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The Impact of Low Appendicular Skeletal Muscle Mass in the Development of Insulin Resistance and Metabolic Syndrome: A Systematic Review of the Literature

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Abstract

Chronic conditions are the leading cause of death and disability. More specifically, cardio-metabolic disease is the number one cause of death worldwide. The tragedy and burden of disease is unrefuted; even more so, evidence indicates that realistic modifications of lifestyle can prevent most chronic disease. Metabolic syndrome and insulin resistance are leading risk factors in the development of cardio-metabolic disease. Presently, chronic disease is treated through symptomatic evaluation of risk. Reframing the lens of care through root cause evaluation is fundamental to optimizing patient outcomes. The purpose of this systematic review is to synthesize literature evaluating the impact of low skeletal muscle mass on the development of metabolic syndrome and insulin resistance in all populations. Health Source: Nursing, CINHAL and MEDLINE were systematically searched for peer-reviewed journal articles that studied generalized populations (P), and the relationship of low appendicular skeletal muscle mass (I), with a comparison of normalized or high relative appendicular skeletal muscle mass (C), on the development of metabolic syndrome and insulin resistance (O) over a randomized period of time (T). Twenty peer-reviewed articles were retrieved; 16 articles were primary studies and 4 articles were systematic reviews in accordance with the PICOT objectives. The included articles referred to a demographic population of eight countries, with no constraint on sex, race or age. Consistently, across the searched literature, low appendicular skeletal muscle mass was directly correlated to metabolic syndrome and insulin resistance. Further research is necessary to inform evidence-based practice. Healthcare professionals and their leadership hold the responsibility to advocate for positive disruption through interventional reform in treating chronic disease.

Keywords: skeletal muscle mass, sarcopenia, chronic disease, metabolic syndrome, insulin resistance.

The impact of low appendicular skeletal muscle mass in the development of insulin resistance and metabolic syndrome: A systematic review of the literature

A chronic condition is a generalized term referring to diseases with an "insidious onset, long incubation period, long and slow course of disease and delayed healing" (Raghupathi & Raghupathi, 2018, pg. 431). The Centers for Disease Control (CDC) classifies the following as chronic diseases: heart disease, stroke, cancer, type 2 diabetes, obesity and arthritis (Bernell & Howard, 2016). The Centers for Medicare and Medicaid Services (CMS) defines a broader spectrum of conditions as chronic, including the addition of Alzheimer's and related dementia, drug, alcohol and substance abuse, hyperlipidemia, hypertension, depression and chronic kidney disease (*Chronic Conditions | CMS*, n.d.). A majority of civilian, non institutionalized adults, 51.8%, within the United States have been diagnosed with one chronic condition; 27.2% of this population presents with multi-morbidity, which refers to the presence of two or more chronic conditions (Boersma, Black & Ward, 2020). Chronic diseases are likely underreported, due to the exclusion of institutionalized adults, the exclusion of children and the variable criteria for chronic disease between professional organizations. The prevalence of multiple chronic conditions is high among women, non-Hispanic white adults, older adults, adults receiving Medicaid, adults in rural areas and dual-eligible adults (Medicare and Medicaid) (Boersma, Black & Ward). Furthermore, as the US adult population ages, the rates of chronic disease are expected to increase. A multi-state population model, developed to analyze credible, evidence-based projections of chronic disease, demonstrated that the number of people in the United States aged 50 years and older will increase by 61.11% in thirty years from 127.25 million 221.13 million in 2050. Furthermore, the number with at least one chronic disease is estimated to increase 99.5% and those with multi morbidity are projected to increase 91.16% (Ansah & Chiu,

2023). These persistent conditions are the nation's leading cause of death and disability. More than two thirds of all deaths result from one or more of these five chronic diseases: heart disease, cancer, stroke, chronic obstructive pulmonary disease and diabetes. Chronic disease kills more than 1.7 million Americans each year and is responsible for 7 out of 10 deaths in the United States. These statistics are stark. More so, in understanding that several lines of evidence indicate that realistic modifications of lifestyle can prevent most chronic disease, the tragedy and burden of disease deepens. Beyond the tragedy of death and disability, chronic conditions have severe economic implications. These conditions are the leading driver of United States' $4.1 trillion annual health care cost. In addition, the downstream affect of disease causes a $147 billion loss in productivity on the job. This economic toll will increase, as outlined by the CDC who state that care and treatment for individuals with Alzheimer's disease is projected to be more than $1.1 trillion by 2050. This projection is not independently associated with Alzheimer's disease, but an anticipated trend associated with all chronic disease (*Health and Economic Costs of Chronic Diseases | CDC,* n.d.).

The transition from acute disease to chronic disease can be matched to the 1950 post-World War II economic expansion, known as the Golden Age of Capitalism ("The Post War United States, 1945-1968", n.d.). This transition was predicated by the introduction of antibiotics, the introduction of public health initiatives causing a submission of infectious disease and the aging population. As the central health problem changed, patient care did not. Following this transition, the emergence of chronic disease was not discussed in medical literature and did not influence medical education and teaching. Through the failure to recognize the burden of chronic disease, the profession failed to rework effective and efficient management of chronic disease (Holman, 2020). One group of researchers from the Johns Hopkins School of Medicine

reported that 66% of practicing clinicians were not prepared to educate patients with chronic disease, manage physiological and social aspects of chronic care and provide nutritional advice. A second group of researchers from the Johns Hopkins School of Medicine reflected academic medicine's low concern for chronic disease after surveying medical program directors to rate the importance of skills or practices in their teaching. The results of the study demonstrated that only 29 of the the 49 skills related to chronic disease management were rated moderately important and 0 of the 49 skills were considered essential (Holman, 2020). Academic medicine's low concern for chronic disease is evident through the lens of curriculum and the statistical presentation of disease within the United States. The AMA Code of Medical Ethics states, "A physician shall be dedicated to providing competent medical care, with compassion and respect for human dignity and rights […] A physician shall regarding responsibility to the patient as paramount" (Association, A. M., 2018, pg. 1). Furthermore, the Provisions of the Code of Ethics for Nurses includes the obligation to practice with compassion, act with commitment to the patient, whether an individual, family, group, community or population, to advocate for the health and safety of the patient and to collaborate with other health professionals to protect human rights and reduce health disparities (Association, A. N., 2001). Patient advocacy is central to the actions of health care providers. The medical profession and its leadership are confronted with the responsibility of rebuilding a practice and healthcare model that more appropriately meets the needs of patients with chronic illness.

Recognition that all chronic diseases have severe implications on an individual's quality of life is necessary to maintain patient dignity (Stephen, Nyashanu, Ossey-Nweze & Serrant, 2021). Meanwhile, prioritization of interventional strategies related to cardiometabolic diseases is appropriate, because of the proportion of individuals affected, the increased risk for

development of future disease and the patients increased mortality risk (World Health Organization: WHO, 2020). The CDC and WHO observe chronic disease to have an insidious start, resulting from a combination of genetic, physiological, environmental and behavioral factors. The ineffectiveness of definitive diagnostic acute intervention for multi-variant manifestations of chronic disease is evidenced in the treatment of chronic vascular disease. Traditional therapy is initiated after an end-stage occurrence, such as angina, stroke or symptomatic peripheral vascular disease, and aims to lower LDL-c levels by statin therapy. This intervention lowered LDL-c levels and resulted in a mere average risk reduction of 30%. A preponderant degree of risk remains, begging the need for primary, secondary and tertiary prevention early in a patient's life to mitigate the occurrence of end-stage events (Mechanick, Farkouh, Newman, et al., 2020).

Management of cardiometabolic risk factors is a tactical approach to evaluate actionable targets for prevention. Insulin resistance and metabolic syndrome are the driving risk factors in the cardiometabolic chronic disease process (Mechanick, Farkouh, Newman, et al., 2020). Metabolic syndrome refers to coexisting conditions that indicate energy dysfunction and predispose a patient to additional health concerns. Diagnostic criteria includes: abdominal obesity, high blood pressure, impaired fasting glucose, high triglyceride levels and low HDL cholesterol (*Metabolic Sybndrome – Symptoms and Causes – Mayo Clinic*, 2021). The AHA diagnoses metabolic syndrome when a patient exhibits three or more of these criteria (*What Is Metabolic Syndrome,* 2023). In relation, insulin resistance, referred to as impaired fasting glucose within the diagnostic criteria of metabolic syndrome, is representative of the inefficient cellular response to the pancreatic release of insulin, the retort to elevated blood glucose levels. Given the driving risk factors, analysis of the specific mechanistic pathways that are early

primary drivers of disease will “expose actionable targets for prevention” to promote optimal patient outcomes (Mechanick, Farkouh, Newman, et al, 2020).

Presently, traditional therapeutic medicine views adiposity as the mechanistic antagonist to positive health outcomes and the perpetuator of metabolic syndrome and insulin resistance, resulting in cardiometabolic chronic disease. The perspective of fat driven disease is evidenced in medical literature and colloquially, through the widespread usage of the phrase *obesity epidemic* to refer to the widespread state of excess body fat (Mitchell, Catenacci, Wyatt & Hill, 2011). This fat-centric model is reinforced under the energy balance model (EBM) of obesity and the carbohydrate insulin model (CIM) of obesity, which both present a hypothesis as to the cause of fat accumulation. The energy balance model posits that adiposity is regulated by the brain in response to external signals from the food environment, which has been greatly altered due to the current hyper-palpable food environment; whereas, the carbohydrate insulin model suggests that a high intake of high glycemic foods perpetuates adiposity. Research conducted on the EBM and CIM of obesity display no conclusive research suggesting optimal patient outcomes, regarding decreased risk of cardiometabolic chronic disease. The evaluation of chronic disease from the lens of adiposity fails to address the root mechanistic pathway of energy metabolism and contradicts the functioning of our bodies (Katz, 2014). Excess adiposity is a symptom of dysfunctional skeletal muscle energy metabolism, not the primary determinant of disease. The hypothesis postulates that optimal patient outcomes, in relation to insulin resistance and metabolic syndrome, the leading risk factors associated with cardiometabolic disease, are related to therapeutic interventions that negate low muscle mass.

Methods

Foreground Research Question

Is low appendicular skeletal muscle mass independently associated with insulin resistance and/or metabolic syndrome?

Information Sources

A systematic review of the research resulted in acquisition of relative study data and supporting research related to the evaluation of skeletal muscle mass on the development of metabolic syndrome and insulin resistance. To complete the literature search, databases Health Source: Nursing, CINHAL and MEDLINE were searched. Primary articles were prioritized, but a select number of systematic reviews and meta-analyses were included and evaluated against the PRISMA checklist and designated search criteria. The PICOT question relies on macro-analysis of trending human data studies, alongside micro-analysis of physiological cellular function. Given the novelty of the muscle-centric perspective, there are limited studies highlighting the physiological cellular function in relation to skeletal muscle mass and metabolic syndrome or insulin resistance; therefore, a manual internet search and usage of select systematic reviews and meta-analyses, related to this topic, was deemed appropriate.

Search Strategy

Within Health Source: Nursing, CINHAL and MEDLINE, subject headings with Boolean operators were used to identify preliminary sources, including: "*skeletal muscle mass OR low muscle mass OR muscle strength and body mass index" AND "metabolic syndrome."* To ensure the search terms accurately addressed the focus of the PICOT question, *"metabolic syndrome"* was changed to *"insulin resistance"* during category search two. Search limiters were applied across all three databases, including: *full text, English language, peer-reviewed, journal article,*

publication date after 2018. A publication date prior to 2018 was considered for a select number of articles that met the following criteria: classical study and published after 2013.

Inclusion/Exclusion Criteria

Articles from Health Source: Nursing, CINHAL and MEDLINE that were representative of the search strategy received initial review. Prior to this initial review, these articles were pre-evaluated through search limiters. A secondary review evaluated if the key terms, which included "*skeletal muscle mass OR low muscle mass OR muscle strength and body mass index" AND "metabolic syndrome/insulin resistance,"* were in relation to chronic disease development or in the context of acute disease. Reflection on efficiency of inclusion/exclusion criteria revealed the need to include the Boolean operator NOT acute disease within the preliminary search of the three database sources. Following the secondary review, duplicate articles were removed. The remaining articles (n=21) were evaluated through a full text review against inclusion and exclusion criteria, rooted in PICOT question. Articles were included if (a) the research modeled a cohort study or cross-sectional data study or a classical meta-analysis, if (b) a unique population parameter was presented in the article OR the population studied was different from comparative literature sources (P), if (c) the research discussed "*skeletal muscle mass or low muscle mass or muscle strength independent and BMI"* in direct relation to the development of metabolic syndrome (I), if (d) the research discussed "*skeletal muscle mass or low muscle mass or muscle strength independent and BMI"* in direct relation to the development of insulin resistance (I), if (e) the cohort study or cross-sectional data study reflected a minimum of 5 anthropometric and vital measurements related to a comparative patient baseline (C), if (f) the research discussed prevalence and incidence of metabolic syndrome and insulin resistance (O) and if (e) a unique timeline parameter was present in the article OR the timeline included was

different from comparative literature sources (T). Articles were not included if (a) the research was a meta-analysis and systematic review (with the exception of novel classical reviews), if (b) the research did not directly discuss or study skeletal muscle mass or low muscle mass or muscle strength independent and BMI (I), if (c) the research prioritized additional outcomes, as compared to insulin resistance or metabolic syndrome (C) and if (d) the participants had a baseline of preexisting acute or chronic disease (O). It is important to note that articles relating adiposity to the development of metabolic disease and insulin resistance were noted, but excluded due to the research not directly discussing or studying skeletal muscle mass or low muscle mass or muscle strength independent and BMI.

Data Extraction

This systematic review contains information and data from the articles that were independently collected. Organization was facilitated by the primary author. The data extraction included: author, study location, study population, study type, study purpose and key findings. Extracted data is synthesized and depicted in Table 1.

Search Results

The outlined search strategy yielded 54 preliminary journal articles from Health Source: Nursing, MEDLINE Complete and CINHAL. The selection process of included studies is depicted by a PRISMA flow-diagram in Figure 1.

Figure 1

Selection Process of Included Studies

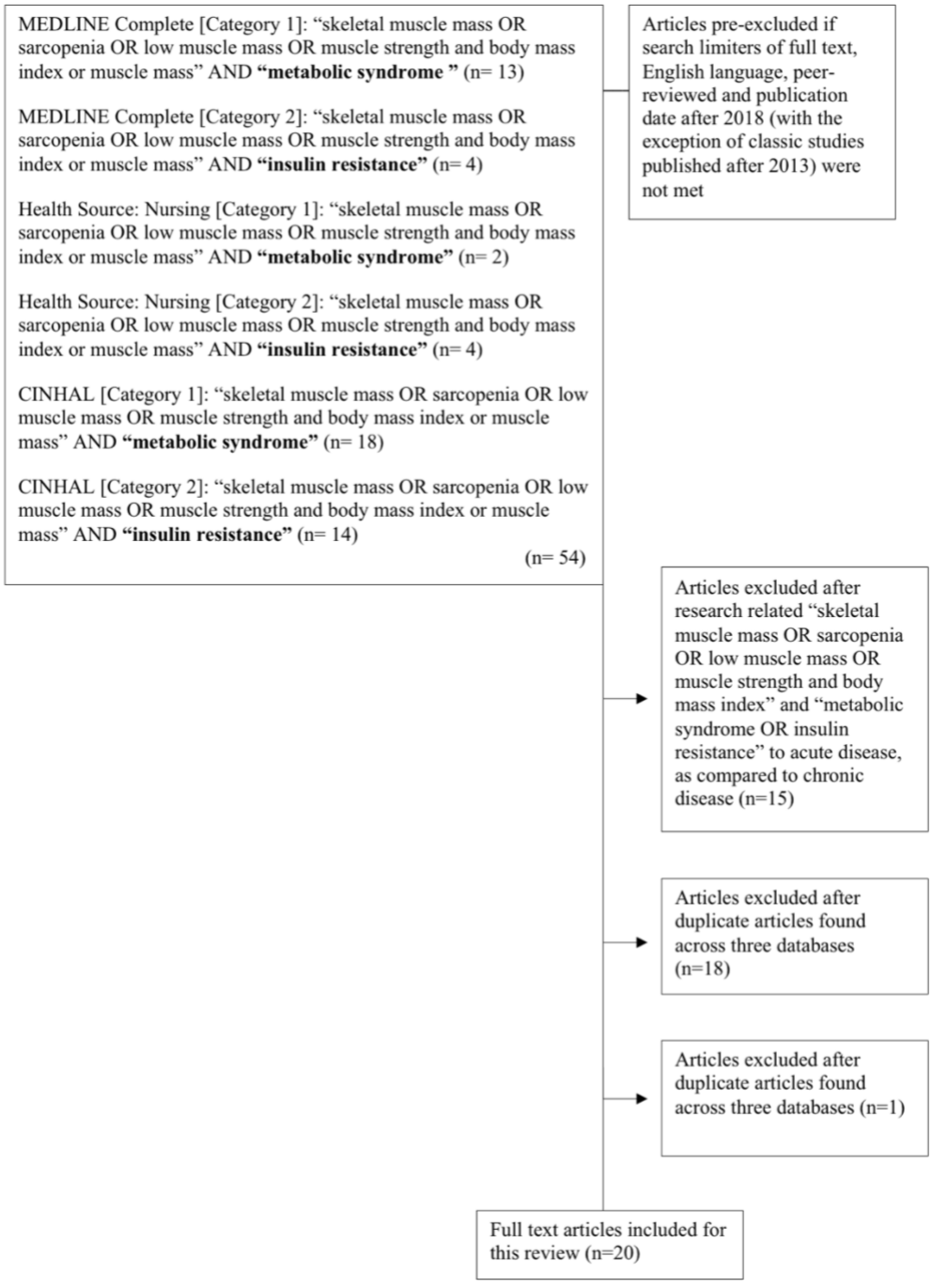

Table 1

Synthesis Table of Included Studies

Author(s)	Study Location	Study Population	Study Type	Study Purpose	Key Findings
Abbatecola, A.M., et al.	N/A	N/A	Peer-Reviewed Meta Analysis	"highlight potential steps involved in sarcopenia over aging, including potential steps involved in sarcopenia over aging, biomolecular mechanisms of insulin resistance on mitochondrial functioning"	Mitochondrial dysfunction is associated with insulin resistance Data promotes a direct role of insulin resistance pathways on mitochondrial dysfunction
Alemán-Mateo, H., et al.	Sonora, Mexico	147 participants older than 60 years	Cohort Study	"whether insulin resistance is associated with low relative appendicular skeletal muscle"	Adjustment for baseline physical activity increased the risk of developing low relative appendicular skeletal mass by 4.5 Low relative appendicular skeletal mass shows a significant association between insulin resistance
Buchanan, N., et al.	Berlin, Germany	1,402 subjects	Cross-Sectional Study	"identify the most suitable method to diagnose sarcopenia in a cohort wit ha high prevalence of metabolic risk factors and MetS"	Residual modeling approach seems to be more reliable to detect sarcopenia in MetS Residual modeling may be suitable to predict future risk

Chen, X., et al.	Guangxi Province, China	1,939 participants aged 50 years and older	Cross-Sectional Study	"examine the difference in the prevalence of osteosarcopenic obesity and hypertension"	Women with osteosarcopenic obesity have a higher risk for hypertension compared to women without osteosarcopenic obesity
Choe, H.J., et al.	Korea	1,515 participants	Cohort Study	"evaluate the effect of hyperglycemia and insulin resistance in the progression of sarcopenia in older adults with diabetes"	Development of diabetes mellitus was associated with a decline in appendicular skeletal muscle (ASM) and relative ASM to body mass index and height Decline of muscle mass indices was significantly greater in subjects with a higher insulin resistance assessment Muscle strength and function are not affected by insulin resistance
Kim, J.H., et al.	Korea	1,420 participants aged 12 to 19 years	Cross-Sectional Study	"assess the relationship between lean muscle mass and metabolic syndrome in Korean adolescents aged 12 to 19 years"	Adolescents with low muscle mass have a high risk of MetS
Kim, S.H., et al.	Korea	Korean elderly men older than 65 years	Cohort Study	"evaluate the interdependent immune-endocrine network in sarcopenia"	Sarcopenia was associated with the highest quartile of WMC counts and the highest quartile of serum vitamin D levels

Kim S.H., Kwon, H.S., & Hwang, H.J.,	Seoul, Republic of Korea	13,620 Korean participants	Cohort Study	"aimed to investigate the association between MetS and multiple body composition parameters, including obesity, visceral adiposity and sarcopenia"	In a healthy population who underwent routine health checkups, sarcopenia is significantly associated with MetS Undesirable body composition parameters increased risk for MetS from 0 to 3
Kwon, S.S., et al.	Korea	8,707 adults	Cross-Sectional Study	"examined the risk factors for IR, especially the effect of sarcopenia on IR"	Obese men with sarcopenia exhibited a significantly higher risk of IR than did obese, non-sarcopenic men Sarcopenia showed an additive effect on IR in the obese population
Lee, D.Y., & Shin, S.	Korea	8,363 participants	Cohort Study	"assessed the association between sarcopenia and metabolic syndrome in Korean adults aged over 50 years"	Both males and females showed a significantly higher prevalence of MetS in participants with sarcopenia
Lee, J.H., Kim, S.Y. & Kim, D.I.	Korea	3,189 Korean adult women	Cohort Study	"to investigate the effects of muscle strength […] on Metabolic syndrome (MetS) risk factors…"	"Low BMI & high muscle strength" had a significantly lower prevalence of MetS Waist circumference, triglycerides and fasting glucose were found to be significantly lower in the high muscle strength group HDL-C was significantly higher in the high muscle strength group

Liu, Z.J., & Zhu, C.F.	N/A	N/A	Peer-Reviewed Meta Analysis	"analysis of pathogenesis of sarcopenia, intrinsic relationship between sarcopenia and insulin resistance"	Insulin resistance and sarcopenia are mutually etiological Role of mitochondria in skeletal muscle in sarcopenia is dysfunctional
Merz, K.E., et al.	N/A	N/A	Peer-Reviewed Meta Analysis	"focus on the role of skeletal muscle in peripheral insulin resistance and the potential for skeletal-muscle targeted therapeutics to combat insulin resistance"	Insulin action on skeletal muscle is pivotal in metabolic homeostasis Resistance exercise improves mitochondrial function through mitochondrial elongation
Nomura, K., et al.	Tokyo, Japan	90 Japanese, female patients aged 65 years and older	Cross-Sectional Study	"aimed to examine the relationship between body composition and cardiovascular risk factors among women in older adulthood"	Lower muscle mass was independently associated with higher cardiovascular risk Negative correlation between appendicular skeletal muscle mass and MetS
Rodríguez-López, C. P., González-Torres, M.C., Cruz-Bautista, I., & Nájera-Medina, O.	Mexico	40 patients aged 18 and older	Cross-Sectional Study	"determine the relationship for visceral adipose tissue and skeletal muscle mass with MetS and resistin in patients with obesity"	Visceral adipose tissue is a main factor in triggering chronic inflammatory processes, alongside skeletal muscle mass and resistin

Rubio-Ruiz, M.E., et al.	N/A	N/A	Peer-Reviewed Meta Analysis	"to review the mechanisms underlying MetS-related sarcopenia"	Cycle between the loss of muscle and accumulation of intramuscular fat might be associated with MetS MetS-related sarcopenia has important health repercussions
Scott, D., et al.	Population based; Tasmanian Older Adult Cohort Study and Korean Sarcopenic Obesity Study	1,381 community dwelling adults with mean age 62 (Australian) and 58 years (Korean)	Cross-Sectional Study	"association of low muscle mass and metabolic syndrome in Asian and Caucasian middle-aged and older men and women"	Low absolute muscle mass is associated with significantly increased likelihood of MetS
Wu, S.E., & Chen, W.L.	Tri-Service General Hospital, Taiwan	6,476 eligible participants	Cohort Study	"examines whether the direction toward or away from lean muscle mass alters the risks of MetS"	Low muscle mass is associated with MetS Changes in metabolic indices are observable preceding a confirmed diagnosis of metabolic diseases
Yakout, S.M., et al.	Riyadh, Kingdom of Saudi Arabia	471 Arab men 20 to 77 years old	Cross-Sectional Study	"determine the prevalence of the coexistence of pre-sarcopenia, sarcopenia and MetS in Arab men"	Elevated glucose and dyslipidemia were the most common MetS risk factors among Arab men with pre-sarcopenia Obesity was also not a risk factor to pre-sarcopenia Lean mass exerts a greater effect than fat mass in regard to bone loss

Yamada, Yosuke, et al.	Tokyo, Japan	346 women aged 26 to 85 years old	Cohort Study	"to examine the association between ALM, leg muscle power, or percent body fat and MetS development"	Low muscular strength index […] was significantly associated with high MetS prevalence Account(ing) for the fat mass and fat-free mass relationship must be constructed

Results

Characteristics of Included Studies

Study Type. Twenty articles were included as a part of this systematic review. Sixteen of the included studies evaluated the relationship between relative muscle mass and the development of metabolic syndrome and insulin resistance through a primary lens; whereas, a selective four studies synthesized the biomolecular mechanisms of insulin resistance and metabolic syndrome in relation to muscle mass through a meta-analysis. All articles were included in the synthesis of information, as each source of information included data from an independent study. Of the primary resources, eight articles reflected data collected from a cohort study and eight articles reflected information collected from a cross-sectional study.

Study Population. The literature included a total of 49, 261 subjects, across eight different countries; including: Mexico, Germany, China, Korea, Japan, Australia, Taiwan and Saudi Arabia. Eight of the sixteen studies took place in Korea, the majority population synthesized in this literature review. This area of research is novel; therefore, related literature, not included within this synthesis, does not extend extensively beyond the countries included in this literature. In addition, population was not limited by constraints on years of age, gender or race. The present objective is to examine whether a trend exists independently of these constraints, hypothesizing a mechanistic approach to therapeutic intervention from the perspective of human physiology. With the publication of more extensive research, the objective may shift to accommodate specialization, to better understand the affect of skeletal muscle under the constraint of age, gender or race. Fifteen of the sixteen studies was reflected of data from adult populations; with one of the sixteen studies reflecting data from the adolescent population. Conceptually, studies can be organized by containing: 0 to 200 participants (small cohort), 200 to

1,000 participants (medium cohort), 1,000 to 5,000 participants (medium large cohort) and 5,000 to x > 5,000 participants (large cohort). Three studies can be categorized into the small cohort, as they contained greater constraints on age and gender. Two studies contained a medium cohort of participants. Six studies included a medium large cohort size; this population of individuals included a majority of individuals greater than 55 years of age. Four studies had a large cohort size. The large cohort studies had no constraints on age, gender or race; with the exception of the pre-existing exclusion related to geographical location.

Intervention. The methodology of the included cross-sectional and cohort studies did not reference intervention. Rather, data was collected observationally without lifestyle intervention. Currently, limited research relates to interventions promoting skeletal muscle mass and the effect on metabolic syndrome and insulin resistance.

Measures of Body Composition and Response Variable. The research reviewed included a primary and secondary patient assessment. Both assessments included the same patient evaluation, with the purpose of trending and analyzing patient data to appropriately address the PICOT question. The baseline data collection included: body composition (with dual x-ray absorptiometry), plasma glucose collection, serum insulin via radioimmunoassay, serum interleukin-6 and C-reactive protein, serum lipid profiles, vital signs, waist circumference, nutritional assessment and a lifestyle assessment. These metrics were consistent across the body of studies, allowing for a greater continuity between results. The response variable is appendicular skeletal muscle mass which was defined as the sum of the lean soft tissue masses of the arms and legs, assuming that all nonfat and non bone tissues were skeletal muscle. This variable was consistent across the body of studies. The collection of appendicular skeletal muscle mass was variable between the literature; dual-energy x-ray absorptiometry was the most

common tool used to evaluate skeletal muscle mass. Dual-energy x-ray absorptiometry is the most accurate metric to measure skeletal muscle mass presently, as no technology as been developed to directly assess muscle mass independent of other components of body composition.

Outcome Measurement: Metabolic Syndrome and Insulin Resistance. The selected articles relate to the affect of low muscle mass and the development of risk factors related to disease. To promote specificity and accuracy, the search criteria was deviated in two to target the specific outcome measurement. Fourteen articles were related to the development of metabolic syndrome. The classification of metabolic syndrome was defined by the AHA standards. The classification of metabolic syndrome was consistent across the literature. Six articles were related to the development of insulin resistance.

Confounding Variables. The literature included in this systematic review was most at risk for confounding variables related to multi-morbidity. Patients were screened prior to the study and not included if they presented with: sarcopenia, unstable body weight, physical dependence, level of consciousness concerns, hypertension, hypothyroidism (uncontrolled), dyslipidemia, generalized chronic disease (uncontrolled) and pre-metabolic syndrome (elevated fasting glucose). Therefore, all patients included in the literature were diagnostically healthily, by the standards of the primary researcher. It is important to note that a select cohort of studies included patients with obesity in the absence of metabolic syndrome or insulin resistance; therefore, they were presumed to be diagnostically healthy. The confounding variables were appropriately addressed in the study designs of the literature included. Statistical analyses were performed to independently address the relationship between appendicular skeletal muscle mass and insulin resistance. This method of data extraction occurred across each article.

Quality Assessment of Included Studies

The literature presented in this review was evaluated by the Critical Appraisal Skills Programmer (CASP), which intends to promote further evaluation of peer-reviewed journal articles. More specifically, the questions in this assessment prompted re-examination of the included articles to ensure accuracy of presented information. Table 2 presents the quality assessment related to the cross-sectional studies. Table 3 presents the quality assessment related to the cohort studies. Systematic reviews were evaluated against PRISMA checklist guidelines for quality assurance. The included articles appropriately met these guidelines.

Major Findings Assessment

Appendicular Skeletal Muscle Mass on Metabolic Syndrome. The literature consistently displayed an inverse relationship between appendicular muscle mass and the development of metabolic syndrome. Meaning, with an increase in appendicular muscle mass, the risk for the development of metabolic syndrome decreased. Kim, S.H., et al. (2021) found that as the number of diagnostic metabolic criteria were identified in the patient population, the percentage of relative appendicular skeletal muscle mass decreased. Furthermore, a significant association between appendicular skeletal muscle mass and metabolic syndrome was confirmed after multivariable adjustments for age, sex, underlying disease, smoking, alcohol intake and inflammatory markers (Kim, S.H., et al., 2021). Buchmann, N., et al. (2016) reflected that low appendicular lean mass, corrected for both height and weight, was associated with a higher metabolic load and impaired physical performance. The author notes that data could not be differentiated between primary, age-related sarcopenia, and secondary sarcopenia amongst study participants; meaning, a relationship exists between low appendicular lean mass and metabolic syndrome, but the data does not allow for a conclusion as to cause and effect. Kim, J.H. & Park,

Y.S. (2016) demonstrated that individuals with low muscle mass were more likely to be obese, have a higher systolic and diastolic BP and higher mean level of triglycerides, total cholesterol, fasting glucose and lower mean levels of HDL cholesterol. Metabolic syndrome was significantly higher in individuals with low lean muscle mass compared to those with a significant percentage of lean muscle mass. Furthermore, a logistic regression analysis was performed to adjust for potential covariates; the previous conclusion, that lean muscle mass is associated with metabolic syndrome, remained significant after adjusting for these variables. One unique component of this study included a relative nutritional assessment, which found that individuals with greater lean muscle mass consumed more protein than those with lower lean muscle mass, regardless of total energy intake. This observation suggests an opportunity for a therapeutic intervention related to supporting appendicular skeletal muscle mass through prioritization of protein intake, as compared to the current prioritization of lowering calories (Kim, J.H. & Park, Y.S., 2016). Lee, D.Y., & Shin, S. (2022) concluded that both male and females showed a significantly higher prevalence of metabolic syndrome if they presented with sarcopenia. The research presented by Lee, D.Y., & Shin, S. (2022) includes individuals above the age of 50; the researchers postulate that the driver of decreased muscle mass is older age. This suggests a target population for therapeutic interventions; meaning, therapeutic interventions reducing the risk of muscle loss should be preventatively implemented for adults over than 50. Nomura, K., et al. (2020) demonstrated that greater muscle mass is related to lower metabolic syndrome risk in older adult women. This study controlled for visceral fat mass. In addition, Nomura, K., et al.(2020) demonstrated that BMI was not significantly related to cardio-metabolic risk; rather, body composition, meaning the relationship between appendicular skeletal muscle mass and adiposity, is of greatest importance in determining metabolic risk. The research

presented by Scott, D., et al. (2016) concluded a similar result, in that low appendicular lean mass is associated with significantly increased likelihood of metabolic syndrome in adults; furthermore, low appendicular lean mass coexisting with a higher overall body mass has an even greater affect on metabolic syndrome. This suggests the need for more research related to sarcopenic obesity, low relative muscle mass in the context of excess adiposity. Wu, S.E., & Chen, W.L. (2021) reflected that as a patient transitions toward a state of lower muscle mass deterioration of metabolic indices occurred which was demonstrated through an increasing hazard ratio for metabolic syndrome, hypertension and type 2 diabetes mellitus. Yakout, S.M., et al. (2019) concluded that pre-sarcopenia and metabolic syndrome have a unique cardio-metabolic profile that increases the patients risk of all cause mortality. This study demonstrates the long-spanning effect of low-muscle mass and suggests a need for further research to determine risk associated with pre-sarcopenia. Conversely, one study demonstrated a positive correlation between appendicular lean muscle mass and metabolic syndrome, meaning as muscle mass increases, the risk for metabolic syndrome increases (Yamada, Y., et al., 2022). However, the researchers accounted for appendicular lean muscle mass related to height, which is not a diagnostically appropriate tool to evaluate the variable of appendicular skeletal muscle mass (Yamada, Y., et al., 2022). This study was highlighted in the CASP quality assessment, due to question of accuracy in data analysis and was included to highlight the importance of accurate and consistent metrics to analyze body composition, specifically appendicular lean mass.

Furthermore, Rubio-Ruiz, M.E., et al. (2019) presented a meta-analysis which postulates the cause for the rising prevalence of metabolic syndrome. These researchers conclude that the loss of muscle and accumulation of intramuscular fat, perpetuating insulin resistance, may be associated with metabolic syndrome in accordance with covariants including: nutritional intake,

physical activity, body fat, oxidative stress, pro inflammatory cytokines, insulin resistance and mitochondrial dysfunction. They also reflects that the lack of medical therapeutic intervention for sarcopenia perpetuates the incidence of metabolic syndrome in all generalized populations. The summation of this literature is a correlative relationship between skeletal muscle mass and the development of metabolic dysfunction.

Appendicular Skeletal Muscle Mass on Insulin Resistance. Alemán-Mateo, H., et al. (2014) conclude that insulin resistance was independently associated with low relative appendicular skeletal muscle mass, as the study accounted for covariates. Sex had no significant effect on the incidence. Given that limited research exists in analyzing the macro-relationship between skeletal muscle mass and insulin resistance, secondary sources were included to analyze the micro-relationship, involving the cellular physiology of skeletal muscle, in relation to insulin dysfunction. The meta-analysis presented by Liu, Z.J. & Zhu, C.F. (2023) reflected that the correlation between insulin resistance and sarcopenia will soon become a priority of research, a pivot from traditional perspectives. Both can be mutually etiological and result in a vicious cycle. The researchers highlighted that pathogenetic mechanisms have been identified that enrich the relationship between both diseases. Furthermore, the human data that has been collected in relation to both diseases suggest a relationship; however, the current information is insufficient to explain the direct pathogenesis, as either mechanism interacts to induce further deterioration (Liu & Zu, 2021). Merz, K.E., et al. (2022) conclude that insulin action in skeletal muscle is an important target in generating therapeutics that combat primarily insulin resistance, as a primary determinant of metabolic disease. This systematic review highlights mitochondrial dysfunction as a large driver of disease. Skeletal muscle has a high mitochondrial density, secondary to the heart. Thus, these researchers postulate the therapeutic potential of resistance exercise to promote

mitochondrial optimization, which inadvertently promotes skeletal muscle which is consistent with the findings presented by Abbatecola, A.M., et al. (2011).

Sarcopenic Obesity. A select number of studies reflected that sarcopenia in the presence of obesity resulted in the most significant risk for the development of insulin resistance and metabolic syndrome (Kwon, S.S., et al., 2017; Chen, X., et al., 2019). This was consistent regardless of sex and reflect the vicious cycle that exists within the development of chronic disease.

Role of Muscle Strength and Muscle Function. Choe, H.J., et al. (2020) included the variable of muscle strength and function. This study concluded that muscle strength and function does not affect the development of metabolic syndrome. This conclusion was reinforced by Lee, J.H., Kim, S.Y., & Kim, D.I. (2022) and emphasizes the need for the target of therapeutic intervention which prioritizes the quality and size of skeletal muscle mass, rather than strength.

Inflammatory Process: Adipose Tissue and Skeletal Muscle. Skeletal muscle is an important factor within inflammatory regulation. Kim, S.H., et al. (2021) found that pro-inflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha are associated with sarcopenia. In addition, the sarcopenia group had higher C-reactive protein levels than the non-sarcopenia group. Furthermore, Rodriguez-Lopez, C.P., et al. (2019) demonstrated that post-sarcopenic accumulation of visceral adipose tissue is a main factor in triggering the chronic inflammatory process. Meaning through the degradation of skeletal muscle which is foundationally inflammatory, the accumulation of visceral adipose tissue compounds to promote further inflammation. Similarly, Kim, S.H., Kwon, H.S., & Hwang, H. Choe, H.J., et al. (2017) reflected that the most important affect from their study was the basis it provided for further studies related to the complex immune-endocrine network for sarcopenia

Table 2

Quality Assessment: CASP Cohort Study

	Alemán-Mateo, H., et al.	Chloe, H.J., et al.	Kim, S.H., et al.	Kim S. H., Kwon, H. S., & Hwang, H. J.	Lee, D. Y., & Shin, S.	Lee, J. H., Kim, S. Y. & Kim, D. I.	Wu, S.-E., & Chen, W.-L.	Yamada, Yosuke, et al.
Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the exposure accurately measured to minimize bias?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Was the outcome accurately measured to minimize bias?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Have the authors identified all important confounding factors? Have they taken account of the confounding factors in the design and/or analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Was the follow up of subjects complete enough? Was the follow up of subjects long enough?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are the results precise?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Do you believe the results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Can the results be applied to the local population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Do the results of this study fit with other available evidence?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Table 2

Quality Assessment: CASP Cohort Study.

	Buchanan, N., et al.	Chen, X., et al.	Kim, J. H., et al.	Kwon, S. S., et al.	Nomura, K., et al.	Yakout, S. M., et al.
Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes	Yes
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes	Yes	Yes
Was the exposure accurately measured to minimize bias?	Yes	Yes	Yes	Yes	Yes	Yes
Was the outcome accurately measured to minimize bias?	Yes	Yes	Yes	Yes	Yes	Yes
Have the authors identified all important confounding factors? Have they taken account of the confounding factors in the design and/or analysis?	Yes	Yes	Yes	Yes	Yes	Yes
Was the follow up of subjects complete enough? Was the follow up of subjects long enough?	Yes	Yes	Yes	Yes	Yes	Yes
Are the results precise?	Yes	Yes	Yes	Yes	Yes	Yes
Do you believe the results?	Yes	Yes	Yes	Yes	Yes	Yes
Can the results be applied to the local population?	Yes	Yes	Yes	Yes	Yes	Yes
Do the results of this study fit with other available evidence?	Yes	Yes	Yes	Yes	Yes	Yes

Discussion

Limitations

Limitations of Included Studies. The variability of geographic location and population across this literature review is not a limitation and rather, contributes to generalizability of the hypothesized physiological mechanism of skeletal muscle mass. With the foundation of literature that exists, there is a platform to continue researching across a more specified range of geographic populations. Given this variability, the population assessed is appropriate and reflective of the PICOT question, which prioritizes the mechanistic property of metabolic dysfunction, independent of covariant factors. Though the foundation of this study is appropriate, the most significant limitation relates to the assessment tools evaluating the density of skeletal muscle. Bioelectrical impedance, dual x-ray absorptiometry, CT and MRI are the current forms of body composition analysis. However, no gold standard for the independent assessment of skeletal muscle mass density exists. Therefore, the assessment of sarcopenia is tampered by limitations intrinsic to the assessment tool. This is significant, because the variable diagnostic criteria of sarcopenia may have variable consequences on the outlined conclusion, altering the relationship between skeletal muscle mass and the development of insulin resistance and metabolic syndrome. Given the significance of the results within the select studies, a margin of error with the assessment tool may not have a significant affect on the conclusion. However, this limitation must be considered when evaluating appropriate therapeutic interventions and prioritized within future research. The shortcomings of this assessment tool also reflect the novelty of the muscle-centric perspective and changing demand of present research.

Bias of Included Studies. The studies included underwent a quality and bias-risk assessment. Each study was at risk for bias related to the non-randomized population.

Limitations of Review. This review was restricted to research articles available to the University of Arkansas. The author of this review has no conflicts of interest.

Bias of Review. Selective reporting bias is a risk within this literature review as a result of including all studies that evaluated or reported on the PICOT question, in any generalized capacity, due to the limited article selection. This does not reflect the studies intended purpose.

Gaps in Literature

Controversy in Literature. Traditional medical literature approaches chronic disease from the lens of adipose-centric medicine. Therefore, the perspective of therapeutic interventions related to skeletal muscle are less widely discussed. The addition of a quality assessment when analyzing the literature was essential to ensure the motive of the article was relative to the stated PICOT question. Limited controversy exists due to the large gap and need for additional research that independently prioritizes skeletal muscle. The consistency displayed within the current literature emphasizes the importance of further research and the demand for altering the traditional perspective associated with chronic disease.

Implication for Nursing Practice. Given the prevalence of chronic disease, the nursing profession and leadership implicitly hold a large responsibility to promote therapeutic evidence-based care. This responsibility starts with advocacy in educational guidelines. Current psychical activity guidelines recommend 150 minutes of moderate-intensity aerobic activity and muscle-strengthening activities two days a week. The CDC claims that more profound health benefits will be achieved by increasing moderate-intensity aerobic activity beyond 150 minutes per week (*Chronic Conditions | CMS*, n. d.). Furthermore, the Department of Health and Human Services (HHS) and Agriculture (USDA) promote dietary guidelines every five years, outlining optimal nutritional choices. This document outlines four central themes regarding nutritional intake:

follow a healthy dietary pattern throughout every life stage, customize to personal values and customs, consume nutrient-dense foods within calorie limits and limit foods with added sugar, saturated fat, sodium and alcohol (*Home | Dietary Guidelines for Americans*, n.d.). The lack of effectiveness and the poor adherence to these behaviors is evidenced by data from the National Health Interview Survey, which reflects that only 24.2% of adults older than 18 years met the 2018 physical activity guidelines (*Chronic Conditions | CMS*, n. d.). Despite the cyclical reintroduction of exercise and nutritional guidelines, adherence remains low and the rates of chronic disease continue to increase.

This concern is multifaceted. From a neurophysiological perspective, this education is contributing to cognitive overload and information paralysis (Peng et al., 2021). The information presented in the *Physical Activity Guidelines for Americans: 2nd Edition* and *Make Every Bite Count with the Dietary Guidelines* totals 282 pages. Given the prevalence of chronic disease across all communities, it is clear that the habits and goals outlined in these guidelines are not intrinsic to human behavior, given the societal lifestyle adopted by the majority. Thus, to adopt these habits, an individual's decision making process' must be utilized. When information exceeds a consumers decision processing capability, decision's will be of lower quality and experience, as evidenced by the underlying neural circuitry. Consumers will utilize less attentional resources when faced with large amounts of information, as compared to those faced with small amounts of information, resulting in decision difficulty and inefficiency (Peng et al., 2021). The information outlined in these guidelines is inefficient in providing concise and consistent education. To perpetuate this concern, most people report a persistent feeling of time poverty, meaning too many tasks and not enough time, signaling a baseline of stress and overwhelm (Giurge et al., 2020). Stress limits the ability to make novel decisions and adapt to

change. There is a strong need to change the educational strategy to overcome the inherent determinants to successful behavior change, in relation to nutrition and exercise. Furthermore, when observing the present guidelines from a psychological perspective, the goal-driven guidelines are vague. Studies consistently demonstrate that effective goal setting is related to specificity and identity-consistent behaviors (Berkman, 2018). Though the guidelines include nonspecific information to promote identify-consistent behaviors, the lack of specificity and the foundational educational deficit in understanding the mechanistic component of nutrition and exercise is a barrier to empowering individuals within their personal preferences, cultural traditions and socioeconomic position. Furthermore, the nutritional guidelines emphasize a limit-based approach to nutrition, as evidenced by the emphasis on staying within calorie limits and limiting certain food groups. The literature consistently demonstrates that self-imposed dieting and food restriction as the strategy for weight loss appears to result in binge eating, preoccupation with food, increasing emotional responsiveness and distractibility (Polivy, 1996). Binge eating disorder is the most common eating disorder in the United States and over 54% of the United States population reported struggling with emotional eating; these statistics call attention to the need to integrate psychology into nutritional education (Polivy, 1996).

Most importantly, the information presented within the nutritional and exercise guidelines is inconsistent with the root mechanistic pathway of metabolic syndrome, the driving risk factor of cardiometabolic disease, a preventable chronic disease. The literature consistently supports the claim that low appendicular skeletal muscle mass is independently associated with the development of all diagnostic criteria of metabolic syndrome, including insulin resistance. More broadly, the literature, also, concludes that low muscle mass is independently associated with elevated risk of all-cause mortality (Wang et al., 2019). Despite the clarity of this research,

the nutritional and exercise guidelines do not prioritize skeletal muscle. The dietary guidelines advise consumption of 5.5 ounces of variable protein sources per day (*Home | Dietary Guidelines for Americans*, n.d.). Given this guideline, the maximum amount of protein an individual would consume in a day would be 48g, if the client were to only consume lean chicken breast. Research consistently demonstrates that consumption of 2.2g per kg of lean body mass is supportive for muscle hypertrophy and tissue integrity, as well as protective against sarcopenia in older adults (Bazer, 2016). Conceptually, the average lean body mass of a five year old is between 34 and 50 pounds; it is appropriate to conclude that the nutritional guideline for protein intake is blatantly inappropriate for the adult population. Furthermore, the mammalian target of rapamycin (m-TOR) signaling pathway is activated within skeletal muscle at the threshold of 2.5g of leucine, an amino acid most prevalently found within animal protein (D'Hulst et al., 2020). The dietary guidelines suggests consistent balance of nutrients across three meals (*Home | Dietary Guidelines for Americans*, n.d.). Referring back to the individual with a daily intake of 48g of protein from lean chicken breast, meaning 16g or 0.6 ounces of protein per meal, the ingestion of leucine would be 0.46g of leucine, a negligent value in activating m-TOR to promote skeletal muscle (D'Hulst et al., 2020). Thus, these guidelines consistently fail to promote skeletal muscle in any adult population. It is important to note that some misconceptions exist that protein-consumption is related to cancer. However, this conclusion is incongruent with the action of m-TOR within the body. The signaling pathway of m-TOR exists in every tissue within the body and the activation is variably sensitive. Chronic stimulation of m-TOR is a concern for those with cancer; however, in most tissues, m-TOR is activated by excess consumption of calories, carbohydrates and insulin. However, within muscle tissue, m-TOR is selectively sensitive to amino acids only (D'Hulst et al., 2020). Therefore, this

conclusion is incongruent and also, not evidenced in any clinical research trial. From this evidenced-based research, nutritional education can be promoted in a concise and specific manner; emphasis on total protein intake relative to lean body mass and intake of sufficient protein per meal, twenty-five to thirty grams, are crucial therapeutic interventions for health promotion and disease prevention. Education framed from this perspective is empowering; instead of promoting restriction and limitation of food groups, the focus is on encouraging sufficient and consistent daily protein intake. In addition, protein is the most effective food macronutrient in satiation, thus this education implicitly encourages an individual to become more a-tune to their inner satiety cues to regulate their food intake, without a self-limiting mindset. In addition, this education highlights a more specific and attainable nutritional goal, while allowing for cultural, personal preference and budget considerations. For example, though the amino acid profile and complimentary profiles of creatinine, taurine and iron of animal based proteins are more efficient in promoting muscle mass, supplementation of branch-chain amino acids is an appropriate solution for individuals who cultural elect to follow a vegan or vegetarian-based diet (D'Hulst et al., 2020). To approach the current exercise guidelines, the current psychical activity guidelines recommend 150 minutes of moderate-intensity aerobic activity and muscle-strengthening activities two days a week. These guidelines emphasize aerobic activity as the driver of health promotion (*Chronic Conditions* | CMS, n.d.). In addition, the outline for muscle-strengthening activity lacks specificity, which is not advantageous for a population that is uneducated about exercise science. The consistently in research relates to total lean body mass; therefore, training strategies should be related to resistance based movements against force that promote usage of more-than one muscle group. Referring back to the perspective of time poverty, implementation of exercise must be considerate of individual

responsibilities, to promote efficiency and consistency. To complement both of these needs, compound-based resistance exercises are most efficient in targeting this goal (Ralston et al., 2018). Given the foundation of evidence-based research that exists, a more actionable and specific guideline for resistance-based exercise can be developed that prioritizes the importance of skeletal muscle mass. Nursing practice is central to chronic disease prevention; re-evaluation of current educational guidelines is crucial to empowering definitive change with lifestyle intervention.

Conclusion

Founding director of Yale University's Prevention Research Center, reflects, "But the blame […] resides not within bodies that work as they ever did, but all around, with the collective actions of the body politic" (Katz, 2014, pg. 1). The obesogenic model of chronic disease intervention postulates that excess adiposity, obesity, is the driver of insulin resistance and metabolic syndrome, the two leading risk factors in the development of cardio-metabolic disease. This model inherently encapsulates blame, as highlighted by Katz. The leading research question of this review proposes a transformation in the lens of chronic disease intervention, postulating skeletal muscle mass as a driver in the prevention of metabolic syndrome and insulin resistance. The literature supports this hypothesis through the consistent demonstration that low appendicular skeletal muscle mass was independently associated with the development of all diagnostic criteria of metabolic syndrome, including insulin resistance. The call to action is blatant in the epidemiology data and anecdotal telling of disease and disability; medical professionals and its leadership are confronted with the responsibility of rebuilding a practice and healthcare model that more appropriately meets the needs of patients with chronic illness. This perspective aims at mediating chronic disease with muscle.

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