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Sarcopenia, Sarcopenic Obesity and Insulin Resistance

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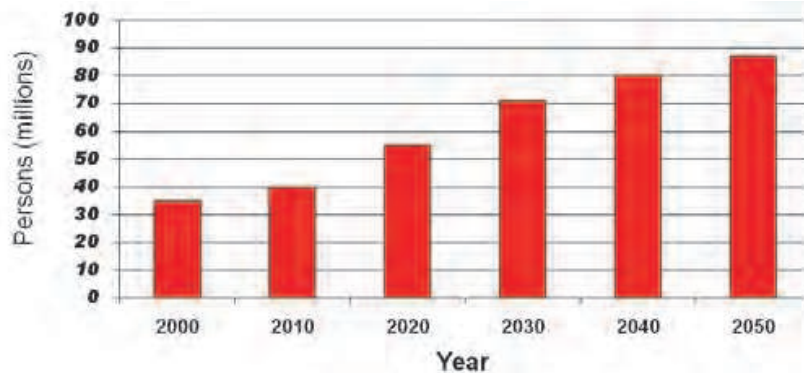
²*Italy*

1. Introduction

The number of people greater than 65 years old will increase from 35.9 million in 2003 (12.4%) to 71.5 million (20%) by the year 2030. Current estimates in the United States demonstrate that this population is numbered at 39.6 million, representing 12.6% of the population, or one in every eight Americans. Women tend to outnumber men and their life expectancy is undoubtedly longer. These numbers reflect predominantly the influx of baby boomers into this age group (Spillman and Lubitz 2000).

Since the early part of 1900, the elderly age group has nearly tripled from 4.1% in 1900 to 12.9% in 2009, and the number of individuals has increased over thirteen times (from 3.1 to 39.6 million). The 'old old', persons aged >80 are one of the fastest growing segments of the population (A Profile of Older Americans 2010). In addition, life expectancy in the elderly has been increasing in the past few decades and continues to do so (Lubitz et al. 2003). For instance, those reaching the age of 65 years, had a mean life expectancy of 19.9 and 17.2 years, respectively, for females and males. Framed alternatively, life expectancy at birth in 2007 was 77.9 years, approximately 30 years longer than a child born in 1900. Compounded with a reduced death rate due to medical advances, patients are living longer than they previously were, much of this due to improved survival from cardiovascular and cerebrovascular diseases (Ford et al. 2007). Figure #1 demonstrates data on the aging population in the United States, and Figure #2 demonstrates estimates from worldwide figures.

In a report published by the Organisation for Economic Co-operation and Development (OECD) in 2007, these trends observed in the United States are paralleled elsewhere. In certain countries, specifically Italy and Japan, one out of every five people is aged 65+ (Trends in Severe Disability Among Elderly People: Assessing the Evidence in 12 OECD Countries and the Future Implications 2007). As in the United States, Table #1 illustrates the proportion of people that will be 85+, which is the fastest growing segment of the population. Understandably these are worrisome trends as these individuals are, from a public health standpoint, the ones with the most number of chronic conditions, disabilities and greatest long-term care needs. It is believed that unless there are significant improvements in functional awareness and improvement, this group poses the largest burden on existing healthcare resources.



Data obtained from the US Census Bureau from the year 2000. www.census.gov

Fig. 1. Projected Elderly Population of the United States: 2000-2050

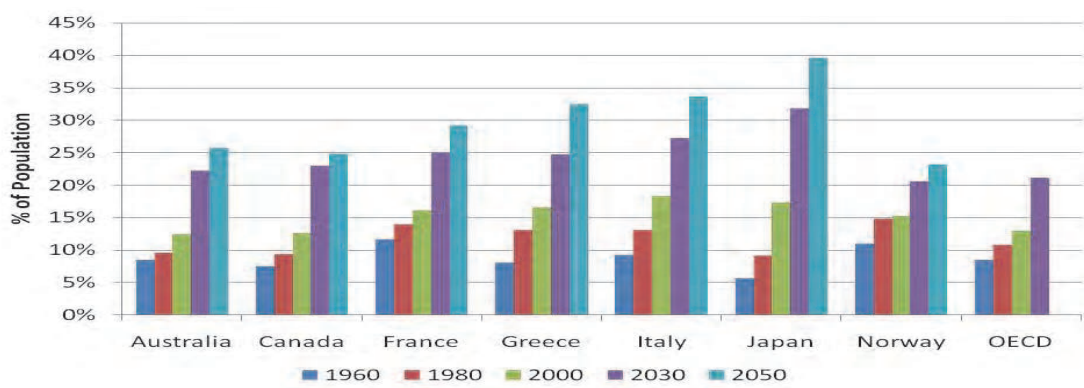


Fig. 2. Population in OECD Countries of Elderly >65 years old. Proportion of People >65 years old in a sample of Organisation for Economic Co-operation and Development (OECD) countries from 1960 to projects at 2050. Lafortune, G. and G. Balestat (2007), "Trends in Severe Disability Among Elderly People: Assessing the Evidence in 12 OECD Countries and the Future Implications", OECD Health Working Papers, No. 26, <http://dx.doi.org/10.1787/217072070078>

| Country | 1960 | 1980 | 2000 | 2030 | 2050 |
|-----------|------|------|------|------|------|
| Australia | 0.4 | 0.7 | 1.3 | 3.2 | 5.7 |
| Canada | 0.4 | 0.8 | 1.3 | 2.7 | 5.8 |
| France | 0.7 | 1.1 | 2.1 | 3.8 | 7.6 |
| Greece | 0.4 | 0.9 | 1.3 | 2.9 | 4.9 |
| Italy | 0.5 | 0.8 | 2.1 | 4.7 | 7.9 |
| Japan | 0.2 | 0.5 | 1.8 | 7.4 | 10.2 |
| Norway | 0.7 | 1.1 | 1.9 | 2.6 | 4.5 |
| OECD | 0.4 | 0.7 | 1.4 | 3.0 | 5.2 |

Table 1. Proportion of Patients Aged >85 years in OECD Countries. All numbers in the table above are percentages Lafortune, G. and G. Balestat (2007), "Trends in Severe Disability Among Elderly People: Assessing the Evidence in 12 OECD Countries and the Future Implications", OECD Health Working Papers, No. 26, <http://dx.doi.org/10.1787/217072070078>

2. Health needs as one gets older

As patients age, health needs escalate, resulting in disproportionate consumption of health care resources (Lakdawalla, Goldman, and Shang 2005). According to a 1995 US Bureau of Census publication, approximately 80% of >65 year olds will have a minimum of one chronic medical illness, with many suffering multiple. A number of elderly subjects report a type of disability, including hearing impairment, visual impairment, cognitive impairment, self-care troubles, or needing higher level of care. A number of studies have demonstrated the impact of aging on disability. An early study by Vita et al (Vita et al. 1998) studied 1,741 university alumni, first surveyed in 1962 (mean age 43 years) and then annually in 1986. Cumulative disability was determined using a health-assessment questionnaire. Those with high health risks at baseline had earlier onset of disability and had a lower follow-up disability index. The onset of disability was postponed by more than 5 years in the low-risk subject group than those with high risk behaviors. Predictors of subsequent disability included smoking, body mass index and exercise patterns in midlife and late-adulthood. These authors concluded that although disability is inevitable, the time frame was compressed into fewer years at the end of life.

In one study the number of geriatric conditions was related to dependency in activities of daily living (Cigolle et al. 2007). These authors used data from the Health and Retirement study survey administered in 2000 on subjects >65 years (n=11,093) residing either in the community or in nursing homes, and assessed the number of geriatric syndromes and dependency of activities of daily living (ADL)s. Of those >65 years, ~49.9% had at least one geriatric syndrome, prevalence rates that were as common as heart disease and diabetes. After adjusting for demographic characteristics and chronic diseases, the risk ratio for dependence on ADLs were 2.1 [95%CI: 1.9-2.4] for one geriatric condition, 3.6 [3.1-4.1] for two conditions, and 6.6 [5.6-7.6] for greater than 3 conditions. This important study highlights the similar prevalences of geriatric conditions to chronic diseases in elderly adults and their strong association to disability. As the authors note, these are often overlooked in the care of older adults. One's reported disability increases with age. In a study by the Administration on Aging in the United States, approximately 56% of persons >80years reported a severe disability and 29% reported the need for some type of assistance (A Profile of Older Americans 2010). This is of course impairs one self-reported health status and may lead to institutionalization.

3. Muscle changes with aging – Sarcopenia

As one ages, there are changes in body composition. As patients age, there is a reduction in lean mass and a progressive increase in fat mass. This normally occurs after the age of 20-30 years and can be extensive, involving up to 40% of a population (Baumgartner et al. 1995; Flynn et al. 1989; Gallagher et al. 1997; Muller et al. 1996). As is demonstrated in Figure #3, maximal fat free mass (muscle mass) is usually reached at about 20 years of age and fat mass peaks at the ages between 60 and 70 years (Baumgartner et al. 1995; Gallagher et al. 1997). Particularly after the age of 70 years, there is a redistribution of body fat and fat free mass, with reductions in peripheral skeletal muscle (Beaufriere and Morio 2000), increases in intramuscular and intrahepatic fat, both of which are associated with insulin resistance (Cree et al. 2004).

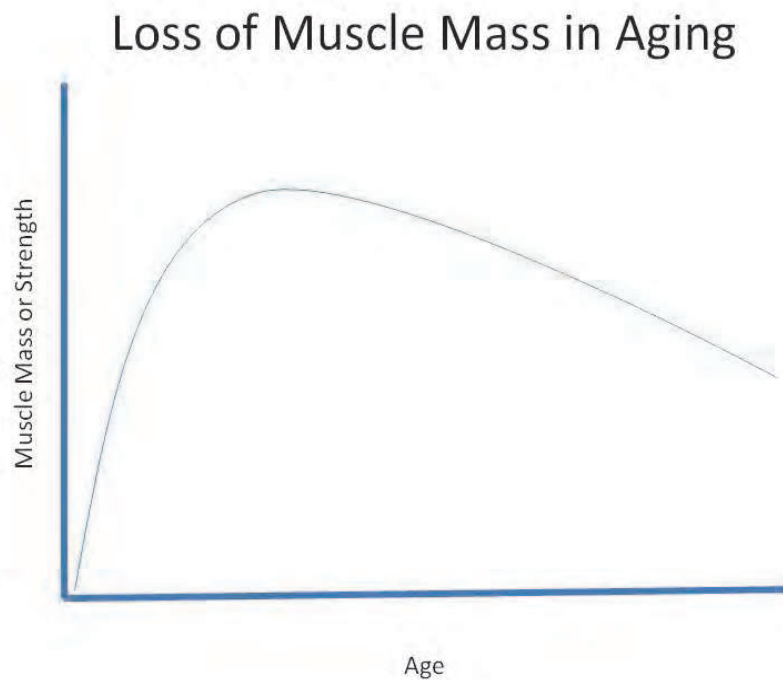


Fig. 3. Muscle Mass Changes with Aging.

Peak muscle mass occurs between the ages of 20 and 30 years, and naturally declines as one ages.

Declining function parallels the concept of sarcopenia. Sarcopenia comes from the Greek word, "Sarcos" meaning flesh, and 'penia' meaning lack of. This age-related decline in lean body mass can affect ambulation, mobility, and functional independence (Morley et al. 2001). An analogy often used is the age-related decline in bone mass, where, once it reaches a critical level, one's risk of fracture is increased. Sarcopenia can be conceptualized on the spectrum of frailty and disability and has been shown to be increasingly prevalent with age. More recently, the concept of declining strength has been incorporated into the definition, although, a widely accepted definition of sarcopenia has yet to be established (Cruz-Jentoft et al. 2010)). Sarcopenia indeed can be considered a geriatric syndrome. These are common, complex and costly entities of impaired health in elderly individuals which involve multiple systems, have a myriad of interactions, and have varied phenotypes. Falls, urinary incontinence and delirium are but some examples of such. Sarcopenia has also been associated with malnutrition and diminished physical function, both of which are associated with geriatric functional decline and mortality. The loss of muscle mass during the aging process is important clinically as it reduces strength and exercise capacity, both which are needed to perform one's activity of daily living. It is hypothesized that subjects reach a given threshold at which impairment in function occurs. Absolute loss of muscle mass leads to reduced muscle function and hence physical performance measures are increasingly being used in the definition and identification of sarcopenia. There are a number of definitions outlined in the literature making standardization, particularly in clinical practice, rather difficult (Baumgartner et al. 1998; Bouchard, Dionne, and Brochu 2009; Davison et al. 2002; Zoico et al. 2004) . Prevalence rates can vary dramatically and is the subject of current investigation. This syndrome has a number of risk factors, a number that are

modifiable over the course of one's life span, but can have profound impact on one's overall state of health and quality of life.

The trajectory of one's muscle loss can be altered by physical exercise and/or the environment. Muscle mass develops up to the age of 20 and 30 years, and is relatively maintained throughout adult life. As one ages, muscle mass decreases and one reaches a threshold whereby low muscle mass will inevitably lead to disability and future complications (Sayer et al. 2008).

Assessing sarcopenia has been a challenge in the research literature. There are a number of definitions that have been proposed, yet they have been developed on different populations and ethnicities, factors which are known to affect body composition. Additionally, muscle quality and strength have yet to be incorporated into such definitions. Recently, there was a European consensus on the definition and diagnosis on Sarcopenia (Cruz-Jentoft et al. 2011). This taskforce suggested the use of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia. The rationale for using these criteria include that muscle mass and muscle strength are not directly correlated to each other (Goodpaster et al. 2006; Janssen et al. 2004). DEXA scanning is unique in that it not only allows ascertainment of muscle mass but can be used concurrently to assess bone density as well. Bioelectrical impedance on the other hand is inexpensive, and easily reproducible with prediction equations available to calculate various measures of body composition (Chumlea et al. 2002) and has been considered as a portable alternative to DEXA. Body water can affect these results, though, and elders' changes in body composition, both in health and disease, may affect such estimates. Unfortunately, the relative availability and cost of DEXA in particular can be prohibitively expensive, not portable, and would be impractical to use for routine use in an office setting (Chien, Kuo, and Wu 2010). Other measures, including grip strength, knee strength, or gait speed have been proposed but no studies have validated such measures. Figure #4 (Cruz-Jentoft et al. 2011) illustrates the proposed mechanisms of sarcopenia. These vary over one's lifespan and are impacted by each other, with interactions that are poorly understood.

4. Aging and obesity

Along with the rise in the number of elderly patients, the number of patients diagnosed with overweight and obesity are increasing. Obesity is defined by the World Health Organization (WHO) as a body mass index (BMI) greater than or equal to over 30kg/m², calculated as the body weight in kilograms divided by the height in meters squared (Quetelet 1871). Little attention has been given to the obese elder, largely due to a paucity of studies including elderly (>65 years old) patients. Yet, current estimates, specifically in the United States population, indicate that the prevalence of obesity continues to rise, and exceeds 35% of the general population, a trend that is also observed in elderly subjects. The prevalence of obesity has increased almost three-fold from 1960-2008, and continues to rise at a frightening rate (Flegal et al. 2011). Latest estimates illustrate by using body mass index as a surrogate for obesity estimates, that 33.6% of women and 37.1% of males are classified as having obesity over the age of 60years (Flegal et al. 2010). These numbers are remarkably higher than estimates in 1999 whereby 31.8% of males were obese, yet prevalence estimates seem to be similar in females. However, trends demonstrate rises in

prevalence rates, in particular subjects with morbid obesity (BMI >40kg/m²). Figure #5 illustrates these trends.

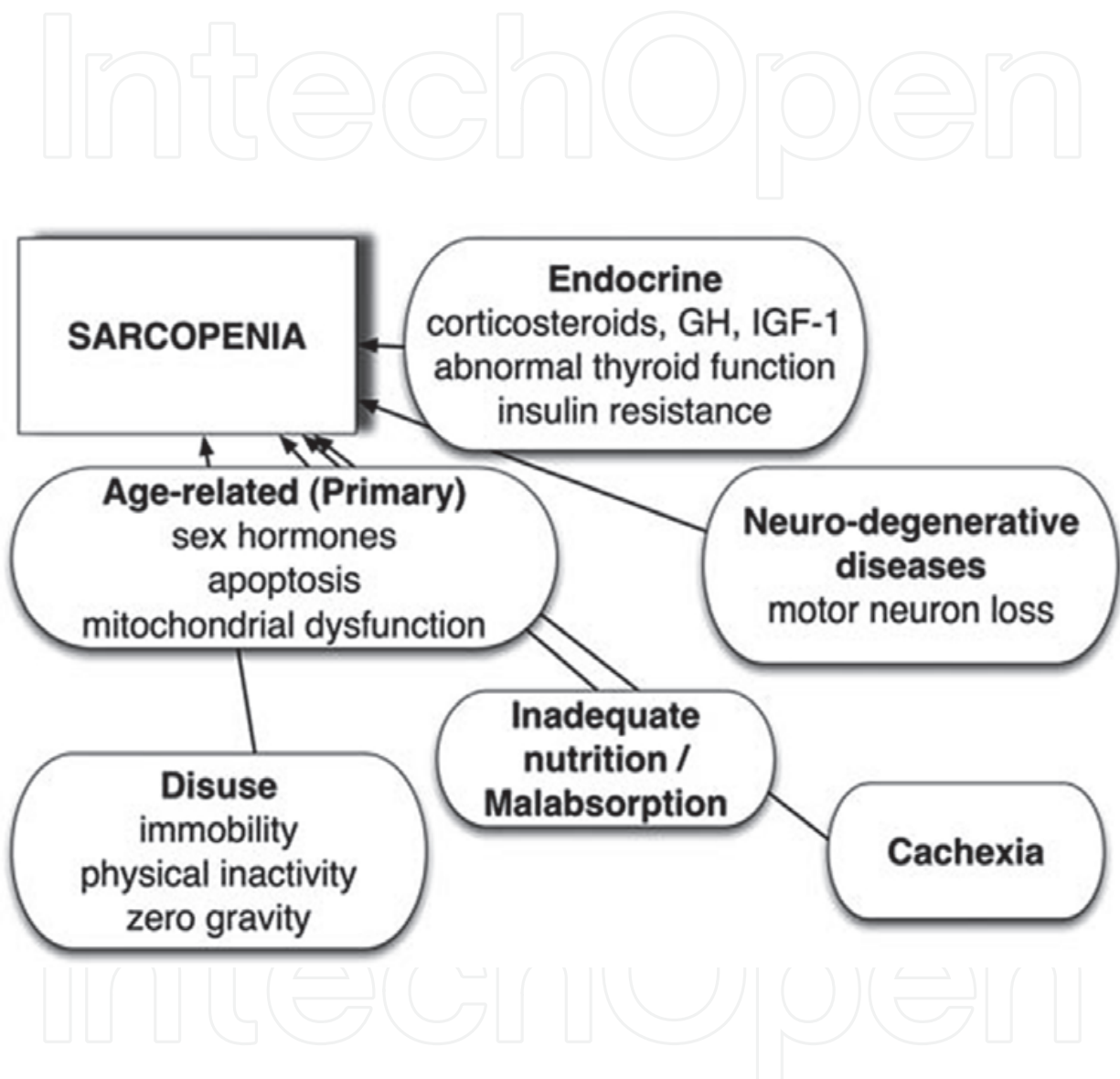


Fig. 4. Mechanisms of Sarcopenia. The Sarcopenia taskforce did conclude the importance of identifying such mechanisms to better understand the underlying pathophysiology, and to allow the identifications of interventions these targets.

Obesity is associated with an increased number of medical conditions and complications, and is a recognized independent cardiovascular risk factor. Obesity is associated with an increased risk of both physical and cognitive disability (Beydoun, Beydoun, and Wang 2008; Jensen 2005). Houston et al used data from the Health, Aging and Body Composition Study in looking the association between overweight and/or obesity in young, middle, and late adulthood and its cumulative effect on incident mobility limitation in 2,845 community dwelling US adults (Houston et al. 2009). The authors identified mobility limitations as difficulty walking $\frac{1}{4}$ mile or climbing 10 steps over a 7-year of follow-up. Men and women who were overweight or obese at all three time points had increased risk of mobility limitations compared to normal weights (HR 1.61 [1.25-2.06], and 2.85 [2.15-3.78]). There appeared to be a graded response ($P < 0.001$) on risk of mobility limitations on the cumulative effect of obesity in men and women. Earlier onset of obesity in life contributed to increased mobility limitations of old age (Houston et al. 2009). This is also observed in Figure #6.

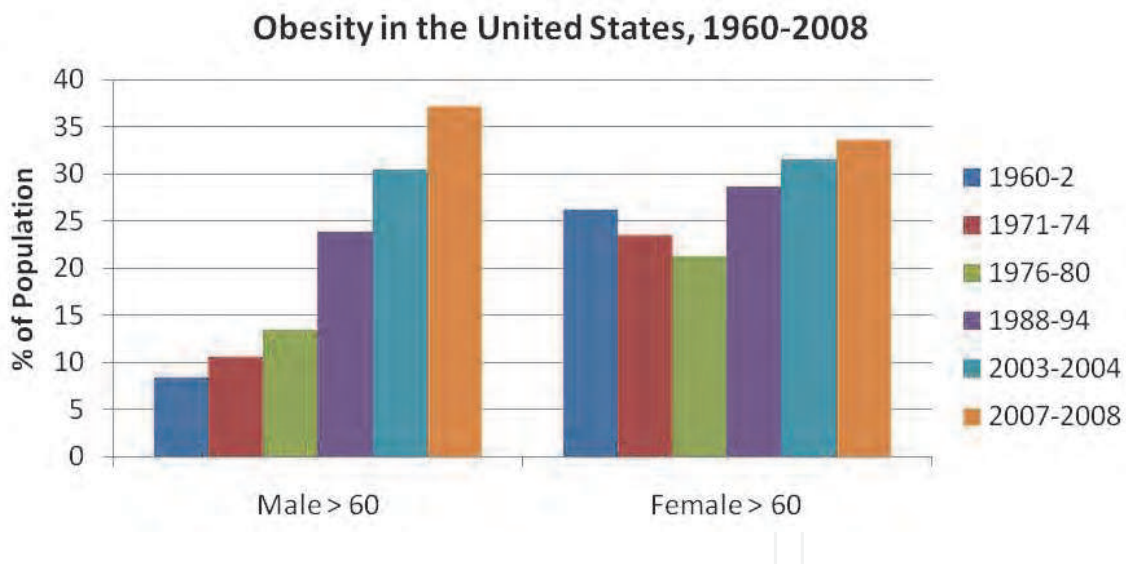
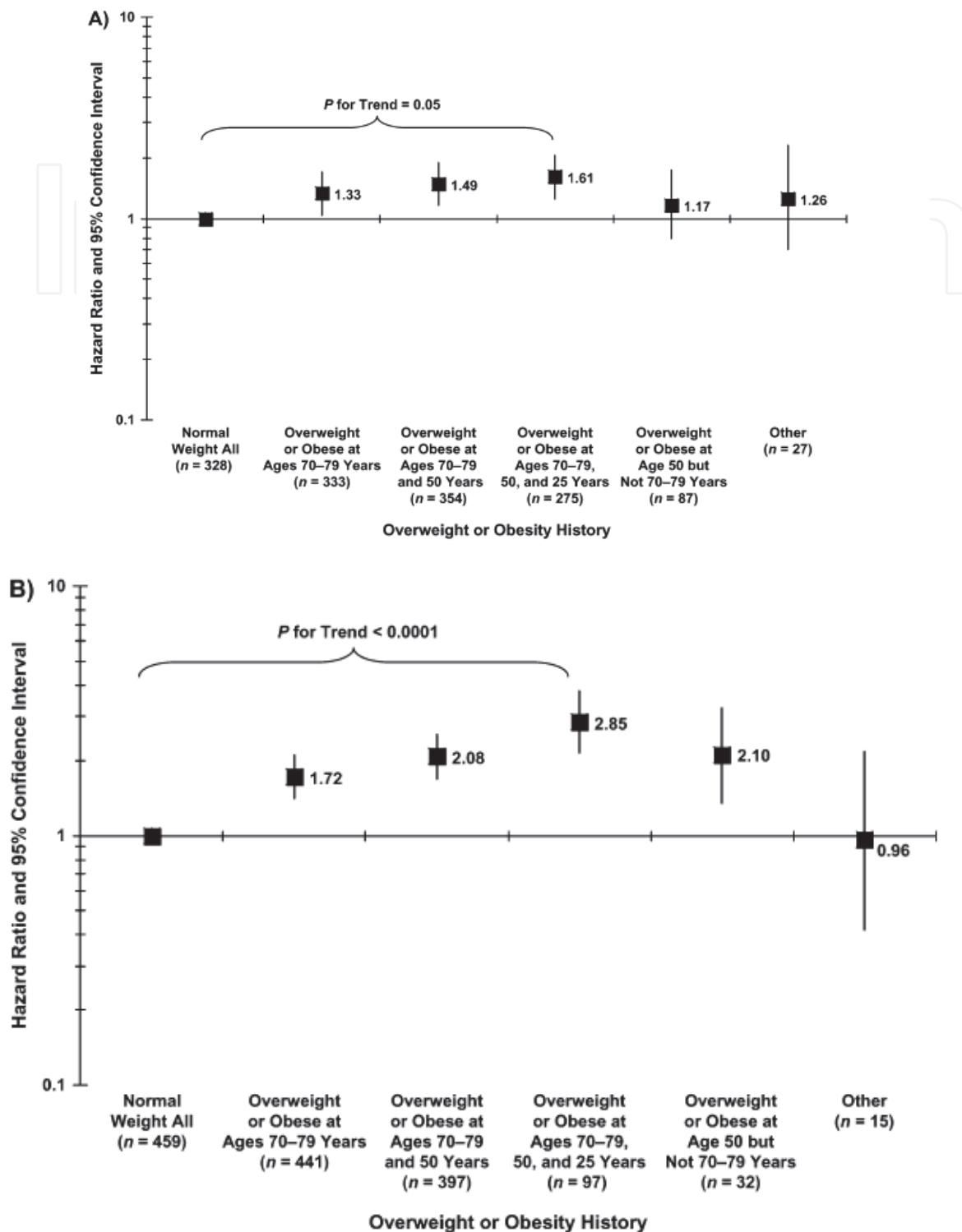


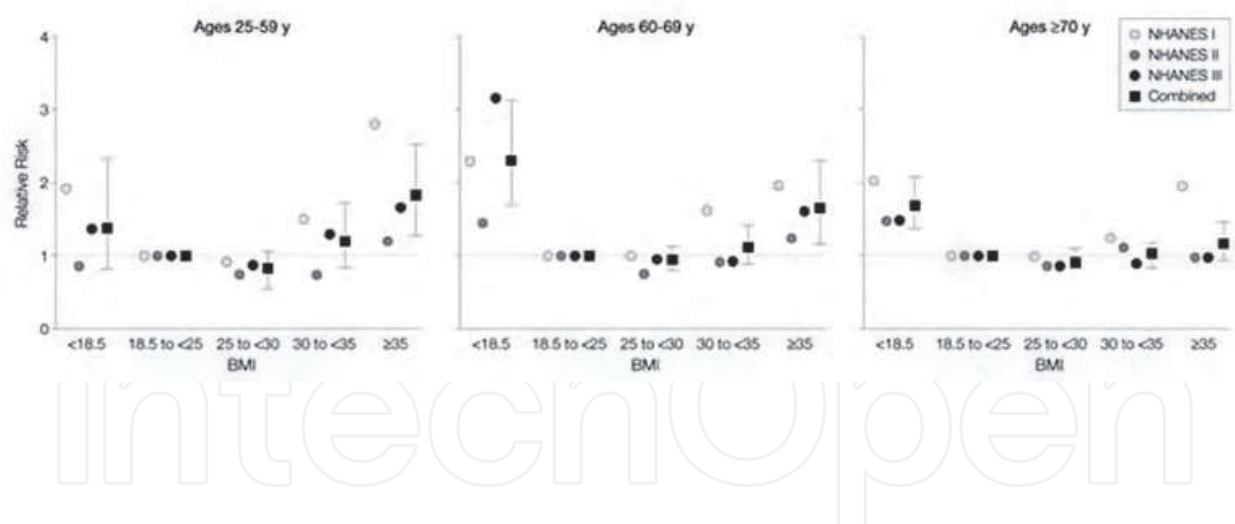
Fig. 5. Obesity in the United States, 1960-2008. Trends in the obesity epidemic in the United States in both males and females over the age of 60 years. In males, the trajectory of multiple epidemiological surveys is that of an increase. In females, there was an initial drop, but subsequent, yet steady increase



Caption: Hazard ratios and 95% confidence intervals for incident mobility limitation among Men (A) and women (B) by history of overweight or obesity (BMI >25kg/m²), the Health, Aging and Body Composition Study, 7 years of followup. Models were adjusted for age, race, field center, education, smoking status, alcohol consumption, and physical activity at study baseline. (Houston et al. 2009)

Fig. 6. Mobility Limitations and Body Size

A recent study using NHANES data demonstrated a J or U-shaped association between overweight/obesity and years of life lost, with the study authors concluding that obesity appears to decrease life expectancy (Figure #7) (Flegal et al. 2005). In addition, recent meta-analyses using body mass index as a surrogate for obesity have demonstrated that regardless of age, mortality is increased in patients with a BMI <22kg/m² and those who are morbidly obese (BMI>35kg/m²) [Figure #8] (Whitlock et al. 2009). Continued debate in the literature with regard to associations of mortality with BMIs between 25 and 35 continue and will not be reviewed here. Obesity has also been demonstrated to be associated with disability, lower quality of life, and increased resource utilization, particularly in elderly subjects (Guralnik, Fried, and Salive 1996). Obesity is associated with nursing home admissions and increasing one's risk to be homebound (Jensen et al. 2006; Valiyeva et al. 2006; Zizza et al. 2002). These issues all create a worrisome public health concern in that, in one study, 9% of all total excess healthcare costs may be attributable to overweight or obesity (Finkelstein, Fiebelkorn, and Wang 2003).



Caption: BMI indicates body mass index, measured as weight in kilograms divided by the square of height in meters. The reference category with relative risk 1.0 is BMI 18 to <25. Error bars indicate 95% confidence intervals. Copyright © American medical Association, JAMA 2005;293:1861-1867, All Rights Reserved. (Flegal et al. 2005)

Fig. 7. Relative Risks of Mortality by Body Mass Index Category by Epidemiological Survey Data

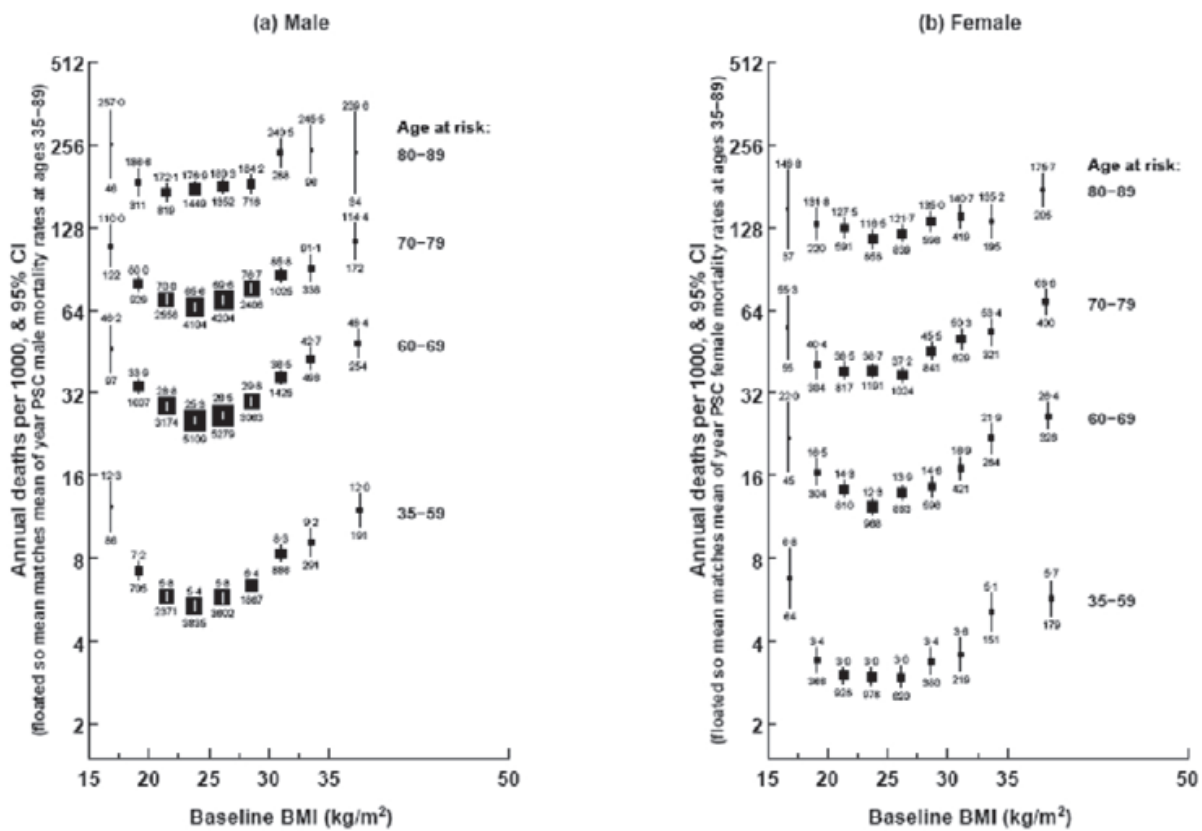


Fig. 8. All-cause mortality vs. Body Mass Index.

These studies demonstrate J-shaped curves in all age groups, in the range 15-50 kg/m² by age at risks (excluding the first 5 years of followup) (Whitlock et al. 2009)

5. Sarcopenic obesity – A subset of sarcopenia and obesity

Often times, we consider sarcopenia in the context of weight loss and cachexia; but sarcopenia can occur with obesity. The impact of obesity on sarcopenia continues to be a subject of investigation and emerging as a public health problem. In subjects who gain weight, there is proportionally an increase in fat mass as compared to lean mass. As described above, both entities lead to disability and the synergistic effects lead to worsening disability. These subjects can also be considered 'fat frail' who suffer from increased weakness from sarcopenia and the requirement to carry additional weight from obesity (Launer et al. 1994).

Common inflammatory pathways have linked sarcopenia and obesity yet the interplay between these two entities is poorly understood. One author hypothesized that both sarcopenia and obesity are similar behaviorally and biologically (Roubenoff 2000). One of the most trophic effects on muscle is physical activity, which normally falls as people age. Concurrently, there is a positive energy balance and weight gain, predominantly fat in nature. Additionally, this loss of fat-free mass (muscle) lowers the amount of tissues that can respond to insulin targeting, thereby promoting insulin resistance, metabolic syndrome and obesity (Reaven 1988). Muscle and fat are both metabolically active, the latter producing TNF- α , IL-6 and adipokines all of which have a direct catabolic effect on the former, and promote insulin resistance. Leptin and low adiponectin concentrations have been found to

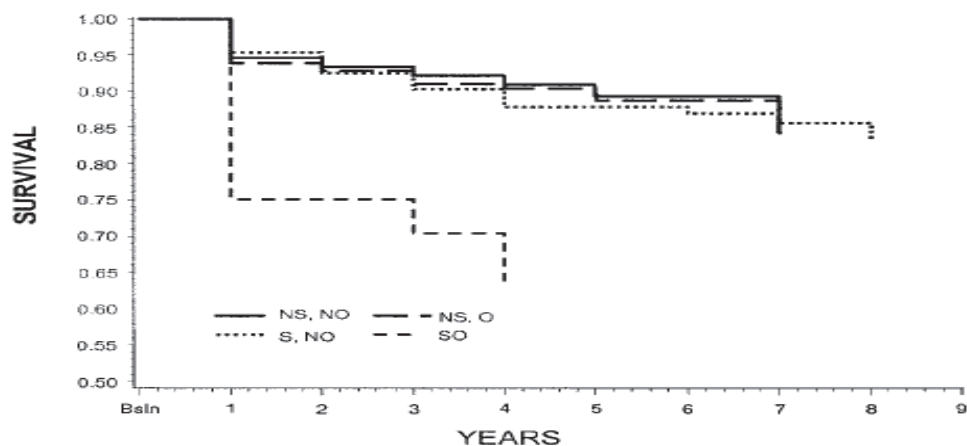
negatively impact muscle mass and lead to a decline in muscle quality (Hamrick et al. 2010). On a biological level, macrophages in adipocytes or in adipose tissue, produce such proinflammatory cytokines (Fantuzzi 2005) which can upregulate the inflammatory response. Cesari et al. evaluated the relationship between body-composition measures and inflammatory markers, using data from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors study (Cesari et al. 2005). These authors demonstrated the positive association of CRP and IL-6 with BMI ($p=0.03$ and $p<0.001$) and total fat mass (<0.001 and <0.001), and inverse association with fat-adjusted appendicular lean mass ($p<0.002$ and $p=0.02$). Using data from the INChianti study, global and central obesity directly affect inflammation, negatively affects muscle strength and can contribute to the development and progression of sarcopenic obesity (Schrager et al. 2007).

This cycle continues until the development of disability and medical illnesses. Furthermore, compounding the decline in neuronal and hormonal signals that occur with aging, malnutrition, and loss of a-motor units and changes in gene expression, further increase the risk of this entity in occurring (Doherty et al. 1993; Marcell 2003; Morley et al. 2001). This pro-inflammatory state leads to a perpetuating cycle of reduced muscle strength among obese subjects inevitably further contributing to functional decline. The aging process also itself leads to elevated IL-6 levels, TNF- α and CRP as well. While a number of chronic medical conditions prevalent in elders, including cancer, COPD and heart failure are associated with elevated pro-inflammatory levels and can lead to loss of muscle mass, the process of age-related sarcopenia is a natural phenomenon and differs from such.

Baumgartner et al. defined sarcopenic obesity as a muscle mass index less than two standard deviations below the sex-specific reference for a young healthy population (Baumgartner 2000). Alternative definitions have been used by other authors (Bouchard, Dionne, and Brochu 2009; Davison et al. 2002; Zoico et al. 2004), yet a harmonious definition has yet to be solidified at this time. More recently, the incorporation of muscle quality into these definitions has been proposed (Cruz-Jentoft et al. 2010). The debate is outside the scope of this chapter.

A number of studies have outlined the differences between those with and without sarcopenia or obesity. In one of the pivotal studies, 52 subjects matched obese elderly, non-obese frail, and non-obese, non-frail were evaluated on objective measures of functional status and health-related quality of life and differences in body composition (Villareal et al. 2004). They discovered that obese and non-obese frail groups had lower and similar scores in physical function, functional status and impairments in strength and walking speed. They concluded that physical frailty in obese elders was associated with lower fat free mass (lean mass), poor muscle quality and worsening quality of life.

One of the more pivotal studies by Baumgartner's group demonstrated the combined effect of obesity and muscle mass or strength on physical functioning or disability (Baumgartner 2000). Baumgartner's group examined the impact of sarcopenic obesity and incident instrumental ADL disability in the New Mexico elder health survey and New Mexico aging process study (Baumgartner et al.). This study ascertained ADLs in patients longitudinally and assigned points (0-2) depending on whether someone could not perform an instrumental activities of daily living, could do it with difficulty, or could do it independently. Their primary outcome was time to a drop in ADL, defined as a drop in 2 points. As can be seen in the Figure #9 below, only those with sarcopenic obesity had a markedly shorter time to drop in ADLs. The other three groups were no different from each other (sarcopenic non-obese, obese non-sarcopenic, and non-obese non-sarcopenic).



SO - sarcopenic obesity; S - sarcopenia; O - obesity; NS - non-sarcopenic; NO - non-obese

Fig. 9. Incident Disability over Time.

The data demonstrate that subjects with Sarcopenic Obesity have worsened disability, than subjects with sarcopenia alone, obesity alone, or neither sarcopenia nor obesity (Baumgartner et al. 2004).

Other cross-sectional studies have demonstrated conflicting results based on NHANES III (Davison et al. 2002) and a sample of elder females in Verona (Zoico et al. 2004). Davison's study looked at 1,526 females and 1,391 males who were 70 years and older. These authors observed that women in the highest quintile for percent body fat were twice as likely to report functional limitations than in the other comparison groups, and weaker but similar relationships were observed in men. Low muscle mass and sarcopenia with obesity, in this study were not associated with additional limitations. In Zoico's cross-sectional study of 167 females, aged 67-78, those in the highest quintile of body fat demonstrated a significantly higher prevalence of functional limitation, but 40% of sarcopenic elderly women and 50% of elderly women with high body fat and normal muscle mass were functionally limited (Figure #10). Functional limitation increased in those with a higher degree of sarcopenia. They demonstrated that isometric leg strength was significantly lower in subjects with sarcopenia and sarcopenic obesity. These two studies used the same categorization to define these entities. It was felt that using muscle mass instead of a functional measure such as strength as an indicator of sarcopenia may have explained the lack of results.

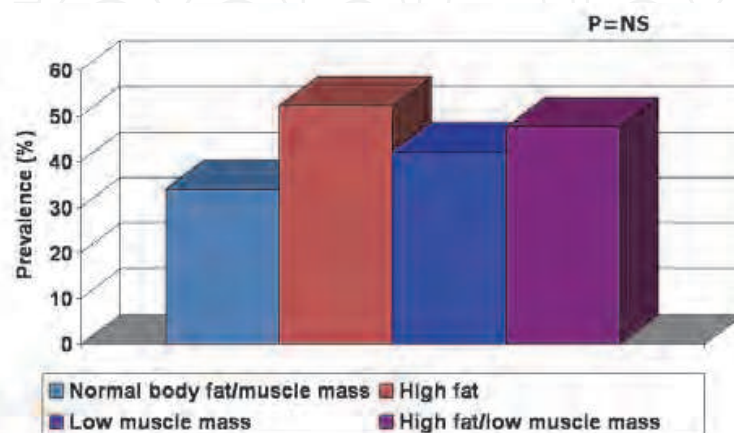


Fig. 10. Self-Reported Functional Limitations

There were no differences between subjects in this cohort on self-reported functional limitations with regard to body composition measures (Zoico et al. 2004).

There are other studies that have demonstrated the relationship between sarcopenic obesity and higher degrees of functional limitations. Stenholm et al (Stenholm et al. 2008) examined the association between different obesity indicators and walking limitations in examining the role of C-reactive protein and handgrip strength. This cross-sectional study of a Finnish population looked at subjects >55 years, and demonstrated that the highest two quartiles of body fat percent and C-reactive protein and the lowest two quartiles of handgrip strength were significantly associated with greater risk of walking limitations after adjusting for chronic diseases and other pertinent co-variables. The prevalence of walking limitations were higher in persons who had high fat and low handgrip (61%) than in those with low fat and high handgrip (7%). Their results are better observed in the figure below:

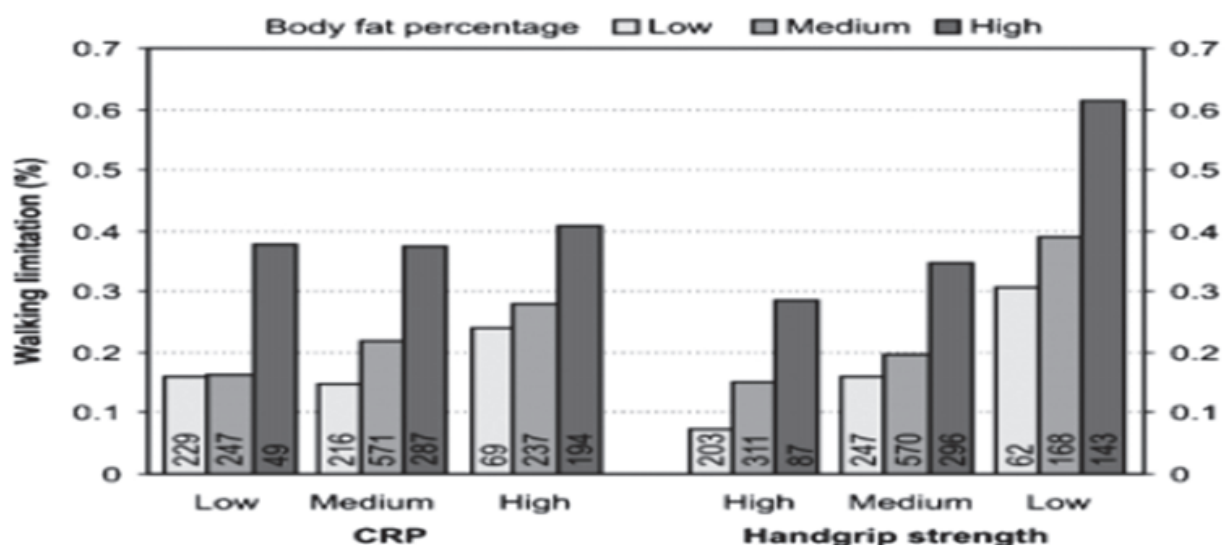


Fig. 11. Walking Limitations, C-reactive Protein and Handgrip Strength.

Age- and sex-adjusted prevalence of walking limitations according to body fat percentage levels according to C-reactive protein (CRP) and handgrip strength. Low, medium and high levels of body fat percentage, CRP and handgrip strength were defined by recoding quartiles of each variable into three categories by combining quartiles II and III. Numbers inside the bars indicate the number of subjects in each category (Stenholm et al. 2008).

Finally, Cesari's group (Cesari et al. 2009), using the InCHIANTI study, analyzed data from 934 participants aged 65 years and older with at least 6 years of follow-up. In unadjusted analyzes, muscle density (HR 0.78 [0.69-0.88]), muscle area (HR 0.75 [0.66-0.86]) and fat area (HR 0.82 [0.73-0.92]) were associated with mortality. However, adjusting for confounders, these associations were no longer significant. Walking speed was associated with mortality risk (HR 0.73 [0.60-0.88]). The relationship with mortality, though, has been examined by other others. Rantanen (Rantanen et al. 2000). Those who were overweight in the lowest grip strength tertile had 1.4 times higher mortality risk compared to normal weight persons in the highest grip strength. Muscle strength has been previously examined as a predictor of mortality (Gale et al. 2007; Newman et al. 2006; Rantanen et al. 2003) and that of obesity has been fully described previously.

6. Aging, sarcopenia, insulin and insulin resistance

There are hormonal changes linking age-related decline in muscle strength and mass, which include insulin, growth hormone, and catecholamines as a few examples. On a cellular level, animal studies have demonstrated a relationship between obesity-related insulin resistance and insulin receptor signaling pathway. A low grade inflammation often is present in most obese patients which is a result of chronic activation of the innate immune system, leading to insulin resistance, impaired fasting glucose and diabetes. The involvement of cytokines and inflammation in obesity in relation to glucose metabolism continues to be controversial. Both IL-6 and TNF- α alter insulin sensitivity by impacting given steps in the insulin signaling pathway. In animal models, resistin induces insulin resistance, but whether this occurs in humans is unclear. Subjects with obesity-related insulin resistance, type 2 diabetes and coronary heart disease have low levels of adiponectin. This hormone is known to inhibit liver gluconeogenesis and can promote fatty acid oxidation in skeletal muscle. These cytokines also are known to impact NF- κ B and JNK systems (Zamboni et al. 2007).

With aging, muscle can be infiltrated with fat, and this may eventually perpetuate insulin resistance. In a large study of 2,964 elderly subjects with a mean age of 73.6 years, despite similar amounts of subcutaneous thigh fat, intermuscular fat was higher in subjects with type 2 diabetes and impaired glucose tolerance than in subjects with normal glucose tolerance ($p < 0.001$) (Goodpaster et al. 2003). As expected higher rates of intermuscular fat and visceral abdominal fat were associated with higher fasting insulin levels. This study concluded that elderly men and women with normal body weight may be at risk for metabolic abnormalities, including type 2 diabetes if they possess an inordinate amount of muscle fat or visceral abdominal fat. A smaller study by the same group elucidated whether thigh fat was a determinant of insulin resistance. They compared a small number of subjects and confirmed that muscle composition reflected increased fat content was associated with insulin resistance (Goodpaster, Thaete, and Kelley 2000).

Furthermore, insulin is well known to be an anabolic hormone which may have a pleiotrophic effect on muscle tissue and protein metabolism. Lower protein synthesis and higher insulin levels occur in elderly subjects compared to younger subjects after food intake. Previous studies have shown that subjects with insulin resistance can negatively predict muscle strength, often seen in elderly subjects with diabetes. The correlation between insulin resistance and muscle strength is quite poor and accelerates the loss of leg muscle strength and quality. In a pilot study examining this relationship examined the homeostasis model assessment (HOMA-IR) in type 2 diabetes, demonstrated that knee extension, adjusted for body weight was significantly correlated with HOMA-IR in both sexes and that this relationship persisted as an independent determinant in a stepwise regression model (Nomura et al. 2007). In another study, the degree of insulin resistance was evaluated using HOMA-IR and muscle strength using handgrip strength. BMI-adjusted handgrip strength correlated positively with physical activity, muscle area, and muscle density (Abbatecola et al. 2005). Physical activity has a positive effect on muscle mass and quality specifically with resistance training (Goodpaster and Brown 2005). This latter activity is also known to improve insulin sensitivity and glycemic control.

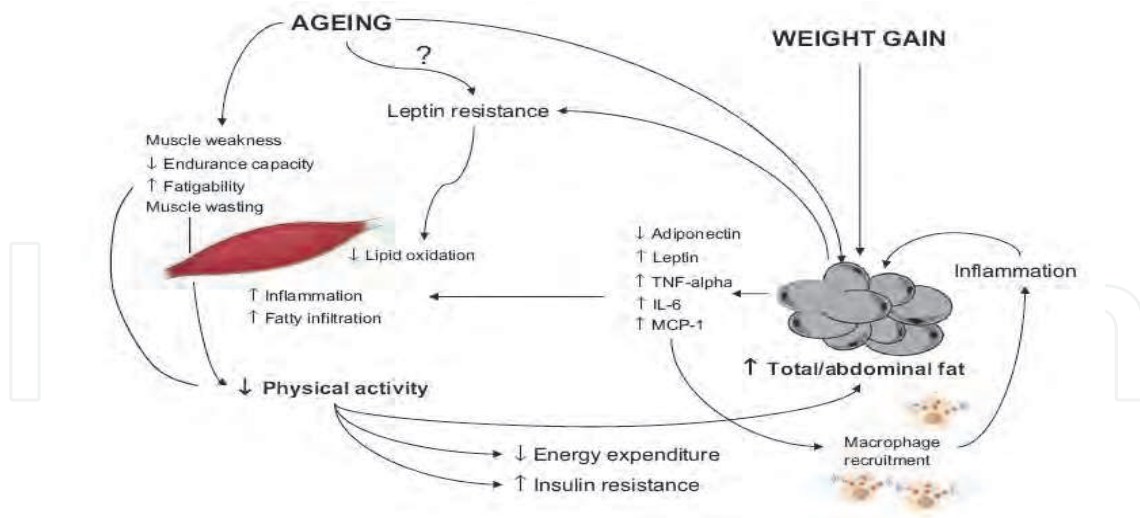


Fig. 12. Possible Mechanisms linking Ageing, Obesity, Sarcopenia and Insulin resistance (Zamboni et al. 2008)

7. Growth hormone and insulin-like growth factor 1

Additional contributors to sarcopenia include insulin-like growth factor-1 (IGF-1) and growth hormone (GH), both of which decline with age. Growth hormone is associated with low fat mass, increased lean body mass and ideal metabolic profile, while IGF-1 can increase protein synthesis in existing muscles. One study partially described the relationship of the hypothalamic pituitary axis in subjects with sarcopenia and sarcopenic obesity. Using DEXA, they ascertained 45 subjects with varying degrees of adiposity and lean mass and measured pituitary function (Waters et al. 2008). They demonstrated that appendicular skeletal muscle mass was independently and negatively correlated with leptin in all groups, even after adjusting for body fat, and that subjects with sarcopenic obesity had lowered and blunted GH responses. Low levels of this anabolic hormone has been proposed to be positively associated with low muscle strength (Ceda et al. 2005). Using data from the Longitudinal Ageing Study Amsterdam (LASA), among subjects aged 65-88 years, serum testosterone levels were positively associated with muscle strength and physical performance (Schaap et al. 2005). With respect to IGF-1 levels, physiologically one would expect that the age-associated decline in IGF-1 levels would be associated with poorer muscle strength and mobility. Data from 617 women from Women's Health and Aging Study were examined and demonstrated a positive association between IGF-1 levels and knee extensor strength ($p=0.004$) and walking speed ($P<0.001$). A decline in IGF-1 levels was associated with difficulty self-reported mobility tasks. It is hypothesized that the aging muscle loses the capability of secreting GH and the responsiveness to IGF-1 is also likely attenuated. Evidence suggests that exercise can reverse the latter. These may be molecular targets in the future to promote muscle building and prevent sarcopenia.

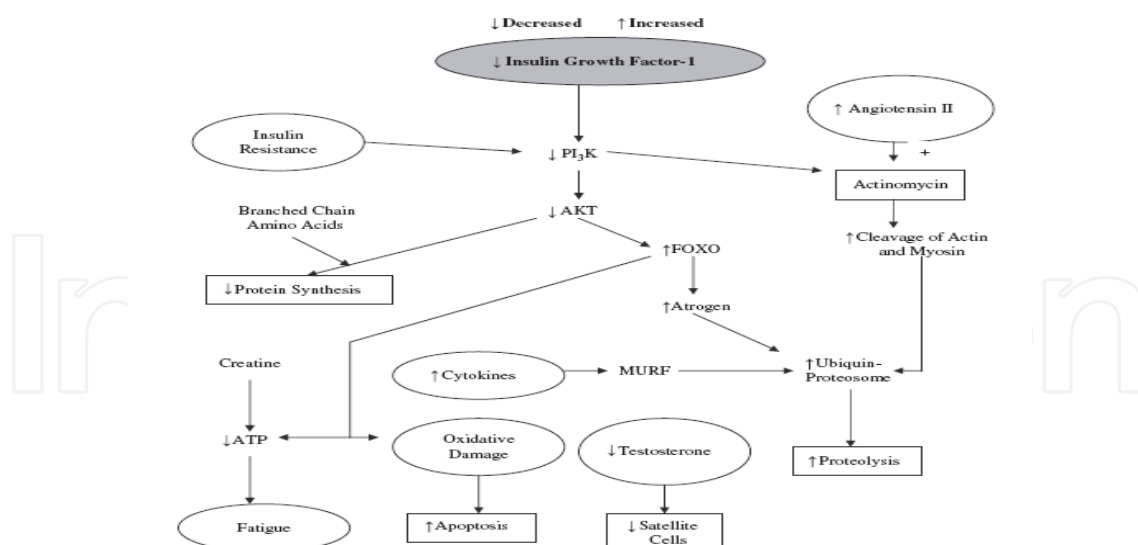
8. Diabetes and geriatric syndromes

Diabetes is associated with an increased incidence of many geriatric syndromes. Many studies have demonstrated the impact of diabetes on functional impairment, including inability to ambulate and perform instrumental ADLs (Volpato et al. 2002; Gregg et al. 2002).

Diabetes itself, on a microvascular level can lead to functional impairment, but notably, complications of diabetes have also been implicated. Diabetes has been implicated in fall risk (Volpato et al. 2005), fractures (Schwartz et al. 2001), urinary incontinence (Ebbesen et al. 2007) and depression (Anderson et al. 2001).

9. Diabetes and sarcopenia

There are a number of similarities between diabetes and sarcopenia. It is known that persons with diabetes have an accelerated aging process leading to disability and frailty. Diabetes is known to lead to each of the components of the operationalized definition of frailty and insulin resistance appears to be a core factor in this pathophysiology (Morley 2008). In the Health, Aging and Body Composition study, type 2 diabetes was associated with lower skeletal muscle strength and quality, as well as excessive skeletal muscle mass loss (Park et al. 2006; Park et al. 2009). Loss of muscle mass has also been associated with type 2 diabetes in elderly subjects. Low grip strength as a surrogate for sarcopenia is associated with features of metabolic syndrome as well, post-prandial glucose levels and HOMA index/ insulin-resistance. It is believed that hyperglycemia directly impairs skeletal muscle contractility and force (Sayer et al. 2005); whether this is due to excessive toxicity of sugar alcohols on muscles remains elusive at this time. Other hypotheses include the accumulation of lipids which may affect insulin signaling (Janssen and Ross 2005; Furler et al. 2001; Shulman 2000), impaired rate of synthesis of muscular proteins, seen in both ageing and insulin resistance (Nair 2005; Rasmussen et al. 2006). Diabetics are at high risk for sarcopenia as there is a 1.5-2.0 fold increased rate of skeletal muscle mass and strength loss (Park et al. 2007). There are a number of similarities between metabolic syndrome and insulin resistance and one study by Sayer examined the relationship between these entities and sarcopenia (Sayer et al. 2007). Their findings suggested that impaired grip strength was associated, not only with individual constructs of the metabolic syndrome but also the composite definition itself. Although the authors acknowledge that further investigation is required to understand the underlying mechanisms, the potential for using grip strength and interventions tested thereof to improve muscle strength, could also potentially improve insulin resistance. The following figure (Figure #13) demonstrates some of the potentiating cellular mechanisms observed in diabetes. There are a number of emerging studies observing the relationship between sarcopenia, obesity, sarcopenic obesity and diabetes. The Korean Sarcopenic Obesity Study examined the prevalence of sarcopenia in Korean subjects with and without type 2 diabetes (Kim et al. 2000). The study included 810 subjects, of which 414 had diabetes and 396 were controls, and demonstrated that the prevalence of sarcopenia was 15.7% and 6.9% in subjects with and without diabetes. Skeletal muscle index (muscle mass adjusted for height squared), as a measure of sarcopenia, was significantly lower in patients with diabetes compared to subjects without diabetes. In their multiple logistic regression model, type 2 diabetes was independently associated with sarcopenia (OR 3.06 [1.42-6.6.62]) than subjects without diabetes after adjusting for age, sex, BMI, smoking, alcohol consumption, physical activity, medications, blood pressure and lipid profiles. Quite interestingly, though, the prevalence of type 2 diabetes was highest in Mexican Americans using NHANES III data with the lowest prevalence of obesity and sarcopenia, while Whites had the highest prevalence of sarcopenic obesity (Castaneda and Janssen 2005). This study challenges whether there indeed is a relationship between sarcopenia and obesity. Whether ethnicities need to be accounted for due to differences in body composition is a matter of further investigation.



↓, decreased, ↑ increased; KT, active human protein kinase (protein kinase-B); FOXO, forkhead protein; MURF, muscle ring finger protein; P13K, phosphatidylinositol-3-kinase (Morley 2008).

Fig. 13. Biochemical Changes in Muscle in Diabetes

In other population, specifically, dialysis subjects, diabetes is thought to be a risk factor for losing lean mass (Pupim et al. 2005). Muscle mass, particularly in dialysis patients, are known to decline continuously and hence this study suggested that controlling a risk factor for incipient sarcopenia (diabetes), would reduce this declining process. Many of the changes suggested, in one editorial, were due to systemic inflammatory cytokines previously described, often which are implicated in diabetes and insulin resistance (Kaysen 2005). This was echoed in another small study looking at changes in inflammatory cytokines implicated in losing lean mass (Pedersen et al. 2003).

Subjects with diabetes are at higher risk of developing peripheral neuropathy, which leads to a decrease in one's motor end plates. This entity is important in maintaining muscle homeostasis and coordination of muscle contraction, therefore their loss can perpetuate and accelerate age-related decline in muscle mass. Diabetics also have impaired levels of growth hormone and pro-inflammatory cytokines. Additionally, the microvascular damage from hypoxia not only affects nerves, renal glomeruli and optic nerves, but also can lead to muscle hypoxia. Macrovascularly, atherosclerosis can lead to diminished peripheral blood flow to leg muscles leading to impaired strength. Other cellular entities are implicated, as well as other endocrine changes as illustrated in the figure below. Undoubtedly there is a relationship between the underlying pathophysiology of sarcopenia, insulin resistance and diabetes.

10. Conclusion

A number of studies are increasingly confirming the relationship between sarcopenia and reduced functional activities and disability. Sarcopenia and obesity are often thought as a prelude to frailty, known to adversely predict hospitalizations, morbidity, institutionalization and mortality (Figure #14). Reduced physical activity and a sedentary lifestyle are important risk factors for developing sarcopenia, which subsequently leads to physical disability and reduced physical performance (Figure #15). More importantly, those

with elevated fat mass with sarcopenia are at even high risk. The relationship between sarcopenia, sarcopenic obesity and insulin resistance requires further investigation. The clinical implications are not insignificant in that globally, sedentary lifestyles are becoming the norm and the potential implications on utilization are not significant.

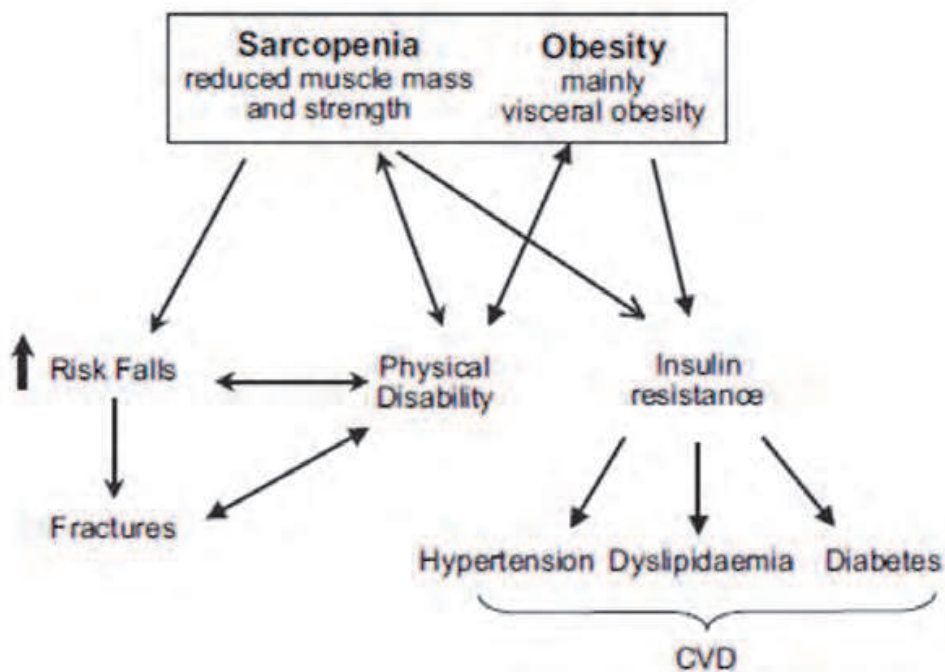


Fig. 14. Possible Consequence of sarcopenic obesity in the Elderly (Zamboni et al. 2008)

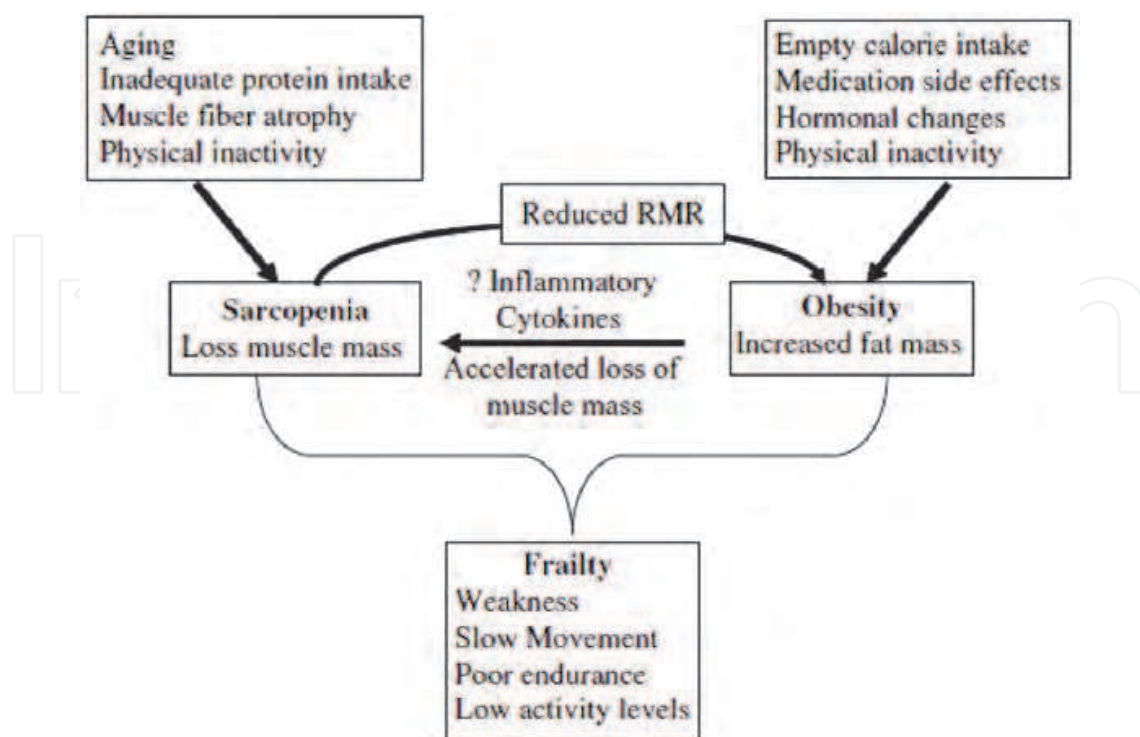


Fig. 15. Body Composition Changes Leading to Sarcopenic Obesity (Jarosz and Bellar 2009)

11. Abbreviations

ADL - Activities of Daily Living

BMI - body mass index

BIA - bioelectrical impedance analysis;

DEXA - Dual Energy X-Ray Absorptiometry

HOMA - homeostatic model assessment

HOMA-IR - homeostasis model of assessment - insulin resistance

OECD - Organisation of Economic Cooperation and Development

US - United States

TNF- α - tumor necrosis factor α

IL-6 - interleukine 6

GH - growth hormone

NK-kB - nuclear factor-kappa B

JNK - Jun N-terminal kinases

IGF-1 - insuline-like growth factor 1

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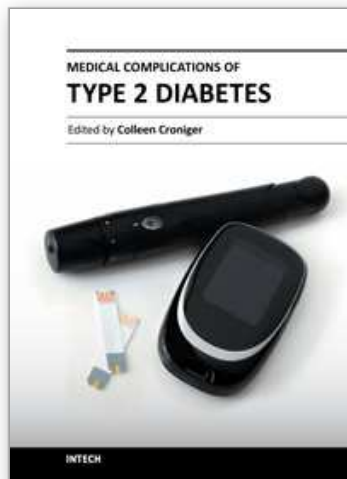
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Medical Complications of Type 2 Diabetes

Edited by Dr. Colleen Croniger

ISBN 978-953-307-363-7

Hard cover, 412 pages

Publisher InTech

Published online 12, September, 2011

Published in print edition September, 2011

Obesity and type 2 diabetes are increasing worldwide problems. In this book we reviewed insulin secretion in both healthy individuals and in patients with type 2 diabetes. Because of the risk associated with progression from insulin resistance to diabetes and cardiovascular complications increases along a continuum, we included several chapters on the damage of endothelial cells in type 2 diabetes and genetic influences on endothelial cell dysfunction. Cardiovascular complications occur at a much lower glucose levels, thus a review on the oral glucose tolerance test compared to other methods was included. The medical conditions associated with type 2 diabetes such as pancreatic cancer, sarcopenia and sleep disordered breathing with diabetes were also discussed. The book concludes with several chapters on the treatments for this disease offering us hope in prevention and successful alleviation of the co-morbidities associated with obesity and type 2 diabetes.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

John A. Batsis and Silvio Buscemi (2011). Sarcopenia, Sarcopenic Obesity and Insulin Resistance, Medical Complications of Type 2 Diabetes, Dr. Colleen Croniger (Ed.), ISBN: 978-953-307-363-7, InTech, Available from: <http://www.intechopen.com/books/medical-complications-of-type-2-diabetes/sarcopenia-sarcopenic-obesity-and-insulin-resistance>

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