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Review Article

Molecular Mechanisms Which Regulate Skeletal Muscle Mass Against Obesity and The Clinicopathological Correlates

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Abstract:

Skeletal muscles constitute the putative force-generating tissue attached to bones which are crucial for sustainability of their mass and health in order that the human body functions in optimum capacity. It becomes imperative to understand how an organism regulates the skeletal muscle formation, growth, development and health. These provide the latitude for the identification and determination of the overall cellular, molecular and metabolic mechanisms which are contributary variables or factors regarding muscle wasting as well as the excoriated muscle functionality during ageing and disease. The provision of non-pharmaceutical and/or clinically relevant therapies for the prevention or reversal of these pathologies will be an immensely beneficial relief to present and future generations. Irrespective of the expansive obesity epidemic in developed and vulnerable populations, there is no extant medical modality to efficiently and effectively stem obesity. Numerous neuromuscular disorders are extant in the absence of adequate therapies due to deficient sustainable models to investigate mechanisms and test quintessential interventions. Regulation of muscle morphology reflects in every dimension of quality of life.

Keywords: exercise; physical activity; obesity; diabetes; sarcopenia; atrophy; hypertrophy; myokines; insulin resistance; quality of life.

Introduction:

Muscle mass and strength dissipation in older adults may lead to a vicious cycle of retarded physical activity, with enhanced muscle wasting and augmented fat aggregation [1]. Extant obesity tends to engender a global chronic epidemic. Relentless obesity, with concomitant inducements of transformations in skeletal muscle morphology are liable to culminate in skeletal muscle atrophy in association with inter alia autophagy, ubiquitin proteasome, interleukin-6, leptin, adiponectin, interleukin-10, tumor necrosis factor-alpha, growth hormone, angiotensin II, glucocorticoid, advanced glycation end-product and myostatin [2]. Cognizance of the deleterious occurrence in obese individuals aged over 65 years with dissipated muscle mass, strength, or sarcopenia is crucial as the global obesity pandemic persistently impacts an excess of 39% adults with associated multiple health risks, such as cardiovascular perturbations, type 2 diabetes, and varied cancer types [3]. Aged obesity patients may exhibit disproportionate decreases in lean muscle mass or the sarcopenic obesity state, with predisposition to frailty, disability, elevated comorbidities and mortality [4, 5]. Sarcopenic obesity aggravates the untoward repercussions of both sarcopenia and obesity with resultant health risk of functional retardation, mobility declination, and diminished quality of life [6]. Extant therapies for the treatment of generalized obesity mainly adheres to decreased total body mass and food consumption. Body mass dissipation perturbs skeletal muscle mass, though [7, 8], with protracted repercussions

for the overall health and well-being of the patient due to the primordial function in entire body energy consumption, thermogenesis, glucose regulations, mobility with elevated risk for sarcopenia, and autonomic roles. Due to restrictions of presenting obesity treatments, there is pertinence for targeted and specific interventions on sarcopenic obesity to address, preserve or enhance muscle mass and function with concomitant diminishing of excess adiposity, culminating in improved whole health prognosis and impactout in elderly obesity patients.

Obesity:

Obesity is a prevalent disorder impacting quality of life globally. The estimated current population of overweight and obese individuals worldwide is respectively, 2 billion and 800 million. Projected estimates depict that overweight subjects may tend towards 60% of global population by the year 2030. Oxidative stress perpetuates obesity development via the stimulation of pre-adipocyte differentiation and resultant adipose storage. Enormous fat deposits discharge excessive quantities of adipocytokines with concomitant chronic inflammation. The obesity-induced chronic inflammation provides the latitude for an expansive array of systemic sequelae, such as diabetes, hyperlipidemia, atherosclerosis, cardiovascular disorders [9, 10] and malignancy. Furthermore, obesity-inducers, such as elevated insulin IGF-1, insulin resistance, and elevated tissue concentration of leptin and low adiponectin levels can result in tissue malignancy development. Enhanced physical activity or exercise in conjunction healthy food consumption is mandatory for obesity management. Anti-obesity medications, such as sibutramine, orlistat, and qsymia: coupled phentermine and topiramate have been applied in variations of therapeutic modalities of efficacy in obesity. Bariatric surgery is applicable in instances of severity as physical functionality and pharmacotherapy become incompetent. In obese patients presenting with diabetes, the choice of hypoglycemic agent is critical. Metformin, and sodium glucose cotransporters 2, SGLT2 inhibitors as antidiabetic drugs can potently decrease body weight, with improvement of cardiorenal functionality [11].

Obesity has culminated in global proportions and epidemics as it preponderates the development of insulin resistance, type 2 diabetes and associated metabolic disorders. Extant interventions against obesity and/or type 2 diabetes, such as calorie restriction, exercise, genetic manipulations or pharmacologic therapeutic strategies have been defied by obesity and/or type 2 diabetes [12]. Novel strategies for the treatment of insulin resistance, type 2 diabetes and obesity ought to be identified and established. Untoward enhanced activity of stress-responsive pathways is connected to insulin resistance pathogenesis in obesity. However, there are polemics that chronic upregulation of MKP-1 in skeletal muscle is partly a stress response involved in insulin resistance, type 2 diabetes and obesity development and preponderance. Thus, MKP-1 suppression in skeletal muscle potentiates the strategy for the treatment of type 2 diabetes and obesity as well as identical diseases [12].

Obesity and osteoporosis are both markedly health issues prevalent within the ageing and aged. The population of those implicated in both perturbations is accelerating. Global estimation places over 600 million adults as obese and an excess of 200 million with osteoporosis [13]. They both share certain common characteristics, such as genetic predisposition and a common origin from bone marrow mesenchymal stromal cells. Obesity characteristically expresses leptin, adiponectin, interleukin 6, IL-6, interleukin 10, IL-10, monocyte chemotactic protein-1, MCP-1, tumor necrosis factor-alpha, TNF-α, macrophage colony stimulating factor, M-CSF, growth hormone, GH, parathyroid hormone, PTH, angiotensin II, Ang II, 5-hydroxy-tryptamine, 5-HT, Advanced glycation endproducts, AGE, and myostatin, which impact via the modulation of signaling pathways in bone and muscle [13]. Chemical messengers, for instance, TNF-α, IL-6, AGE, and leptins which are upregulated or downregulated due to obesity act as negative regulators of osteoblasts, osteocytes and muscles, including positive regulators of osteoclasts. These additive impacts of obesity culminate in elevated risk for osteoporosis and muscle atrophy. Research tends to unravel the potential cellular mechanisms whereby obesity tends to potentiate osteoporosis, muscle atrophy and bone fractures [13].

Sarcopenia:

Sarcopenia constitutes a muscle-wasting syndrome featuring progressive and generalized degenerative dissipation of skeletal muscle mass, quality, and strength depicted in normal ageing. Sarcopenia patients mostly exhibit muscle strength loss and mobility derangement leading to depreciated quality of life, and at higher risk for morbidity, such as falls, bone fracture, metabolic disorders and mortality. Numerous molecular mechanisms are implicated as aetiologies for sarcopenia with reference to specifically disparate stages of muscle physiology [14]. These mechanisms encompass inter alia function of hormones, for instance, IGF-1 and Insulin, composition and neuromuscular drive of muscle fibres, myo-satellite cell potential for differentiation and proliferation, inflammatory pathways and intracellular processes of proteostasis and mitochondrial activity. Researchers have identified sarcopenia as a disparate muscle-wasting syndrome from other atrophic disorders, with molecular aetiologies of sarcopenia development necessitating further research to determine optimum therapeutic interventions, efficient lifestyle, and improved quality of life.

Thus, sarcopenia, an age-associated diminishing impact of skeletal muscle mass, quality, strength and activity correlates with chronic low-grade inflammation and an augmented probability for poor prognosis. Regulation of skeletal muscle mass during ageing is intricately complex and necessitates a fine balance between the synthesis and degradation of muscle protein. The secretion and transfer of cytokines, long non-coding RNAs, lncRNAs and microRNAs, miRNAs, are conducted discretely within extracellular vesicles. These are substantial communication channels between tissues; and are indicated factors in the regulation of skeletal muscle mass and pathophysiology, with perturbation of excess adiposity. Adipose tissue contributes perceptibly in inter-organ communication, and obesity promulgates macrophage accumulation, cellular senescence [15, 16], and the formation and secretion of pro-inflammatory factors. Age-related sarcopenia has been more indicted in obesity; but these

impacts are masked due to comorbidities [17] and exercise presentation. Adiposity can exacerbate age-related sarcopenia, with certain nascent concepts of adipose-skeletal muscle communication, secretion and processing of emergent myokines and adipokines as well as the activity of extracellular vesicles during inter-tissue cross talk through lncRNAs and miRNAs in association of sarcopenia, ageing, and obesity. Advances in proteomics and transcriptomics as well as other procedures to determine extracellular vesicles, emphasising translational, longitudinal human factors are pertinent to unravel the physiological importance of these prevailing variables, their interrelatedness with obesity, and potentials as therapeutic targets against muscle wasting [18].

Obesity sarcopenia:

Thus, obese or obesity sarcopenia is representative of an adverse and prevalent abnormality in the ageing and aged ambient. In comparison to mere sarcopenia, the rapidity, severity, development and advancement of obesity sarcopenia. Furthermore, aetiologic diagnosis of adipocyte accumulation conveys adverse sequelae with no effective therapeutic remedy. Chronic inflammation is an aetiology of sarcopenia [19]. Obese patients susceptible to chronic inflammation development may concurrently present with obesity and sarcopenia as perceptible in mitochondria metabolic abnormalities which encompass a constellation of untoward mtDNA release, mitochondrial autophagy, and dynamic mitochondrial perturbations in tissue cells of subjects having obesity and sarcopenia [19].

Sarcopenic obesity correlates with dissipated skeletal muscle mass and functionality, excess adiposity, persistently nontreatable health issue, diminished quality of life and elevated mortality risk. It is inexplicable, how and why, in certain adults, especially the ageing and aged presenting with obesity succumb to muscle depreciation due to anabolic stimulus in conjunction with lean mass retention [20].

Regulation and related sources of energy:

Regulation of muscle growth and atrophy involves the IGF-I/insulin-Akt-mTOR pathway as the principal regulatory mechanism; and the pathway is predominantly induced by non-sedentary or physical activity, nutrition, and diverse debilitating states. Skeletal muscle mass or growth is regulated via two principal signaling pathways which are the insulin-like growth factor 1– phosphoinositide-3-kinase–Akt/protein kinase B–mammalian rapamycin target (IGF1–PI3K–Akt/PKB–mTOR) pathway functioning as a positive muscle growth regulator, and the myostatin–Smad3 pathway functions as a negative regulator.

Skeletal muscle has attachment to bones and is associated with skeletal motions. The peripheral aspect of the central nervous system, CNS regulates the skeletal muscles; thereby, these muscles are invariably regulated voluntarily. The functional mechanisms in skeletal muscle uniquely depict its capability to adapt its morphology to diverse stimuli. The nascent application of molecular biology technology correlates that human skeletal muscle exercise stimuli precipitate an accelerated elevation in DNA transcription sequences for metabolic and regulatory genes into messenger RNA. The three primordial mechanisms of factors which promote or induce muscle growth or body hypertrophic response include mechanical tension, muscle derangement and metabolic stress. The mechanisms which regulate skeletal muscles entail the somatic nervous system, the somatomotor or somatic efferent nervous system that provides motor impulses to the skeletal muscles, given that these nerves allow conscious control of the skeletal muscles, it is perspicuously referred to as the voluntary nervous system.

Adenosine triphosphate, ATP is acquired by the skeletal muscles by means of three mechanisms. In the sustenance or maintenance of muscle contraction, it is pertinent for ATP to undergo regeneration at a commensurable rate to ATP demand. Phosphagen, glycolytic and mitochondrial respiration are the three energy systems acting for the replenishment of ATP in muscle. Generally, glucose constitutes the major energy source for cellular metabolism, catabolized via three major mechanisms or processes, to wit: glycolysis, tricarboxylic acid cycle, TCA or Krebs cycle, and ultimately oxidative phosphorylation resulting in ATP generation or production. The sole source of fuel in skeletal muscle for contractility is ATP. In less than a second, the ATP muscle storage is diminished within penultimate maximal intense physical activity or exercise. Thus, for the mantenance of physiologic ontractility, ATP must be incessantly resynthesized. The ATP role in metabolism regulation is as the energy source. The human body is a complex entity that requires energy for adequate maintenance and functioning. At the cellular level, ATP is the source of energy for storage and consumption. The energy is derived by breaking the phosphate bond of ATP according to requirements, wherein ATP and ADP have three and two phosphate bonds, respectively according to energy demands. The two major regulating mechanisms for metabolic activity are coarse control of the quantity of an enzyme, and fine control of the enzyme activity. The former is a retarded mechanism concerned with protein synthesis, whereas the latter is an accelerated process associated with transforming the enzyme activity in cells. Summarily, the four fundamental mechanisms of metabolic regulation are explicated as catabolite, nitrogen and phosphate regulations, as well as the impacts of acidic pH, heat shock and nutrient starvation on metabolic regulations. The liver is responsible and has a pivotal role in every metabolic mechanism of the body [21, 22].

Enzymes which regulate metabolism comprise an expansive magnitude of disparate protein categories, such as carboxylases, dehydrogenases, lipoxygenases, oxidoreductases, kinases [23], lyases and transferases. Enzyme regulation in metabolism inculcates coordination of numerous increasingly inextricably-linked biochemical functions, such as the (i) transport of inorganic ions and metabolites across membrane barriers, (ii) translocation of ions and (iii) metabolites to diverse organs, as well as feasible mechanical energy expressions. The rates and trajectory of the catabolic mechanisms need to be regulated for the discrete and optimum provision and supply of energy and catabolites which are wholesomely necessitated in the biosynthesis of all the endproducts pertinent for macromolecular elaboration. The rates of the biosynthetic processes must be regulated for the achievement of equilibria in apportionment of the usual precursors in competing

pathways for proper supply of every endproduct for ultimate assemblage into the macromolecular ingredients of the cell.[24]. The five methods or major pathways of metabolic regulation include: glycolysis, glycogen synthesis and degradation, tricarboxylic acid cycle, lipogenesis, and gluconeogenesis.

The thyroid hormone, TH regulates metabolic processes pertinent for normal growth and development including metabolism regulation in adults [25-28]. The status of thyroid hormone correlates with body mass and energy expenditure. Concisely, the basal metabolic rate of the body is regulated by the thyroid hormones thyroxine, T4 and triiodothyronine T3. The anterior pituitary gland produces thyroid stimulating hormone, TSH that regulatesT3 and T4 release from the thyroid gland. The thyroid is the most essential regulator of body metabolism, while the parathyroid glands are active in the regulation of calcium balance in the body. A vast magnitude of the metabolic regulation involves hormones which are conducted via the bloodstream and function via defined cellular receptors.

How contractions are exhibited in skeletal muscle functions:

The molecular mechanism of skeletal muscle contraction is exhibited sequentially in twitch skeletal muscle[29], to wit: (i) initiating and perpetuating an action potential along the plasma membrane, (ii) the potential spread in the entire transverse tubule system (T-tubule system), (iii) dihydropyridine receptors (DHPR)-mediated unraveling of alterations in membrane potential, (iv) allosteric interaction between DHPR and sarcoplasmic reticulum, SR, ryanodine receptors, RyR, (v) release of Ca2+ from the SR and transient increase of Ca2+ concentration in the myoplasm, (vi) myoplasmic Ca2+ buffering system and the contractile apparatus activation, with concomitant (vii) Ca2+ dissipation from the myoplasm mediated principally due to its reuptake by the SR via the SR Ca2+ adenosine triphosphatase, SERCA and in diverse states moved to the mitochondria and extruded by the Na+/Ca2+ exchanger, NCX. The rudiments of ECC in skeletal muscle and the procedures utilised in its study, may highlight newfangled advances and elicit lacunae in knowledge on specific issues associated with ECC, such as (i) DHPR-RyR molecular interaction, (ii) variations per fibres, (iii) modifications as muscle fatigue ensues, (iv) the function of mitochondria and store-operated Ca2+ entry in the overall ECC sequence, (v) contractile potentiators, and (vi) Ca2+ sparks [29]. Overall, the molecular mechanisms for muscle contractility occurs as the thin actin and thick myosin filaments slide past one another, as the action is influenced by cross-bridges extending from the myosin filaments and cyclical interaction with the actin filaments during ATP hydrolysis.

Putative factors which influence skeletal muscle growth and development:

Disparate internal and extraneous variables, such as exercise, nutrition, inflammation, and cancer-related cachexia influence the regulation of skeletal muscle mass. Skeletal muscle critically regulates the entire body metabolism, and does not merely function as a motor for locomotion. The augmentation and sustenance of muscle mass and functionality are pertinent to sustain health and quality of life as well as mitigate morbidity and mortality associated with disorders concerning muscle wasting. The determination of processes which regulate skeletal muscle mass is required for the physical and nutritional monitoring, evaluation and management, of both athletes and patients undergoing muscle wasting disorders [30]. The plasticity of the skeletal muscle enables it to respond to diverse physiologic and pathologic conditions in protein synthesis or degradation. Certain anabolic stimuli result in muscle hypertrophy, whereas inactivity, denervation, spinal cord section, and other inert states induce skeletal muscle atrophy. Skeletal muscle present as an endocrine organ vital roles, such as power formation, motion, respiration, glycemic regulation, metabolic homeostasis and metabolic gene control. Thus, dissipation of muscle mass influences homeostasis and precipitates to insulin resistance, type 2 diabetes, and obesity with resultant increased morbidity and mortality. Although, the main anabolic pathway regulating protein synthesis in skeletal muscle is IGF1/PI3K-Akt-mTOR signaling pathway, the myostatin-Smad2/3 pathway functions significantly in protein synthesis suppression. Conversely, the ATP-dependent ubiquitin-proteasome and the cytosolic calcium-dependent calpain systems as well as the lysosomal proteases participate significantly in muscle atrophy. The pathways which regulate protein synthesis and degradation function in consonance. Elucidation of the molecular mechanisms which regulate protein balance in the skeletal muscle is pertinent in the development of therapeutic and rehabilitation regimen for the maintenance of muscle tissue functionality [31].

A patterned Western diet accelerates muscle atrophy. Diverse mechanisms and stimuli constitute molecular variables and significant therapeutic targets contribute to muscle atrophy, such as oxidative stress, mitochondrial impairment, glucocorticoids, inflammatory cytokines per TNF-α, IL-1β, and IL-6, and myostatin are associated with skeletal muscle atrophy.[32]

Mitochondria and skeletal muscle: Mitochondria are crucial in the maintenance of cellular homeostasis and skeletal muscle sustainability. Mitochondrial derangement may culminate in an expansive array of pathophysiologic alterations and an intricately complex skeletal muscle atrophy [33]. Elucidation of the pathogenesis of mitochondrial dysfunctionality is pertinent for the prevention and treatment, drug discovery and target of skeletal muscle atrophy, and modulate mitochondrial function and dysfunction in skeletal muscle, as well as the Incorporated molecular mechanisms and the regulatory roles of disparate signaling pathways, such as AMPK-SIRT1-PGC-1α, IGF-1-PI3K-Akt-mTOR, FoxOs, JAK-STAT3, TGF-β-Smad2/3 and NF-κB pathways. The analysis of the emergence of mitochondrial dysfunction in muscle atrophy resulting from disease variations is vital[33, 34]. Our understanding of the role of mitochondria in skeletal muscle atrophy has progressed considerably over the last few years. Mitochondria play a very important role in skeletal muscle growth and development, and mitochondrial dysfunction is an important cause of skeletal muscle atrophy. Therefore, the molecular mechanisms by which mitochondrial dysfunction induces skeletal muscle atrophy have attracted the interest of scientists. An understanding of these mechanisms could benefit the development of clinical treatment options for skeletal muscle atrophy, and future therapeutic strategies targeting mitochondria

may be a key measure to prevent or treat different types of skeletal muscle atrophy. Currently, the common therapeutic approaches are drug therapy, gene therapy, stem cell therapy and physiotherapy, and if additional combination therapeutic strategies can be developed or the feasibility of mitochondrial transplantation can be increased, the quality of life would be greatly improved in patients with muscle atrophy.

The nervous system and skeletal muscle: For optimum adaptation in metabolically constrained ambients, the central nervous system (CNS) regulates the metabolism of peripheral organs and skeletal muscle. In mice, neurons of the dorsomedial and central aspects of the ventromedial hypothalamic nucleus, VMHdm/c which express steroidogenic factor-1, VMHdm/cSF-1 neurons are pivotal for metabolic adaptation to physical activity or exercise and elevated basal metabolic rate and skeletal muscle mass [35]. It has been ostensibly indicated in mice that VMHdm/cSF-1 neurons enhance the sympathoadrenal functionality and control skeletal muscle peroxisome proliferator-activated receptor gamma coactivator 1 alpha, PGC-1α by means of varied downstream nodes. Optogenetics was particularly applied to configure VMHdm/cSF-1 neurons in conjunction with genetically-engineered mice and surgical configuration of the sympathoadrenal functionality. Optogenetic activation of VMHdm/cSF-1 neurons markedly elevated mRNA concentrations of skeletal muscle Pgc-1α which influence a spectrum of skeletal muscle activity, protein synthesis and metabolism. Mechanistically, the sympathoadrenal drive in conjunction with β2 adrenergic receptor, β2AdR is pertinent for VMHdm/cSF-1 neurons-mediated increments in skeletal muscle PGC1-α. Succinctly put, both adrenalectomy and β2AdR knockout block augmented skeletal muscle PGC1-α by VMHdm/cSF-1 neuronal activation [35]. Optogenetic functional mapping perspicuously exhibits downstream nodes of VMHdm/cSF-1 neurons are actively ubiquitous, and thus, augment circulating epinephrine and skeletal muscle PGC1-α. It is suggested that VMHdm/cSF-1 neurons-skeletal muscle pathway, VMHdm/cSF-1 neurons→multiple downstream nodes→the adrenal gland→skeletal muscle β2AdR, undergird enhanced skeletal muscle functionality for metabolic adaptations [35].

Exercise or physical activity and skeletal muscle: Exercise or physical activity constitutes a primordial defence stance against inflammatory disorders, such as metabolic and infectious diseases. On the contrary, a sedentary lifestyle in consonance with obesity, type 2 diabetes and cardiovascular derangements inimically impacts on health and overwhelming susceptibility to infectious diseases [36]. The impact mediated via moderate exercise on viral adverse impact by regulating biological processes associated with crosstalk between skeletal muscle, the immune system and adipose tissue showed the effects mediated through modulation of the expression of inflammation markers. An inextricably-linked association between exercise and diminished inflammation provided effective counteraction of SARS-CoV-2 imbroglio, making it imperative for optimum and regular physical activity [37].

Vitamin D and skeletal muscle: Vitamin D (vitD) deficiency associates with numerous chronic disorders and elevated metabolic dysregulation as determined in obesity, insulin resistance [38], hyperlipidemia, hepatic impairment and hypertension. Investigation of the genetic relatedness between 25-hydroxyvitamin D (25[OH]D)-associated genes and obesity traits, indicates that the variation in the vitD receptor, VDR gene expresses the main crux of the findings. Polymorphisms in the VDR gene are linked with obesity traits in certain studies, depicting such as inconclusive. Genes other than those from VDR investigated with regard to obesity-related traits, have also been submerged in inconsistencies. However, findings indicate that the DBP/GC gene may represent a vital protein connecting obesity and vitD status. Obversely, vitD as a result of its fat solubility is retained by adipose tissue and has the propensity to metabolize 25(OH)-D locally, with capacity for transforming in obesity. Moreover, vitD can regulate gene expression related to adipogenesis, inflammation, oxidative stress, and metabolism in mature adipocytes [39].

Gut microbiota: Both internal and external factors are Incorporated in the management of local and global health because disease is putatively a geopolitical aspect correlated to gain-of-function research whereby health diplomacy is primordial in present and future global scenarios with appreciations in the emergence and reemergence of infectious diseases [40]. Microbiota are defined as low microbial diversity undergoing unstable composition over time associated with modifications of skeletal muscle metabolism and functions. Bile acids synthesized in the liver as primary bile acid, and altered by intestinal microbiota into a plethora of metabolically active metabolites function as ligands for the farnesoid X receptor, FXR and effect skeletal muscle physiology. Probiotics manipulation of gut microbiota expresses novel and reassuring modality for the prevention and/or treatment of an expansive arrray of disorders, for instance, age-associated sarcopenia. Targeting gut microbiota and FXR signaling by discrete probiotics and diet, such as protein and amino acids may improve host microbiota function and skeletal muscle phenotype in ageing and aged subjects. Monitoring, evaluation and management of intestinal microbiota indicate strategy to combat or diminish a plethora of extant chronic perturbations [41,42] as gut microbiota metabolically regulate human metabolism. Research must be cautious of infectious diseases and harmful microbiota, especially since the SARS outbreak of 2003 [43]. Intact gut microbiota play active role in host homeostasis, whereas compositional disruptions, referred to as dysbiosis are implicated with a litany of conditions. Dysbiosis and the concomitant dissipation of microbiota-derived metabolites culminate in profound modification of skeletal muscle metabolism [1], since bile acids produced in the liver with extrapolated metabolization by intestinal microbiota regulate diverse host metabolic pathways via activation of nuclear receptors and the farnesoid X receptor, FXR. Changes in gut microbiota may result in skeletal muscle atrophy via bile acid–FXR pathway [44]. Over the past decades, considerable progress has been achieved in the field of 'gut–muscle axis'.

Due to their pertinence, the underlying mechanisms in intestinal microbiota and skeletal muscle metabolism have involved disparate scientific and innovative research underpinnings, for instance, sports medicine and inflammaging cancer-associated cachexia. The gut microbiota is suggested to contribute to skeletal muscle growth and performance; while preclinical findings suggest

a trajectory linking gut microbiota, bile acids and skeletal muscle mass, with gut microbiota as a novel and promising therapeutic target [45].

Maintenance of skeletal muscle: Skeletal muscle maintenance portends benefits in obesity and type 2 diabetes. Mechanical stimulation may regulate the differentiation, growth and metabolism of skeletal muscle[46]. SWELL1, Lrrc8a encodes a swell-activated anion channel involved in the regulatory function of PI3K-AKT, ERK1/2, mTOR signalling, skeletal muscle differentiation, fusion of myoblast, cellular oxygen consumption, and cellular glycolysis. LRRC8A over-expression in Lrrc8a KO myotubes induces PI3K-AKT-mTOR signaling to supra-normalcy with full restoration of myotube formation. Skeletal muscle-targeted Lrrc8a KO mice present smaller myofibres, produce decreased force ex vivo, and depict diminished exercise tolerance related to augmented adiposity within basal states, as well as glucose intolerance and insulin resistance when fed on a high-fat diet in contradistinction to wild-type, WT mice. These indicate that LRRC8 complex regulates insulin-PI3K-AKT-mTOR signalling in skeletal muscle to effect the differentiation of skeletal muscle in vitro and the size of skeletal myofibres, muscle functionality, adiposity and systemic metabolism in vivo [46].

Hypertrophy and atrophy: Skeletal muscle constitutes the protein reservoir of the body and crucially controls glucose and lipid homeostasis. On that score, the development and growth or dissipation of muscle mass may govern overall metabolism, locomotion, food consumption and respiration [47]. Thus, excessive muscle dissipation depicts a poor prognosis for diverse disorders, such as cancer, organ impairment, infections and unsuccessful ageing [48]. Muscle action is effected by variations of quality systems which control the a activities of contractile proteins and organelles. These systems are under the influence of transcription-dependent programmes which promote muscle cells to be susceptible to environmental and nutritional inducements. Mechanical, oxidative, nutritional and energy stresses, growth factors or cytokines modulate signaling pathways which invariably culminate in protein and organelle turnover [47]. Nascent conditions which generally regulate such intricately complex network are characterised by incessant emergence. Exposing the mechanisms which regulate skeletal muscle mass may provide therapeutic targets and treatments for skeletal muscle mass dissipation in hereditary and non-hereditary disorders and quality of life improvement and maintenance [47].

Hypertrophy is the mechanism whereby skeletal mass is enhanced during postnatal development and in adult skeletal muscle due to contractile activity or physical exercise, and defined hormones, such as androgens and β-adrenergic agonists. Muscle hypertrophy presents as the rate of protein synthesis is in excess of protein degradation. The IGF1–Akt–mTOR pathway as a positive regulator, and the myostatin–Smad2/3 pathway as a negative regulator are the two prominent signalling pathways regulating protein synthesis. Proliferation and fusion of satellite cells which culminate in elevated myonuclei have the propensity to enhance muscle growth and development during early but not late postnatal developmental stages, and in select forms of muscle hypertrophy in adults. Muscle atrophy may be precipitated in adult skeletal muscle in a plethora of disorders, such as starvation, denervation, cancer cachexia, heart failure and ageing. The two main protein degradation pathways active in muscle atrophy and can contribute to the dissipation of muscle mass are the proteasomal and the autophagic–lysosomal pathways. The pathways involve variations of atrophy-related genes or atrogenes regulated by unique transcription factors, FoxO3, negatively regulated by Akt, and NF-κB, activated by inflammatory cytokines [49].

Muscle wasting is consequential to pathophysiologic modifications identified as elevated catabolic activity with progressive or resultant loss of skeletal muscle mass and strength. A litany of diseases, such as cancer, organ failure, infection, and ageing-related debilities correlate with muscle wasting. Cancer cachexia is a multifactorial syndrome exhibiting loss of skeletal muscle mass in the presence of absence of loss of fat mass leading to functional depreciation and diminished quality of life due to upregulation of systemic inflammation and catabolic stimuli causing suppression of protein synthesis and enhanced muscle catabolism [50]. Cancer patients are commonly subjected to sequelae emerging from cachexia depicted by loss of functional muscle mass and adipose tissue.

Signaling pathways: It is trite that the interplay between multiple signaling pathways regulates sustenance and consolidation of skeletal muscles. A network of inextricably-linked signals coordinates hypertrophic and atrophic inputs, resulting in a delicate balance between muscle protein synthesis and proteolysis under physiological conditions. The dissipation of skeletal muscle mass or atrophy is diagnostically characteristic of cachexia as exhibited in cancer, cardiac disorders, and chronic obstructive pulmonary disease [51].

Although, the signaling pathways regulating skeletal muscle mass are inextricably-linked, IGF-I/insulin signaling constitutes a critical regulator of skeletal muscle protein homeostasis, not merely via its interaction with protein kinases [52], such as Akt and its downstream effectors, mTOR and transcription factor EB, TFEB, but due to its susceptibility to exercise, myostatin, and anabolic hormones. The maintenance of skeletal muscle evolves dynamically process with incessant reparation and regeneration; however, its regenerative capacity diminishes in obesity patients. Skeletal muscle maintenance is crucial for ambulation, pertinent insulin signaling, and glucose homeostasis. Obesity-associated dissipated muscle mass propagates a cycle of incessant metabolic derangement, associated hepatic impairment, and augmented muscle dissipation. Proper modalities to target obesity-related muscle wasting must take into consideration multiple systemic modifications which are resultant impacts as well as elevated inflammatory mediators, circulating FFA, metabolic disequilibrium and insulin resistance. Rigorous research is pertinent to identify and establish specific molecular mechanisms which restrict skeletal muscle regeneration and propagate atrophy in an obese condition [53].

Insulin and insulin resistance: Glucose uptake is necessary for cell homeostasis and a healthy organism, but in a sedentary state, skeletal muscle relies on insulin for glucose uptake. Following binding to its membrane receptor, insulin induces a cascade of

intracellular reactions resulting in the activation of inter alia glucose transporter 4, GLUT4 [54]. Migration of the transporter to the plasma membrane contributes in glucose internalization; although, in certain instances, such as physical activity or exercise, modifications in concentrations of intracellular molecules, for instance, ATP and calcium, there is action for the regulation of GLUT4 translocation and glucose uptake in skeletal muscle despite insulin concentrations. Incessant exercise resulting from stimulating pathways associated with glucose uptake is a veritable non-pharmacologic intervention for the improvement of glycemic control in obesity and diabetes. The main mechanisms concerned in glucose uptake in skeletal muscle as a response to muscle contraction are pertinent for investigation [54].

Insulin influences ageing and lifespan, and presents a mechanism for gene manipulations for prolonged and healthier lives. Preserved insulin sensitivity is associated with longevity. Insulin function is dependent on mechanisms which are determinants of its circulating levelssecretion, clearance and sensitivity in its target tissues. Ageing enhances deranging impacts on these processes which debilitate insulin functionality, resulting in augmented risk for morbidity, untoward sequelae and mortality [55]. Certain models of impaired insulin signaling are associated with prolonged longevity or resistance to life-threatening factors, such as oxidative stress. Insulin and insulin signaling are associated with successful ageing and longevity. Calorie restriction enhances lifespan in numerous species. Adequate control of factors associated with risks for obesity, diabetes, cardiovascular disease, and other insulin and ageing sequelae can be retarded in the elderly with optimum sustenance of their lifestyles [55].

The essence of insulin sensitivity versus secretion and insulin resistance in the clinical strategy for the treatment, lifestyle changes, prompt interventions and control of diabetes is important. Progressive decline of glucose tolerance with advancing age has been associated with type 2 diabetes pathogenesis due to peripheral insulin resistance and impaired β cell function. In elderly persons, insulin secretion is deranged with concurrent diminished insulin clearance rate and augmented circulating proinsulin concentration that ostensibly explicates age-related hyperglycemia. Insulin is associated with abundant pathophysiological processes exhibited during brain function in learning and memory, as well as the regulation of ageing, metabolic syndrome, obesity, diabetes and cardiovascular diseases [56]. Elevated chronic peripheral insulin, decreased insulin action and brain insulin contents are pathognomonic of the insulin resistance syndrome. All these are associated through specific mechanisms in the pathophysiology of ageing and insulin in concert with risk factors and the concomitant complications. Ostensibly, progressive excess insulin induces synchronous elevated levels of oxidative stress and inflammatory impacts which exacerbate or are exacerbated by advancing age, culminating as inimical consequences to healthy lifestyles, longevity or extended lifespan. Therapeutics and other healthcare measures may be beneficial in order to prevent, mitigate or amend insulin aberrations in the elderly and during the ageing process [56]. Insulin emergence provides the latitude for diabetes from fatal diagnosis to manageable chronic status. Insulin is appreciated as a prime peptide hormone that mediates systemic glucose metabolism in discrete tissues. Insulin resistance, IR is a deranged biological response to stimulate insulin via the perturbation of disparate molecular pathways in target tissues. Acquired presentations and genetic variables are indicated in IR, and that the dysregulated metabolic mediators released by adipose tissue and adipokines, cytokines, chemokines, excess lipids and toxic lipid metabolites induce IR in extraneous tissues. IR is associated with diverse entities of untoward syndromes, such as obesity, diabetes, metabolic dysfunction-associated fatty liver disease, MAFLD, cardiovascular disorder, polycystic ovary syndrome PCOS, and other perturbations or sequelae [57].

Insulin resistance, IR is a state whereby insulin-mediated regulation of glucose metabolism in body tissues, namely liver, adipose tissue and skeletal muscle are perturbed. IR is a characteristic marker of type 2 diabetes and cardiovascular disorder; and is usually associated with metabolic abnormalities, hyperinsulinemia, impaired glucose homeostasis, hyperlipidemia and obesity. IR can emerge from pathologic, genetic and environmental factors or from a combination of these factors [58]. Adipose tissue is crucial in the IR development via discharge of lipids and various circulating factors. These extracellular factors impact the intracellular concentrations of intermediates including ceramide and various lipids which govern cell response to insulin. These intermediates may promote IR by suppressing one or more ingredients of insulin signaling pathway, for instance, insulin receptor and insulin receptor substrate proteins [58]. Dysregulation of skeletal muscle metabolism affects whole-body insulin sensitivity and glucose homeostasis. It is stipulated that type 2 diabetes–associated changes [59] in the plasma metabolome influence skeletal muscle immunometabolism and consequential insulin resistance development.

Glutamine: has been stipulated as a prime amino acid that inversely correlates with BMI and insulin resistance index, HOMA-IR in men exhibiting normal glucose tolerance or type 2 diabetes. Glutamine concentration influences the inflammatory responsiveness of skeletal muscle and regulates the adaptor protein, GRB10 expression that suppresses insulin signaling. Systemic elevated glutamine concentrations in a mouse model of obesity improves insulin sensitivity with restoration of glucose homeostasis. Glutamine supplementation may pose as a potential therapeutic regimen in the prevention or retardation of insulin resistance onset in obesity by diminishing inflammatory markers and inducing skeletal muscle insulin sensitivity [60].

Insulin resistance in women: Whole-body insulin resistance in lean women presenting with hyperandrogenism and PCOS was unrelated to alterations in the proximal aspect of the insulin signaling cascade in skeletal muscle irrespective of accumulated lipid [61]. On the contrary, decreased insulin sensitivity invariably associated with plasma adiponectin concentrations contributing a modulating impact in human skeletal muscle through AMPK. Also, untoward PDH regulation may play a role in the decrement whole-body metabolic pliability with concomitant insulin resistance [61]. Findings suggest that triglyceride accumulation in skeletal muscle in obesity emanate from diminished propensity for fat oxidation. Furthermore, malleability in fat oxidation regulation has greater impact than fatty acid uptake in interrelatedness with insulin resistance [62].

Insulin resistance, obesity and type 2 diabetes: Insulin resistance and type 2 diabetes pose as prime pathogenic aspects of metabolic diseases, and depicted as reduced responsiveness of insulin-targeting tissues to physiologic insulin concentrations [63]. Obesity is associated with chronic inflammation, with contribution to insulin resistance and type 2 diabetes. Generally, skeletal muscle is implicated in insulin-stimulated disposal of whole-body glucose. Thus, skeletal muscle metabolism dysregulation patently influences whole-body glucose homeostasis and insulin sensitivity. Inflammation results in skeletal muscle in obesity and evidently depicts as augmented immune cell infiltration and proinflammatory activation in intermyocellular and perimuscular adipose tissue. Secretion of proinflammatory molecules, immune cells can potentiate myocyte inflammation, control myocyte metabolism adversely, and effect insulin resistance through paracrine influence. Elevated fatty acid entry and inflammatory molecules from certain tissues, especiallyvisceral adipose tissue, may contribute to muscle inflammation and untowardly regulate myocyte metabolism with resultant insulin resistance [64].

Nitric oxide, NO: Ageing, sedentary lifestyle or diminished physical activity, malnutrition, inflammation, and cancer-related cachexia are responsible for wasting of skeletal muscle and undesirably perturbs quality of life. In skeletal muscle mass regulation, NO is a signalling molecule that is inextricably-linked to numerous pertinent pathways, such as AMPK, PGC-1α, and PI3K/Akt-mTOR signaling pathways for the maintenance of both skeletal muscle integrity and signaling mechanisms in order to adapt to mechanical and metabolic stimulation. Conversely, the untoward dissemination and augmented NO production from muscle inactivity and inflammation predispose to non-physiological ROS and RNS generation resulting in catabolic responses and muscle atrophy by means of UPS and autophagy. Invariably, NO, as a freely diffusible and highly reactive radical, its life span is rapidly extinguished, whether beneficial or harmful, especially in skeletal muscle, where NO scavengers such as myoglobin and glutathione are in proximity to nascent NO [65] and significantly perturbed by its concentration and distribution, since its bioavailability is dependent on the modality of its administration, such as diet of nitrate-rich vegetables [66], nitrite/nitrate supplements and L-arginine/citrulline substrates for NOSs [67, 68] and drugs as NO donors [69, 70]. With increasing participatory evidence of NO in skeletal muscle mass regulation, future research must be focused on NO-mediated therapeutics in disease and health [30].

Myokines: In the body, skeletal muscle is the largest organ; and it secretes circulating factors, and myokines, concerned with several cellular signaling mechanism, and it characteristically expresses both as an endocrine and paracrine organ. th are inextricably-linked with disability and physical frailty. Since skeletal muscle is important for metabolism and physiology, it has a vital function in insulin-mediated glucose disposal. Myokines exhibit autocrine, paracrine, and endocrine activities as threshold regulators of myogenic differentiation, fibre-type switching, and maintainance muscle mass [71]. Myokines expansively influence energy metabolism and inflammation as well as the pathophysiology of type 2 diabetes and several other metabolic disorders. Myokines can elevate insulin sensitivity leading to the improvement of glucose disposal and the regulation of glucose and lipid metabolisms [71]. The muscle-derived secretory proteins, myokines mediate interactions between skeletal muscle mass and certain organs, such as the liver, adipose tissue, pancreas, and bone as well as the cardiovascular system. During ageing, diminishing levels of exercise and sarcopenia are related to physical debility and disability which subsequently contribute to metabolic untoward presentations, such as metabolic syndrome and non-alcoholic fatty liver derangement [72]. The dissipation of skeletal muscle mass is contributary to metabolic impairment.

Future Research:

Skeletal muscle constitutes the pivotal organ for not merely physical functionalities, but its responsibilities encompass nutrient metabolism, entire-body glucose homeostasis and insulin sensitivity. On that score, dissipated muscle mass and activities can impair general health and frustrate quality of life. Muscle atrophy is associated with diverse pathophysiologicl states [73], such as obesity, diabetes, sarcopenia, Alzheimer's disease, cancer cachexia and cardiovascular failure. Research proposals are pertinent to harness and maintain molecular mechanisms in the regulation of skeletal muscle mass and function for the identification of new therapeutic strategies against obesity and related disorders. The spheres may encompass characterisation of human-derived skeletal muscle tissue, biopsies, primary skeletal myotubes extracted from candidates presenting with obesity, sarcopenic obesity, or afterweight dissipation, as well as identification of nascent genes, proteins, or pathways indicted in energy metabolism, and invariable sustenance of lean muscle mass in concurrent weight dissipation. Furthermore, next generation and single cell sequencing or advanced proteomic strategies are pertinent. Information systems modalities which may unravel diminished adiposity involving enhanced lean muscle with wet laboratory modalities for mechanistic validation are relevant. Also, of relevance is the identification of pathway and/or gene with preliminary validation as a skeletal muscle modality depicting a defined human disease interrelatedness in obesity, sarcopenia or associated conditions. Proper resolutions must enact newfangled therapeutic measures for the treatment of generalized obesity, sarcopenic obesity, or sarcopenia candidates for the improvement of their metabolic health and quality of life. It is relevant to explicate and elucidate putative (i) regulating mechanisms in metabolic flexibility, and (ii) the functionality of adaptive thermogenic mechanisms per futile cycles; (iii) determine and establish drug targets which can transform lipid storage and turnover, and (iv) enhance mitochondrial role, and activate futile cycles [74].

Discussion:

Skeletal muscle atrophy is prevalent in a plethora of pathological states, viz: diabetes, denervation, prolonged immobility, malnutrition, sarcopenia, obesity, Alzheimer's disease, and cachexia [32]. The major deranging impact of muscle atrophy is the overall diminished quality of life from functional debility, augmented fracture risk, reduced basal metabolic rate, and deficient bone mineral density. In humans, a vast majority of skeletal muscles have forms of slow oxidative, fast oxidative, and

fast glycolytic muscle fibres. Regarding the pathological state, the oxidative or glycolytic muscle form may be perturbed to a greater magnitude than the other. The pathological state, whether oxidative or glycolytic muscle variety determines the magnitude of the perturbation. Skeletal muscle maintenance is an immense sustainability mechanism for obesity and type 2 diabetes patients. Mechanised stimulation is capable of regulating skeletal muscle differentiation, growth and metabolism but the molecular mechanosensor is unelucidated. Healthy muscles are primordial for general well-being and quality of life for the protection and sustenance against obesity and obesity-related disorders as observed in type 2 diabetes and nonalcoholic fatty liver disease [22, 46].

Obesity is characteristic of an intricately complex, chronic disorder and global public health dilemma that exhibits excess body fat accumulation. Obesity markedly elevates the risk of numerous disorders and sequelae in type 2 diabetes, cardiovascular aberrations, nonalcoholic fatty liver disease, and associated with diminished life expectancy. Although, lifestyle interventions via diet and exercise have outstanding impacts in weight management, but achieving long-term prognosis regarding weight loss is well-impossible, while obesity prevalence remains unabated globally. The pathophysiology of obesity has been rigorously researched with exponential signal transduction pathways associated with obesity; thus, rendering it cumbersome to suppress obesity with efficient, effective and optimistic strategies. Advances in obesity pathophysiology and pathogenesis from both experimental and clinical studies, must pertinently focus on signaling pathways [75] and effects in the regulation of food consumption, glucose homeostasis, adipogenesis, thermogenesis, and chronic inflammation [75] amongst others. This article presents the essence of insulin sensitivity, secretion and resistance in the treatment, lifestyle modifications, interventions and control of diabetes, obesity and related disorders [76]. It is critical to determine how muscles respond at the molecular level to exercise. The cellular basis and signaling pathways implicated for the sustainability of physical activity in general health have been intensively researched. Regulatory T cells existentially contribute to proper muscle functionality. The newfangled insights create the trajectory for precision medicine target on untoward metabolic aberrations, such as obesity and diabetes, as well as muscle-related conditions [77] and their sequelae. Obesity and type 2 diabetes are both inextricably-linked conditions which have been indicted in neurological aberrations [78]. This review provides the opportunity to explore the extant information in the characterizations of epigenetic formulations, such as ageing, susceptibility to pollutant and irritant exposure, and skeletal muscle contribution to the pathogenesis of obesity and clinicopathological correlates [79-82].

Conclusion:

The regulation and maintenance of skeletal muscle mass are intricately influenced through protein synthesis and degradation. Skeletal muscle mass is augmented due to a resultant net gain in protein synthesis from progressive exercise training. The peripheral aspect of the central nervous system, CNS regulates skeletal muscles; therefore, the skeletal muscles are consciously or voluntarily regulated. The mechanisms of action in skeletal muscle hypertrophy may be triggered by hormones and growth factors functioning directly as positive regulators of muscle growth or acting indirectly via the neutralisation of negative regulators, and mechanical signals which mediate the impact of resistance exercise. Using targeted approaches, it is possible to identify and validate molecular mechanisms which regulate skeletal muscle mass and functionality to elevate weight dissipation and improvement in the cardiometabolic outcomes in obesity and inextricably-linked conditions or disorders. In most instances, benefits are mediated via expansive metabolic and molecular remodeling of skeletal muscle from exercise or physical therapy or activity. For instance, sarcopenia, characterised as an age-related depreciation of skeletal muscle mass, strength, quality and functionality is connected with chronic low-grade inflammation and an appreciable propensity for adverse health impact and prognosis can be improved by any or all of these modalities.

References:

1. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, and Zamboni M. Sarcopenia: revised European consensus ondefinition and diagnosis. *Age and Ageing*, 2019; 48(1): 16-31.
2. Luo L, Yang J-P, Wang S-T, Liao X, and Zhan W Advances of Molecular Mechanisms on Obesity Inducing Muscle Atrophy (review). The Chinese Journal of Rehabilitation Theory and Practice. 2017; 23(5): 553-557.
3. World Health Organization. (2021). Obesity and overweight. Retrieved from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
4. Antuña E, Cachán-Vega C, Bermejo-Millo JC, Potes Y, Caballero B, Vega-NaredoI, Coto-Montes A, and Garcia-Gonzalez C. Inflammaging: Implications in Sarcopenia.*Int J Mol Sci. 2022*; 23: 15039.
5. Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB and Ferrucci L. Sarcopenic obesity: definition, cause and consequences. *Curr Opin Clin Nutr Metab Care.* 2008; 11(6): 693-700.
6. Batsis JA and Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiologyand treatment strategies *Nat Rev Endocrinol.* 2018; 14(9): 513-537.
7. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal L. F, Lingvay I, McGowan BM, Rosenstock J, Tran MT D, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner R F, STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021; 384(11):989-1002.
8. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A, SURMOUNT-1 Investigators.Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med.* 2022; 387: 205-216.
9. Chukwuma Sr C. Ecological features of the association between mortality and determinants or salient risk factors of cardiovascular disease. IJCBR; 2020; 6(3): 18-23.
10. Chukwuma Sr C. Ecological attributes between the association

of mortality and putative risk factors of cardiovascular disease. Int J Clin Biomed Res. 2020; 6(3): 18-23
11. Saeeda Al J, Athena C, Zulqarnain S, Ojha et al. Obesity: Molecular Mechanisms, Epidemiology, Complications and Pharmacotherapy. In: Cellular and Biochemical Mechanisms of Obesity. Advances in Biochemistry in Health and Disease . Springer, 2021; pp. 249-266.
12. Bennett AM, Lawan A. Improving Obesity and Insulin Resistance by Targeting Skeletal Muscle MKP-1. J Cell Signal. 2020; 1(4): 160-168.
13. Bipradas Roy B, Curtis ME, Fears LS et al. Molecular Mechanisms of Obesity-Induced Osteoporosis and Muscle Atrophy. Front. Physiol. Sec. Lipid and Fatty Acid Research. Volume 7 - 2016.
14. Wiedmer P, Jung T, Castro JP et al. Sarcopenia – Molecular mechanisms and open questions,. Ageing Research Reviews, 2021; 65: 101200.
15. Chukwuma Sr C. Aging, cellular senescence and diabetes mellitus: Clinicopathological correlates, trends and targets. IGRPS. Research Article IJPIT. 2020; 2(1): 105.
16. Chukwuma Sr C. Aging, cellular senescence and diabetes mellitus: Clinicopathological correlates, trends and targets. Archives of Health Science. 2020; 10.31829-2641-7456-ahs2020-4(1)-131.
17. Chukwuma Sr C. Co-morbid presentations and coronary heart disease risks with type 1 diabetes mellitus. Austin Medical Sciences, 2019; 4(2): id1037. ams-v4-1037.pdf.
18. Wilhelmsen A, Tsintzas K and Jones SW. Recent advances and future avenues in understanding the role of adipose tissue cross talk in mediating skeletal muscle mass and function with ageing. GeroScience. 2021; 43: 85–110.
19. Liao T, Xiong L, Wang X et al. Mitochondrial disorders as a mechanism for the development of obese Sarcopenia. Diabetol Metab Syndr. 2023; 15: 224.
20. Axelrod CL, Dantas WS, and Kirwan JP. Sarcopenic obesity: emerging mechanisms and therapeutic potential. Metabolism: Clinical and Experimental. 2023; 146: 155639.
21. Kumar A, Hashmi MF, Mehta D. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Feb 19, 2023. Rotor Syndrome.
22. Chukwuma Sr C. Human hepatocytes response to pathological shifts in liver fibrosis. The Journal of Medical Research. 2024; 10(1): 37-41.
23. Chukwuma Sr C. Exploring the complex interplay in the regulation of cardiac pathophysiological functions by protein kinases and phosphatases. Int J Biosci & Biochem. 2021; 3(2): 1-7.
24. Stadtman ER. Mechanisms of Enzyme Regulation in Metabolism. Editor(s): Paul D. Boyer. The Enzymes. Academic Press, Volume 1, 1970, Pages 397-459.
25. Oetting A, and Yen PM. New insights into thyroid hormone action. Best Pract Res Clin Endocrinol Metab. 2007; 21: 193–208.
26. Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. Endocr Rev. 2010. 31: 139–170.
27. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest. 2012; 122: 3035–3043.
28. Mullur R, Liu Y-Y, and Brent GA. Thyroid Hormone Regulation of Metabolism. Physiol Rev. 2014; 94(2): 355–382.
29. Calderón JC, Bolaños P and Caputo C. The excitation–contraction coupling mechanism in skeletal muscle. Biophys Rev. 2014; 6(1): 133–160.
30. Kobayashi J, Uchida H, Kofuji A et al. Molecular regulation of skeletal muscle mass and the contribution of nitric oxide: A review. FASEB Bioadv. 2019; 1(6):364-374.
31. Akin S, Ozerklig B, Turkel I, et al. The molecular mechanisms regulating skeletal muscle mass. Turk J AkinSports Med. 2019; 54(2):133-42.
32. Jun L, Robinson M, Geetha T, Broderick TL and Babu JR. Prevalence and mechanisms of skeletal muscle atrophy in metabolic conditions. Int. J. Mol. Sci. 2023; 24(3): 2973;
33. Chen X, Ji Y, Liu R. et al. Mitochondrial dysfunction: roles in skeletal muscle atrophy. J Transl Med. 2023; 21: 503.
34. Chukwuma Sr C. Probing research precincts focused on systematic determination of the biological effects of macromolecular interactions. International Journal of Applied Science and Engineering Review (IJASER). 2020; vol 1 issue 6.
35. Takuya YT, Mina FM, Scotlynn FS, et al. VMHdm/cSF-1 neuronal circuits regulate skeletal muscle PGC1-α via the sympathoadrenal drive, Molecular Metabolism. 2023; 77: 101792.
36. Chukwuma Sr C. Paradigm for implementing sustainable modalities against the emergence and re-emergence of parasitoses and infectious diseases. Applied Sciences Reports. 2015; 9(3): 129-138.
37. Nigro E, Polito R, Alfieri A et al. Molecular mechanisms involved in the positive effects of physical activity on coping with COVID-19. Eur J Appl Physiol. 2020; 120: 2569–2582.
38. Chukwuma Sr C. Insulin and Ageing: Interventions for Healthier Lifestyle and Prolonged Lifespan. Int J Med Case Reports & Reviews. 2023; 2(1).
39. Ruiz-Ojeda FJ, Anguita-Ruiz A; Leis R and Aguilera CM. Genetic Factors and Molecular Mechanisms of Vitamin D and Obesity Relationship. Ann Nutr Metab. 2018; 73 (2): 89–99.
40. Chukwuma Sr C. Gain-Of-Function Research and Geopolitics in the Emergence and Reemergence of Infectious Diseases and Microbiome Variants. 2021.
41. Chukwuma Sr C. Syndemics of chronic and acute diseases in vulnerable populations. Acta Medica Scientia. 2017; 04(01).
42. Chukwuma Sr C. The complexity of communicable and non-communicable diseases in vulnerable populations. ABBSR. 2020; vol 3 issue 1.
43. Chukwuma Sr C. Geopolitical issues in health and biosecurity concerning gain-of-function research, emergence and re-emergence of infectious diseases. International Journal of Clinical Virology. 2022; 6:11-16.
44. Mancin L, Wu GD and Paoli A. Gut microbiota-bile acid-skeletal muscle axis. Trends in Microbiology. 2023; 31(3): P254-269.
45. Mancin L, Wu GD, and Paoli A. Gut microbiota–bile acid–skeletal muscle axis. 2022.
46. Kumar A, Xie L, Chau M et al. SWELL1 regulates skeletal muscle cell size, intracellular signaling, adiposity and glucose metabolism eLife. 2020; 9:e58941.
47. Sartori R, Romanello V and Sandri M. Mechanisms of muscle atrophy and hypertrophy: implications in health and disease.

Nat Commun. 2021; 12: 330.
48. Chukwuma Sr C. Is Diabetes a Model for Gene-environment Interaction in Premature Senescence? 2014; Vol 4, No. 25.
49. Schiaffino S, Dyar KA, Ciciliot S et al. Mechanisms regulating skeletal muscle growth and atrophy. eFEBS Journal. 2013; 280(17): 4294-4314.
50. Setiawan T, Sari IN, Wijaya YT et al. Cancer cachexia: molecular mechanisms and treatment strategies. J Hematol Oncol. 2023; 16: 54.
51. Sakuma K and Yamaguchi A. Molecular Mechanisms Controlling Skeletal Muscle Mass [Internet]. Muscle Cell and Tissue. InTech; 2015.
52. Chukwuma Sr C. The complex interplay in the regulation of cardiac pathophysiologic functionalities by protein kinases and phosphatases. J Cardiology & Cardiovasc Med, JCCM. 2021; 6: 048-054.
53. Sinha I, Sakthivel D and Varon DE. Systemic Regulators of Skeletal Muscle Regeneration in Obesity. Front Endocrinol (Lausanne). 2017; 8:29.
54. Pereira RM, Pereira de Moura L, Muñoz VR et al. Molecular mechanisms of glucose uptake in skeletal muscle at rest and in response to exercise. Motriz. rev. educ. fis. 23 (spe). 2017.
55. Chukwuma Sr C. Pathophysiology of Insulin and Ageing with Concomitant Risk Variables and Sequelae. Int J Diabetes. 2023; 5(1): 173-178.
56. Chukwuma Sr C. Ageing and Insulin: Inter Alia Diabetes, Obesity and Fitness Concerns. Middle East Res J. Pharm. Sci. 2023; 3(2): 37-45. DOI: 10.36348/merjps.2023.v03i02.005.
57. Li M, Chi X, Wang Y et al. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. Sig Transduct Target Ther. 2022; 7: 216.
58. Singh A, Ghai N, Singh M and Bedi P. Molecular Mechanisms Involved in Insulin Resistance: Recent Updates and Future Challenges. Evolving Concepts in Insulin Resistance. IntechOpen. 2022.
59. Chukwuma Sr C. Convergence on the constraints and challenges in the awareness, prevention, treatment and control of type 2 diabetes and related conditions. GJMR. 2018; 8 vol 17 issue 3 version 1.0.
60. Dollet L, Kuefner M, Caria E et al. Glutamine Regulates Skeletal Muscle Immunometabolism in Type 2 Diabetes. Diabetes. 2022; 71(4): 624–636.
61. Hansen SL, Svendsen PF, Jeppesen JF et al. Molecular Mechanisms in Skeletal Muscle Underlying Insulin Resistance in Women Who Are Lean With Polycystic Ovary Syndrome, The Journal of Clinical Endocrinology & Metabolism, 2019; 104(5): 1841–1854.
62. Kelley DE, Goodpaster B, Wing RR and Simoneau J-A. Amer J. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. Amer J Physiology Endocrinology and Metabolism.
63. Lee S-H, Park S-Y and Choi CS. Insulin Resistance: From Mechanisms to Therapeutic Strategies. Diabetes & Metabolism Journal. 2021; 46(1): 15-37.
64. Wu H and Ballantyne CM. Skeletal muscle inflammation and insulin resistance in obesity. J Clin Invest. 2017; 127(1): 43-54.
65. Hall DT, Ma JF, Di Marco S, Gallouzi IE. Inducible nitric oxide synthase (iNOS) in muscle wasting syndrome, sarcopenia, and cachexia. Aging (Albany NY). 2011; 3: 702.
66. Lundberg JO, Carlström M, and Weitzberg E. Metabolic effects of dietary nitrate in health and disease. Cell Metab. 2018; 28: 9-22.
67. Jobgen W, Meininger CJ, Jobgen SC, et al. Dietary L-arginine supplementation reduces white fat gain and enhances skeletal muscle and brown fat masses in diet-induced obese rats. J Nutr. 2008; 139: 230-237.
68. Ham DJ, Gleeson BG, Chee A, et al. L-Citrulline protects skeletal muscle cells from cachectic stimuli through an iNOS-dependent mechanism. PLoS One. 2015;10:e0141572.
69. Tengan CH, Kiyomoto BH, Godinho RO, et al. The role of nitric oxide in muscle fibers with oxidative phosphorylation defects. Biochem Biophys Res Commun. 2007; 359: 771-777.
70. Okutsu M, Call JA, Lira VA, et al. Extracellular superoxide dismutase ameliorates skeletal muscle abnormalities, cachexia and exercise intolerance in mice with congestive heart failure. Circ Heart Fail. 2014; 7: 519-530.
71. Balakrishnan R and Thurmond DC. Mechanisms by Which Skeletal Muscle Myokines Ameliorate Insulin Resistance. Int. J. Mol. Sci. 2022. 23(9): 4636.
72. Kim G and Kim JH. Impact of Skeletal Muscle Mass on Metabolic Health. Endocrinology and Metabolism 2020; 35(1):1-6.
73. Chukwuma Sr C. The complex interplay in the regulation of cardiac pathophysiologic functionalities by protein kinases and phosphatases. J Cardiology & Cardiovasc Med, JCCM. 6: 048-054.
74. Mengeste AM, Rustan AC, and Lund J. Skeletal muscle energy metabolism in obesity. Obesity. 2021; 29(10): 1582-95.
75. Wen X, Zhang B, Wu B et al. Signaling pathways in obesity: mechanisms and therapeutic interventions. Sig Transduct Target Ther. 2022; 7: 298.
76. Chukwuma Sr C. Understanding the aetiologies, pathogenesis, evaluation and management of ageing and insulin. Comprehensive Research and Reviews in Multidisciplinary Studies. 2022; 01(01): 062–069.
77. Munich H. Exercise and muscle regulation: implications for diabetes and obesity. Science Daily. 2023.
78. Chukwuma Sr C. An Overview of the Neurological Consequences of Obesity and Diabetes.J Neurosci Neuropsyc. 2020; 3: 166.
79. Chukwuma Sr C . Epigenetics and its essence in understanding human growth, development and disease. JMR. 2022; 8(5):165-172.
80. Chukwuma Sr C. The Impacts of Non-Ferrous Metal Mining Operations: Pollution, Sustainable and Geopolitical Dimensions. 2024. Journal of Geotechnical Studies 9(1):31-41.
81. Chukwuma Sr C. Geopolitics of the nature and crises of the environment, economics and health in a sustainable society for human progress and survival. 2024. Journal of Scientific and Innovative Research 13(1):16-21.
82. Sheptulina AF, Antyukh KY, Kiselev AR, Mitkovskaya and Drapkina OM. Possible Mechanisms Linking Obesity, Steroidogenesis, and Skeletal Muscle Dysfunction. Life. 2023; 13(6): 1415.