310–21.
185. Wang M, Tan Y, Shi Y, Wang X, Liao Z, Wei P. Diabetes and sarcopenic obesity: Pathogenesis, diagnosis, and treatments. Front Endocrinol. 2020; 11: 568. doi: 10.3389/fendo.2020.00568.
186. Cheah KJ, Cheah LJ. Benefits and side effects of protein supplementation and exercise in sarcopenic obesity: A scoping review. Nutr J. 2023; 22(1): 52. doi: 10.1186/s12937-023-00880-7.
187. Meiliana A, Dewi NM, Wijaya A. Nutritional influences on epigenetics, aging and disease. Indones Biomed J. 2019; 11(1): 16–29.
188. Backx EMP, Tieland M, Borgonjen-Van Den Berg KJ, Claessen PR, Van Loon LJC, De Groot LCPGM. Protein intake and lean body mass preservation during energy intake restriction in overweight older adults. Int J Obes. 2016; 40(2): 299–304.
189. Petroni ML, Caletti MT, Grave RD, Bazzocchi A, Aparisi Gómez MP, Marchesini G. Prevention and treatment of sarcopenic obesity in women. Nutrients. 2019; 11(6): 1302. doi: 10.3390/nu11061302.
190. Nicklas BJ, Chmelo E, Delbono O, Carr JJ, Lyles MF, Marsh AP. Effects of resistance training with and without caloric restriction on physical function and mobility in overweight and obese older adults: a randomized controlled trial. Am J Clin Nutr. 2015; 101(5): 991–9.
191. Bellia A, Garcovich C, D'Adamo M, Lombardo M, Tesauro M, Donadel G, *et al.* Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects. Intern Emerg Med. 2013; 8(1): 33–40.
192. Hassan-Smith ZK, Jenkinson C, Smith DJ, Hernandez I, Stuart AM, Crabtree NJ, *et al.* 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 exert distinct effects on human skeletal muscle function and gene expression. PLoS One. 2017; 12(2): e0170665. doi: 10.1371/journal.pone.0170665.
193. Moyer VA. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2013; 158(9): 691–6.
194. Sohl E, De Jongh RT, Heijboer AC, Swart KMA, Brouwer-Brolsma EM, Enneman AW, *et al.* Vitamin D status is associated with physical performance: The results of three independent cohorts. Osteoporos Int. 2013; 24(1): 187–96.
195. Jung UJ. Sarcopenic obesity: Involvement of oxidative stress and beneficial role of antioxidant flavonoids. Antioxidants. 2023; 12(5): 1063. doi: 10.3390/antiox12051063.
196. Kim JS, Wilson JM, Lee SR. Dietary implications on mechanisms of sarcopenia: roles of protein, amino acids and antioxidants. J Nutr Biochem. 2010; 21(1): 1–13.
197. Kim J, Lee Y, Kye S, Chung YS, Kim KM. Association of vegetables and fruits consumption with sarcopenia in older adults: The Fourth Korea National Health and Nutrition Examination Survey. Age Ageing. 2015; 44(1): 96–102.
198. Hutchins-Wiese HL, Kleppinger A, Annis K, Liva E, Lammi-Keefe CJ, Durham HA, *et al.* The impact of supplemental N-3 long chain polyunsaturated fatty acids and dietary antioxidants on physical performance in postmenopausal women. J Nutr Health Aging. 2013; 17(1): 76–80.
199. Cesari M, Demougeot L, Boccalon H, Guyonnet S, Vellas B, Andrieu S. The multidomain intervention to prevent disability in elders (MINDED) project: Rationale and study design of a pilot study. Contemp Clin Trials. 2014; 38(1): 145–54.
200. Tikkanen P, Lönnroos E, Sipilä S, Nykänen I, Sulkava R, Hartikainen S. Effects of comprehensive geriatric assessment-based individually targeted interventions on mobility of pre-frail and frail community-dwelling older people. Geriatr Gerontol Int. 2015; 15(1): 80–8.