

The Persistent Incurable Prevalence and Impact of Sarcopenia, Obesity and Rare Disorders, Including Gene Expression and Drug Response Using Functional Genomics Strategies

Chrysanthus Chukwuma Sr*

Executive Director Department of Future Studies, The Chrysanthus Centre for Future-oriented Studies, Abakaliki, Ebonyi State, Nigeria

***Corresponding author:** Chrysanthus Chukwuma Sr, Executive Director Department of Future Studies, The Chrysanthus Centre for Future-oriented Studies, Abakaliki, Ebonyi State, Nigeria

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ABSTRACT

Comorbidities of sarcopenia, age-associated diminutive presentations in skeletal muscle mass and functionality with obesity is ubiquitous with the global prevalence of sarcopenic obesity, type 2, cancer and other anomalies in older adults. Since there are no extant recognisable drugs which target sarcopenia, it is pertinent to establish or configure therapeutic formulations. The approaches of functional genomics have become increasingly formidable in the pursuit for disease aetiology, drug target and discovery, as well as genetic variation impact on human biology. Sarcopenia significantly predicts all-cause mortality among elderly persons. It is, therefore, relevant to diagnose and treat sarcopenia to mitigate morbidity and mortality rates in aged individuals. Sarcopenia, the loss in skeletal muscle mass and functionality is ubiquitous in persons with obesity caused by metabolic alterations due to inter alia sedentary lifestyle, adipose tissue derangements, comorbidities of acute and chronic disorders and ageing. Immunotherapy is at the forefront of cancer research, rapidly advancing our understanding and treatment options. The humoral and cellular immune response network orchestrates the activation, proliferation, and direction of immune cells, and supports human body defenses in sarcopenia and obesity in consonance with promising biomedical research and therapeutic development.

This review presents sarcopenia as a muscle-depreciating syndrome exclusive of other aberrant atrophic biological phenomena with presentations of the recent theme on molecular aetiologies of the development of sarcopenia including overt challenges, constraints, issues and opportunities in advancing research for sustainable lifestyle and therapeutic interventions. Furthermore, progress in omics, genomics, epigenomics, transcriptomics, proteomics, and metabolomics provide novel opportunities for the identification of novel targets to explicate sarcopenia pathophysiology. Functional genomics aids in the identification of the appropriate targets for drug discovery, unravelling genes and biological mechanisms which can be targeted to assist in the retardation or reversal of disorders.

Keywords: Sarcopenic Obesity; Bioinformatics; Type 2 Diabetes; Cancer; Quality of Life; Gene Expression; Drug Response

Abbreviations: HTS: High Throughput Screening, SAGE: Serial Analysis of Gene Expression; MPSS: Massively Parallel Signature Sequence; RNA seq: RNA Sequencing; RDA: Representational Difference Analysis; SSH: Suppression Subtractive Hybridization; NAFLD: Non-Alcoholic Fatty Liver Disease; DGE: Differential Gene Expression; RNA-seq: RNA-Sequencing; RDS: Reward Deficiency Syndrome; SO: Sarcopenic Obesity; IR: Insulin Resistance; FTO: Fat Mass and Obesity Associated Gene; MC4R: Melanocortin-4 Receptor; ADRB2: Beta-2-Adrenergic Receptor; mHSPC: Metastatic Hormone-Sensitive Prostate Cancer; DEXA: Dual Energy X-Ray Absorptiometry; SARMS: Select Androgen Receptor Modulators; CVDs: Cardiovascular Diseases; MSCs: Mesenchymal Stromal Cells; GWAS: Genome-Wide Association Study; LBM: Lean Body Mass, ASM: Skeletal Muscle Mass; SNPs: Significant Single Nucleotide Polymorphisms; NGS: Next-Generation Sequencing; AHO: Albright Hereditary Osteodystrophy; LEP: Leptin, LEPR: Leptin Receptor; POMC: Proopiomelanocortin; PCSK1: Prohormone Convertase 1; MC4R: Melanocortin 4 Receptor; SIM1: Single-Minded Homolog 1; BDNF: Brain-Derived Neurotrophic Factor; NTRK2: Neurotrophic Tyrosine Kinase Receptor Type 2 Gene

Introduction

There are circa 100,000 genes coding for 30,000 proteins in the human genome. Certain proteins represent therapeutic targets for human disorders. RNA-protein [1] expression profiling tools which provide the latitude in research for the authentication of the molecular basis of ageing and drug discovery [2]. Physiologically, age-associated and disease-associated muscle, progressively diminish during entire life. Sarcopenia depicted as dissipation of muscle mass and depletion of functional status in either muscle power and/or physical potential may present during ageing or in aged persons [3]. However, there is no universal agreement on the methods for its veritable evaluation or validation. The major challenge in this extreme biological event is the confounding multifactorial aetiology. Functional genomics approaches tend to model the related scientific modalities by means of a newfangled insight on sarcopenia. Gene and drug high-throughput screening coupled with functional genomics permit the generation and interpretation of a vast quantity of data in sarcopenia and therapeutics [4]. High throughput screening (HTS) utilises automated equipment to accelerate testing inordinate number of samples for biological functionality at the organismal, pathway, cellular or molecular level. Technologically, the trajectories in HTS involve miniaturization, automation, and assay readout stagewise: samples and compound libraries preparation as well as determination of a procedure tenable for laboratory automation. Functional genomics are genome-wide research with intent to unravel genotype-phenotype associations to determine human genetic diversity impact on physiology and pathophysiology [5].

The Identification of therapeutic target genes is the basis in functional genomics-based treatment. Contextually, the disease heterogeneity, exogenous factors and intricately-complex genomic morphology depict significant challenges, issues and opportunities. Functional genomics posits to subvert such constraints by determining the gene functionalities, thereby depicting disease-aetiological genes as therapeutic agents and targets. Genomic technologies advance the modification of investigation on ageing muscle, exercise response and drug discovery [6] and target [2]. Functional genomics approaches, such as differential gene expression strategies, microarray, serial analysis of gene expression (SAGE), massively parallel signature sequence (MPSS), RNA sequencing (RNA seq), representational difference analysis (RDA), and suppression subtractive hybridization (SSH) have been analysed [6], as well as modalities to unravel newfangled therapeutic targets regarding certain complex diseases [6-9]; with application of these instruments in modulating skeletal muscle transcriptome [6].

Multomics Research

Sarcopenia constitutes a systemic anomaly presenting generalised, progressive and aberrant skeletal muscle dysfunction depicted by age-related depleted muscle mass, elevated concentration of

muscle retarded fibres, and diminished muscle functionality [3,10]. The risk of sarcopenia and muscle phenotypes are heritable [10], but the genetic framework and molecular mechanisms in the disorder are undecipherable. Remarkable advance tends to elucidate susceptibility loci by employing genome-wide association investigation. No sole technology is capable of holistically harnessing the intricate biological complexity of the anomaly, whereas integrative multi-omics analyses confer the latitude to unravel novel insights via sarcopenia multi-omics research for elucidating sarcopenia pathogenesis. Leverage on multi-omics data provides comprehensive view of sarcopenia aetiology with resultant nascent clinical applications, with projections in the guidance and recommendations [10] for sarcopenia basic studies, newfangled perspectives, preventive, control and therapeutic interventions.

Transcriptomics

Among the elderly, the high prevalence of non-alcoholic fatty liver disease (NAFLD) and sarcopenia are confronting tremendous challenged to local, regional and global health systems [3,11]. NAFLD is characterized by lipid accumulation in the liver, resulting in liver fibrosis deterioration [12,13], cirrhosis and culminating in liver cancer [12,14]. About 25% of the global population presents with NAFLD, and NAFLD patients are becoming younger, and not confined to the elderly [15]. It is, therefore, pertinent to tackle the underlying mechanisms of NAFLD in order to develop effective and efficient therapeutic agents. Hepatic steatosis is associated with ageing and metabolic syndromes, such as high-fat diet [16], hyperlipidemia, toxins, drugs, and diseases [17]. NAFLD pathogenesis is notably regarded as a two-strike and multiple-strike theory, however, the molecular mechanism of the development and existence of NAFLD remains elusive [18], but other ageing anomalies inextricably-linked with lipid metabolism and fibrosis are likely to exacerbate NAFLD. Transcriptome analysis is capable of determining and quantifying modifications in transcription levels in multifarious conditions [19]. Transcriptomics have been broadly applied in a vast majority of the life sciences [20,21]. With increasing challenges, issues and opportunities changed, novel approaches for transcriptome research will be focused on low cell numbers, with emergence of accurately targeted sequencing [22]. Transcriptome technology can be of immense research to accurately understand pathogenesis and the association between specific RNA and diseases. On the clarification of the precise regulation of diverse genes in diseases, transcriptome technology may be of immense benefit in the production of new drugs and relevant applications in the prevention and therapeutic regimen of tumours. The integrative analysis of biological data employing bioinformatics contributes veritably to life science studies, such as predicting patient-related biomarkers using network algorithm or Random Forest [23].

Combination of transcriptome data and dual disease analysis can enhance the understanding of the pathological molecular mechanisms in diseases. The investigation of coexpressed genes in NAFLD

and sarcopenia patients, stringently identified injury pathways of lipid metabolism and oxidative stress, with the possibility of NAFLD and sarcopenia transcriptome regulatory pathways in ageing individuals [11]. An entire transcription pattern mapping was conducted for the identification of the core genes, underlying biological mechanisms, and probable therapeutic targets which regulate ageing in NAFLD and sarcopenia patients [11]. This provides novel insights and evidence of diminishing the increased sarcopenia prevalence in the elderly population due to NAFLD. The functionalities of bioinformatics, computational biology, omics techniques and transcriptomics have advanced significantly in biomedicine and healthcare, especially to identify biomarkers for drug discovery and precision. Differential gene expression (DGE) analysis is a ubiquitously appreciated technique for RNA-sequencing (RNA-seq) data analysis. The tool identifies differentially expressed genes across two or more sample sets. Functional enrichment analyses are performed to annotate and contextualize the resultant gene lists [24]. The studies allow for pertinent data regarding aetiopathologic mechanisms to identify molecular targets for novel therapeutics.

Metabolic Processes

Functional genomics conceptualises how genes and intergenic segments of the genome contribute to disparate metabolic pathways or gene expression pattern. Objectively, functional genomics resolves the trajectory specific segment of an organism combinatorially form a specific phenotype [25]. Besides the function of skeletal muscle in movement and locomotion, the muscle critically participates in a vast spectrum of metabolic processes which may contribute to improved health or disease risk as evident in sarcopenia. Muscle constitutes the primordial insulin-stimulated glucose disposal locus and the most expansive aspect of basal metabolic rate, invariably impacts bone density, forms myokines with pleiotropic effect on muscle, brain and other tissues, stores essential amino acids for the sustainability of protein synthesis during stress and restricted food intake. Derangement of skeletal muscle health, operationalized as depletion of muscle mass and muscle power constitute as potent risk factor and major repercussion of chronic disorders [26], morbidity, mortality and incapacitation. The plasticity of skeletal muscle is more extreme than other tissues, exhibiting rapid alterations in protein synthesis and degradation rates in response to invariable physical status, inflammation, nutritional and hormonal status, with concomitant advancement in the production of therapies to enhance muscle mass or obliterate muscle dissipation [27]. Nutrition is evidenced as a modifiable risk factor for sarcopenia; characterising the nutritional and metabolic profile of sarcopenia via exploration of expansive spheres of blood biomarkers associated with muscle protein metabolism and transcriptomic signatures among elderly community dwellers [28]. The characterization of a sarcopenic nutritional and metabolic signature basically and potentially identifies precise targets and trajectories for the nutritional strategy to prevent and treat sarcopenia during the ageing process.

Vitamin D

Vitamin D (vitD) deficiency correlates with diverse chronic anomalies and accelerated metabolic dysregulation, as in obesity, insulin resistance [29], hyperlipidemia, hepatic derangement and hypertension. The investigation of the genetic relationship between 25-hydroxyvitamin D (25[OH]D)-related genes and obesity traits shows that the variation in the vitD receptor, VDR gene expresses the main crux of the findings. Polymorphisms in the VDR gene are associated with obesity traits in select studies, thus inconclusive. Genes disparate from VDR investigated regarding obesity-related traits, have also been indicted in contradictions. However, there are indications that the DBP/GC gene represent a vital protein interlacing obesity and vitD status. Obversely, vitD due to its fat solubility is retained by adipose tissue with the potential to metabolise 25(OH)-D locally, and capacity for modification in obesity. Also, vitD regulates gene expression in association with adipogenesis, inflammation, oxidative stress, and metabolism in mature adipocytes [30]. As sarcopenia is a muscle-wasting syndrome featuring generalized, progressive and degenerative and dissipating skeletal muscle mass, quality, and power occurring during the normal ageing process [3], sarcopenia patients mainly undergo loss of muscle strength and confront mobility disorders impairing their quality of life, thus, are at exacerbating morbidity risk, such as precipitations/falls, bone fractures and metabolic diseases as well as mortality. Numerous molecular mechanisms have been attributed as aetiologies for sarcopenia which prefer to distinct disparate levels of muscle physiology. These mechanisms encumber hormone function, such as IGF-1 and Insulin, muscle fiber encapsulation and neuromuscular drive, potential of myo-satellite cell for differentiation and proliferation, as well as inflammatory pathways and intracellular mechanisms in proteostasis and mitochondrial functionality [31].

Ageing, Sex, and Skeletal Muscles

Since sarcopenia is an age-associated anomaly featuring loss of muscle mass and muscle functionality [3,32], unravelling or elucidating the pathogenesis and mechanisms may provide strategies to diagnosis and treat the disorder. Sex presents as a critical biological factor, and impact of biological sex on the modification of gene expression in ageing skeletal muscle has not been completely understood. The mRNA expression profiles were determined from the Gene Expression Omnibus database, wherein primordial genes were established via analyses of differential expression and weighted gene co-expression network [32]. Functional with enrichment analysis was conducted by gene set enrichment analysis software and Molecular Signatures Database. A protein-protein interaction [33] network was configured by STRING and visualized in Cytoscape. The findings were compared and contrasted among subgroups of female and male subjects. Uniquely expressed genes and enriched pathways in disparate sex subgroups merely shared restricted similarities. The pathways enriched in the female subgroup presented higher similarity to the pathways enriched in the older groups in the absence of sex differ-

ence consideration. In both the aged female and male samples, the muscle myosin filament pathways were downregulated whereas up-regulation occurred in transforming growth factor beta pathway and extracellular matrix-related pathways. In muscle ageing, the metabolism-related pathways, protein synthesis and degradation pathways, findings of predicted immune cell infiltration, and gene cluster related with slow-type myofibres markedly differed between the female and male subgroups. This suggests that alterations in muscle type during ageing contrast between sexes in vastus lateralis muscle [34].

Ageing, Skeletal Muscles, and Transcriptome

Evaluation of invariable primary and secondary ageing evidenced in molecular and cellular ageing mechanisms is a challenging and daunting unresolved task. A study presented the initial exemplification of the select functionality of primary ageing and chronic inflammation/physical nonfunctionality, the markedly significant drivers of secondary ageing in regulating transcriptomic and proteomic profiles in human skeletal muscle [35]. This was determined using young healthy persons and older patients with knee/hip osteoarthritis, a model on the impact of long-run inactivity and chronic inflammation on the vastus lateralis muscle. Results showed expansive and profound age-related alterations of gene expression in older patients to young healthy people (circa 4000 genes regulating mitochondrial function, proteostasis, cell membrane, secretory and immune response) during long-run physical inactivity and chronic inflammation in lieu of primary ageing. Primary ageing contributed predominantly to the gene regulation (approximately 200) encoding nuclear proteins (DNA repair regulators, RNA processing and transcription), mitochondrial proteins (genes encoding respiratory enzymes, mitochondrial complex assembly factors, regulators of cristae formation and mitochondrial reactive oxygen species formation), including proteostasis regulators [35]. Proteins associated with ageing were regulated mostly at the post-transcriptional level. The defined primary ageing genes and concomitant potential transcriptional regulators can be useful for future targeted research investigating specific genes and associated transcription variables in a novel senescent cell phenotype.

Obesity

Obesity may aggravate the effects of sarcopenia on skeletal muscle structure and function in the elderly. There has not been any research to identify [36], determine or establish the gene variants associated with sarcopenia in obese women, but in the elderly, obesity can exacerbate sarcopenia impacts on skeletal muscle morphology. Three gene variants, ACTN3 rs1815739, MTHFR rs1801131, and MTHFR rs1537516, respectively suggested to affect muscle function, homocysteine metabolism, or DNA methylation, were linked with sarcopenia in obese elderly women [36]. Globally, there is incessant obesity epidemic increase despite expressed preventative modalities [37,38]. Pharmacological therapeutics advance measures to deplete total fat mass; but medications are likely to present morbidities with concomitant mortalities. Studies have provided evidence to corroborate the

Reward Deficiency Syndrome (RDS) in obesity and the linkage of catecholaminergic pathways in substance craving stance as it pertains to carbohydrate compulsion. The genetic basis and futuristic genetic examination of children for risk of anomalous generalized craving behavior are regarded as preventive approach. Evidence undergirds the utility of precursor amino acid therapeutics and enkephalinase, MOA, and COMT inhibition modulation in pivotal brain spheres.

These therapies are observable in advanced concentrations of dopamine/norepinephrine, GABA, serotonin, and enkephalins. Findings substantiate insulin sensitivity augmentation using chromium salts as influenced in the regulation of dopamine neuronal synthesis. A discrete concoction of natural components may induce multiple pathways culminating in the advancement of quality of life and conventional healthy metabolic functionality. Sarcopenia has been observed to diminish angiogenesis and probable cerebral blood flow [38]. Exercise ostensibly significantly overcomes this obesity-enhancing dissipation of muscle density [3,38], mass and volume. Utilization of nutrigenomic formulae enacted on combined genetic obesity risk testing advances generalized anti-craving of carbohydrates and suppresses carbohydrate compulsive consumption and triggering substantial healthy fat loss and relapse prevention [38], control or obliteration.

How Obesity Influences Gene Expression

It has been implicated obesity results in chronic pro-inflammatory condition that potentiates immunosenescence, culminating in prompt immune risk profile and health decadence associated with immunity in adulthood [39]. Despite comorbidities, obesity triggers enhanced gene expression of markers related to inflammation and immunosenescence in circulating leukocytes in obese middle-aged persons in comparison to a eutrophic group of similar age. Furthermore, increased adipose tissue and markers of chronic inflammation and immunosenescence have been associated in deranged cardiorespiratory health of obese middle-aged persons [39].

What Comprise the Genetic Markers for Obesity?

The ubiquitous obesity variant in proximity to Melanocortin-4 receptor (MC4R) gene is associated in women with elevated intakes of total energy and dietary fat, weight modification and diabetes risk [40]. MC4R significantly regulates food intake and energy balance. Genome wide scans revealed common variants proximate to MC4R related to obesity and insulin resistance. The usual SNP rs17782313 near MC4R gene [40].

Sarcopenic Obesity

Sarcopenic obesity (SO) pertains to the comorbidity of excess adiposity and diminished muscle mass/functionality [3,41]; being widely established clinical and functional characteristics which aberrantly impact patient-centred outcomes or prognosis. Effective and efficient SO preventative and therapeutic approaches are pertinent, however, sustainable strategies are impeded due to deficient universally ac-

cepted definition and diagnostic criteria for SO. These have culminated in polemics, contradictions and inconsistencies, with anomalies in asserting the SO prevalence and clinical patency for health prognosis per risk variables, clinical symptoms, evaluated or validated questionnaires [3,41] or surveys. Diagnostic procedures initially including assessment of skeletal muscle function, accompanied by assessment and evaluation of body composition exhibiting excess adiposity and depleted skeletal muscle mass or associated body cubicles assert SO diagnostic characterisations. SO individuals need to be classified via stage I devoid of clinical sequelae or stage II where cases are associated with sequelae intertwined to aberrant body composition or skeletal muscle impairment which must be incorporated in routine clinical trials and practice as part of SO definition and diagnostic criteria [41]. Prospective research and secondary analysis of extant data sets are pertinent per predictive value, therapeutic efficacy and clinical impact of the definition of SO.

Thus, SO is the coexistence of obesity and sarcopenia, with a defined diagnostic criteria depicting degraded skeletal muscle function and aberrant body components, such as elevated fat mass and depleted muscle mass [42]. With poorly understood mechanism, this entails ageing and its sequelae, chronic inflammation, insulin resistance (IR), and hormonal alterations. Ostensibly, underlying genetic heritability is indicted in isolated pathogenesis of obesity, that is frequently polygenic with characteristic superimposed impact of diverse genetic components [10,42]. The SO genetic aetiopathogenesis is not strictly adhered to, however, multiple data affirm extant pathogenic gene variants, such as Fat Mass and Obesity Associated Gene (FTO), beta-2-adrenergic receptor (ADRB2) gene, as well as melanocortin-4 receptor (MC4R) with obesity and inexplicable functionalities [42]. Conversely, associated systemic inflammation resulting from augmented SO adipose tissue significantly influences its pathophysiology via the synthesis of disparate cytokines, such as monocyte chemoattractant protein-1 (MCP-1), IL-1Ra, IL-15, adiponectin or CRP. The deficiency of anti-inflammatory cytokine (IL-15) may enhance SO risk [42].

mRNA Expression Obesity Sarcopenia

A further definition relates SO as a distinct state of sarcopenia in obesity context having compounding health risks of both phenotypes. Differential expression of microRNAs (miRNAs) in obesity and sarcopenia individuals have been disparately observed; and ostensibly signifies a role in sarcopenic obesity pathogenesis [43]. Twenty-four miRNAs were revealed as generally dysregulated in obesity and sarcopenia with functions and targets in SO pathogenesis. With the excruciating health prognosis, unravelling the pathogenesis underlying the phenotype may potentiate sustainable screening, monitoring and therapeutic approaches [43].

Cancer/Cachexia, Sarcopenia, and Therapy

The application and the role of functional genomics in drug discovery are of immense importance in oncological research. The dis-

covery that the gene HER2 is over-expressed in select breast cancers resulted in the development of Herceptin (The HER2 Journey) [44]. As exemplified, sarcopenia, the progressive depreciation in skeletal muscle mass and function is detected in multiple states, such as cancer and ageing [3,45]. The intricately complex molecular biology of sarcopenia presents issues for the development or production of approved therapeutics which have merely being utilised as dietary supplements. A single gene as target does not suffice to suppress the extensive mechanisms related to muscle dissipation [45]. Analysis of gene expression signatures associated with cancer development and 5-FU chemotherapy-induced muscle depreciation suggested that dimenhydrinate, an admixture of 8-chlorotheophylline and diphenhydramine is a promising sarcopenia therapeutic. In vitro study indicated that dimenhydrinate enhances muscle progenitor cell proliferation via the phosphorylation of Nrf2 by 8-chlorotheophylline and augments myotube development via diphenhydramine-induced autophagy. Moreover, in multiple in vivo sarcopenia models, dimenhydrinate accelerated regeneration of muscle tissue, such as in animals with Duchenne muscular dystrophy (DMD) and induced muscle and fat recovery in animals with chemotherapy-facilitated sarcopenia.

Dimenhydrinate has been found to be amenable for sarcopenia treatment after a relatively short development span, advancing succour for patients presenting with the aberrant state [45]. Cachexia presents in chronic disease patients wherein systemic inflammation culminates in fatigue, debilitation, depreciated physical activity and sarcopenia. The cachexia-associated sarcopenia pathogenesis is not completely elucidated [46]. It is well-nigh impossible to compare findings across studies and disease because evidence on gene expression in human skeletal muscles having chronic disease-associated cachexia and/or sarcopenia is heterogenous and not well-established. Thus, it is difficult to compare results across studies and diseases. Since sarcopenia is a labile prognostic variable in diverse cancers, it is suggested that sarcopenia has deleterious effects in metastatic hormone-sensitive prostate cancer (mHSPC) patients [47]. Sarcopenia was detected to be an independent prognostic variable for derelict failure-free survival and period to prostate-specific antigen advancement in mHSPC patients on prompt docetaxel or abiraterone acetate therapy. RNA sequencing of primary tumors was conducted to further explicate the biological sphere of mHSPC sarcopenia. Transcriptomic disparities were detected between primary tumors presenting sarcopenia or not [47]. In patients, this may potentiate the relationship between sarcopenia and retarded clinical outcomes or prognosis.

Speculations are rife that cachexia is due to cancer and anorexia from chemotherapy toxicity or targeted anti-cancer agents. However, it is posited that chemotherapy and certain targeted agents propagate sarcopenia leading to deficit in physical activity and quality of life. Pre-therapeutic sarcopenia predicts chemotherapy toxicity, decreased response, enhanced disability, depreciated anti-tumor response and survival. Erstwhile bioelectrical impedance and dual energy X-ray absorptiometry (DEXA) scans for estimation of body

composition, revealed that CT scan cuts at the 3rd lumbar vertebra level, measurements of skeletal muscle and visceral and subcutaneous fat precincts are presently conventional approaches [48]. Non-pharmacological modalities to mitigate sarcopenia utilizing chemotherapy are resistance training and dietary/nutritional counselling. Pharmacological therapies may involve replenishment with vitamin D [29,30,48], omega-3 fatty acids, testosterone and select androgen receptor modulators (SARMS) and ghrelin. An encompassing multimodal and multiple drug strategy may be a more realistic mode until tested and proven. The repercussions in sarcopenia intervention, prevention or reversal sarcopenia per clinical outcomes or prognosis and regarding tolerance to cancer therapy, physical activity, tumor response and quality of life need to be established. Sarcopenia reversal, outcomes and prognosis for improved health must be the objective for cancer therapy [48].

The definition of sarcopenia as dissipated muscle mass, strength and physical function highlights the disorder as a hallmark of ageing and inextricable-linkage with perturbed amino acid metabolism, aggravated muscle protein catabolism relative to anabolism, and muscle fibre loss [49].

As universally indicated, it is associated with overall loss of body mass, or coexistence/comorbidity with obesity, SO. The multiple comorbidities of sarcopenia in older adults may not be more aggravated than in patients presenting malignant disorders where the contribution to poor surgical outcomes or prognosis may exacerbate chemotherapy toxicity compounded by both cytotoxic and targeted agents, with adverse impact on quality of life and survival. Although, sarcopenia development may be a usual age-associated event, the concomitant catabolic mechanisms are ostensibly exacerbated by physical dysfunctionality, deficient dietary component, systemic low-grade inflammation, intrinsic muscle and molecular malformations, mitochondrial impairment and anomalous muscle stem cell regenerative potential [49]. Augmented physical prowess and improved protein consumption can mitigate presenting and aggravating sarcopenia in cancer patients. Inordinate number of aged cancer patients may not accomplish physical functionality and nutrition requirements, thereby making it well-nigh impossible for cancer therapy to provide comfortable quality of life.

Diabetes, Sarcopenia and Therapy

Another definition associates Sarcopenia as an age-related loss of muscle strength and mass or quality of a ubiquitous state with excruciating presentations. Despite the deficient understanding of its pathophysiology, there are familiar mechanisms between sarcopenia and accelerated ageing observed in diabetes. Drugs in extant usage for type 2 diabetes therapy may contribute to the mitigation, prevention and treatment of sarcopenia patients and the general population for those with type 2 diabetes and those without diabetes [50]. Cellular and animal models present challenging possibilities beneficial

to skeletal muscle function for certain categories of drugs in diabetes control, such as metformin and SGLT2 inhibitors. A vast majority of the human evidence regarding effects of drugs are from observational and intervention type 2 diabetes populations [50]. Not all diabetes treatments may be conducive for non-diabetic individuals because of variable side effects across board.

Cardiovascular Disease and Sarcopenia

Sarcopenia is characterised as a clinical syndrome emerging from a progressive and extensive deterioration in skeletal muscle mass, muscle strength, and functionality expose sarcopenia and cardiovascular diseases (CVDs) in comorbidity which further decline the quality of life, and heighten the mortality rate of patients [3,51]. MicroRNAs (miRNAs) constitute discrete posttranscriptional gene expression regulators with not clearly explicated roles in ageing-related sarcopenia and CVDs [51]. Sarcopenia prevalence has been detected to be substantially directly proportional to CVRF ingredients. For instance, hypertension and dyslipidemia were highly associated with a higher sarcopenia risk in adjusted models. Also, c-miRNAs are possible biomarkers for sarcopenia as a nascent diagnostic tool for monitoring and evaluating drug response to develop and improve clinical outcomes [51] or prognosis.

Sarcopenia Therapy and Diagnosis

In recapitulation, sarcopenia, the loss of skeletal muscle mass and function with ageing was initially given cognizance as a disease in the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) (M62. 84), and brought to the fore with increased ageing populations. The extant sarcopenia clinical and diagnostic criteria are somewhat contradictory, controversial and elusive. There are no extant approved therapeutic modalities for sarcopenia prevention, control and treatment given that intrinsic and extrinsic factors are contributory to its emergence and establishment. A compendium of sarcopenia drugs, such as myostatin/ActR2 signaling inhibitors, exercise mimetics, anabolic hormones and natural compounds are currently under investigation [52]. As previously stated, a combined non-drug therapeutics, exercise and nutritional components are viable due to easier economic access and intervention approaches against sarcopenia in lieu of solely pharmaceutical treatments. Numerous extant strategies to suppress the emergence of sarcopenia may result in healthy and successful ageing.

Gene Analysis Disorders

Functional analysis in genetics describes gene characteristics and the concomitant products in an organism, categorising data into three spheres of biological research. The levels permit the description of gene function, relationship in metabolic pathways and cellular locale. The systemic gene interactions and the underlying mechanisms featuring during osteoporosis are yet to be elucidated. Mesenchymal stromal cells (MSCs) analyzed from bone marrow samples obtained

from healthy subjects detected 24 genes associated with diabetes and obesity, in which 10 genes were connected in a network involved in bone and energy metabolism [53]. The results may be indicative of prevention and therapeutic regimen of osteoporosis in sarcopenia. Sarcopenia hypoplasia is the decrement in muscle mass that metamorphoses into sarcopenia and involves both a depreciation in muscle fibre size or atrophy and quantity or hypoplasia [3]. The genes associated with muscle fibre size or atrophy are the atrophy-related genes, FoxO1 and metallothionein 1 (Mt1) depicting persistent up-regulation following 14 days [54] of observation. FoxO1 poses as a forkhead-type transcription factor and triggers the expression of atrophy-associated genes, atrogin-1 and cathepsin L, in diverse muscle atrophy-associated states [55,56]. The genes found to be associated with sarcopenia are MYH8, HOXB2, C1QA, CDKN1A, and SLC38A1 [57], and in another study, LGR5, SERPINA5, and TPPP3 genes were detected to be epigenetically [58] for the first time associated with Sarcopenia [59].

Genome-Wide Association Study

Since the characterisations of the genetic biomarkers for sarcopenia are not well established, a study investigated the genetic variabilities associated with the diseases in a relatively aged cohort applying genome-wide association study (GWAS) meta-analyses of lean body mass (LBM) in 6961 candidates. Analyses and subgroup GWAS were performed for appendicular skeletal muscle mass (ASM) and skeletal muscle index. Experimentation was conducted on the impacts of significant single nucleotide polymorphisms (SNPs) on gene expression applying multiple expression quantitative trait loci datasets, differentially expressed gene analysis, and gene ontology analysis [60]. The identification of novel genetic biomarkers was performed for LBM (rs1187118; rs3768582) and ASM (rs6772958). The associated genes, as well as RPS10, NUDT3, NCF2, SMG7, and ARPC5, were expressed differentially in skeletal muscle tissue, whereas there was no differential expression regarding GPD1L. Also, the “mRNA destabilisation” biological process was embellished for sarcopenia. The investigation depicted RPS10, NUDT3, and GPD1L as prominent genetic biomarkers for sarcopenia. The genetic loci were associated with lipid and energy metabolism [60]. The findings suggest that genes linked in metabolic dysregulation culminate in age-associated sarcopenia pathogenesis.

On the assumption that sarcopenia is a skeletal muscle anomaly of clinical significance present in old age and in numerous disease sub-categories, broadening the sphere of information concerning the genetics of muscle mass and strength is relevant because it becomes possible to detect patients having an increased risk in the development of sarcopenia or any defined musculoskeletal disease relying on genetic markers [61]. Transcriptome Wide Association Studies, TWAS, methods aggregating GWAS and eQTL concise statistics were beneficial in statistically stratifying genes and their related SNPs for the

sarcopenia phenotype of investigation. The regulatory SNPs related with these genes, and the genes increasingly categorized via a scoring system are wet lab clarified regarding the phenotype hypothetically affected [61]. These are significant in screening characteristic genes associated with sarcopenia using bioinformatics and machine learning, and for the verification of the accuracy of characteristic genes in sarcopenia diagnosis [57]. In sarcopenia patients, the following genes depicted high accuracy in sarcopenia diagnosis and the expression of TPPP3, C1QA, TPPP3, C1QA, LGR5, MYH8, and CDKN1A genes up-regulated, and the expression of SLC38A1, SERPINA5, and HOXB2 genes downregulated. The research results provide newfangled approaches for the diagnosis and research processes for sarcopenia. The findings suggest the expression of TPP3, C1QA, LGR5, MYH8, and CDKN1A genes are upregulated in sarcopenic patients, whereas expression of SLC38A1, SERPINA5, and HOXB2 genes are downregulated and are utilisable as biomarkers for sarcopenic patients' diagnosis [57].

Discussion

Sarcopenia constitutes the age-related dissipation of skeletal muscle mass and functionality. It is a global health issue in the ageing population, contributing to morbidity, mortality, physical disability [62] and economic burden to society and the healthcare system. The pronounced depreciation in skeletal muscle mass, power, gait, speed, dizziness, precipitations/falls and retention of all other corresponding vital human components signify severe sarcopenia which ostensibly depend on genetic risk variables. Multiple genome-wide crucial single nucleotide polymorphisms (SNPs) related to handgrip power, lean mass and gait were determined in the UK Biobank cohort. The pleiotropic impacts on three phenotypes have not been decidedly investigated, but GWAS of handgrip strength, lean mass and walking pace indicated that sarcopenia [3], obesity [63] and type 2 diabetes [64] shared multiple common risk alleles [65]. Obesity is a complex multifactorial disorder influenced via gene-environment interactions [66] or genetic and environmental variations. There is an extant progressive global increase in the incidence and prevalence of obesity [63]. The enactment of GWAS and next-generation sequencing (NGS) increased the genetic relationships and realizations of monogenic and polygenic aetiologies of obesity. Genetics of obesity is categorisable into syndromic and non-syndromic obesity.

Prader-Willi, fragile X, Bardet-Biedl, Cohen, and Albright Hereditary Osteodystrophy (AHO) syndromes are instances of syndromic obesity associated with developmentally retarded and early onset obesity. Non-syndromic obesity may be either monogenic, polygenic, or chromosomal in origin. Monogenic obesity emanates from variants of single genes while polygenic obesity are multiple genes related to members of gene families [66]. Newfangled progress in genetic testing has detected obesity-related genes. Leptin (LEP), the leptin receptor (LEPR), proopiomelanocortin (POMC), prohormone convertase 1 (PCSK1), the melanocortin 4 receptor (MC4R), single-minded homo-

log 1 (SIM1), brain-derived neurotrophic factor (BDNF), and the neurotrophic tyrosine kinase receptor type 2 gene (NTRK2) have been identified as obesity aetiologic genes. NGS is currently applied; and has emerged in clinical settings as an essential tool to seek for candidate genes in obesity [66].

Conclusion

The rationale for functional genomics is to identify the disparate ingredients of a biological system to function cooperatively in the production of a specific phenotype. Functional genomics emphasizes on the dynamic expression of gene products in a specific context at inception or during the course of a disease. Sarcopenia relates to both genetic and environmental factors as pivotal contributors. Genetic factors including polymorphisms influence sarcopenia development. Genetics and their interplay with environmental factors make inter-individual differences possible. Genes account for a comparatively and disproportionately percentage of human disorders, however, a significant proportion of the remainder, a vast majority of disease risk have. the environment as a determinant of diseases as well as modifiable lifestyle, such as nutrition, stress conditions and physical activity. Functional genomics considers the modifications in gene expression in diverse states, such as dietary compartments, ageing mechanisms, and physical exercise. Gene expression is crucial to identify the molecular signature of disease and to correlate a pharmacodynamic marker to the dose-dependent cellular response of drug exposure. Alterations in gene expression essentially function in differentiation and cell fate regulation including stress adaptation and metabolic control. Thus, these are important in implementing development programmes, fix internal errors, and to sustainably maintain metabolic homeostasis in a changing milieu. Furthermore, risk alleles for both sarcopenia and augmented adiposity pose as genomic predictors of sarcopenic obesity.

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Chrysanthus Chukwuma Sr. Biomed J Sci & Tech Res



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