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Obesity and osteoarthritis: disease genesis and nonpharmacologic weight management

Stephen P. Messier, Ph.D.

Synopsis

The mechanisms by which obesity affects osteoarthritis are of great concern to osteoarthritis researchers and clinicians who manage this disease. Inflammation and joint loads are pathways commonly thought to cause or to exacerbate the disease process. This paper reviews the physiologic and mechanical consequences of obesity on older adults with knee OA; the effects of long-term exercise and weight-loss interventions, the most effective non-pharmacological treatments for obesity; and the utility and feasibility of translating these results to clinical practice.

Keywords

knee osteoarthritis; degenerative joint disease; obesity; inflammation; gait

Risk of Obesity on OA Development

First documented in 1945,¹ the strong association between obesity and knee osteoarthritis (OA) has been widely verified. Leach et al.² found that 83% of their female subjects with knee OA were obese compared with 42% of the control group. In a case-controlled study of 675 matched pairs, Coggon et al.³ determined that the risk of knee OA in people with a BMI ≥ 30 kg/m² was 6.8 times that of normal weight controls. Felson et al.⁴ showed that a 5.1 kg loss in body mass over a 10-year period reduced the odds of developing OA by more than 50%. Ettinger et al.⁵ examined the effects of co-morbid diseases on disability and found that people with a BMI >30 kg/m² were 4.2 times more likely to have knee OA than leaner people. Knee OA and obesity were each significantly associated with poorer physical function, with odds ratios of 4.3 and 1.7, respectively; when obesity was combined with knee OA, the odds ratio increased to 9.8. Taken together, these studies indicate that obesity is a major risk factor for knee OA and associated functional impairment. A high BMI is also associated with faster disease progression⁶.

OA is most commonly located in the small joints of the hand. Unlike knee OA, the association between obesity and hand OA is not strong. Doherty et al.⁷ reviewed the literature on hand OA and concluded that BMI and waist circumference were not risk factors, especially in older adults. Similarly, Kalichman and Kobyliansky⁸ used an observational, cross-sectional design to study 745 women with hand OA and saw no relationship with BMI or waist circumference. The authors suggested that obesity might be a mechanical rather than a systemic risk factor for

Address for Correspondence: Stephen P. Messier, Ph.D., Department of Health and Exercise Science, Wake Forest University, Winston-Salem, NC 27109, Email: messier@wfu.edu Voice: 336-758-5849, Fax: 336-758-4680.

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OA, which would explain its strong association with OA in weight-bearing joints relative to the small joints of the hand.

Impact of Obesity on Function and Gait

The NHANES I and Epidemiologic Follow-up (NHEFS) studies revealed that obesity at baseline increased upper and lower body disability across 20 years.^{5;9} More recently, Jenkins¹⁰ found that functional impairment in older adults increased with BMI. In the Cardiovascular Health Study, an adjusted odds ratio of 2.94 for self-reported mobility-related disability was found for those in the highest versus the lowest quintile of fat mass.¹¹

As body weight increases, both fat mass and fat-free mass increase.¹² The relationship between fat-free mass and BMI is stronger in men, suggesting that increased BMI in women is due predominantly to an increase in fat mass. Although these data seem to imply that obese people are stronger than non-obese counterparts, the opposite is true. Specifically, when strength is represented as a function of body weight, both obese men and women are weaker, irrespective of age.¹³ In obese men aged 60–80, mean knee strength is 65% of body weight, as compared to 77% for controls; for their female counterparts, mean knee strength is 50% of body weight, compared to 62% for nonobese women.

Muscle weakness in older adults can have dire consequences. It is the second leading cause of falls in the elderly, accounting for 17%.¹⁴ Falls are the leading cause of death by injury in older adults, and 75% of deaths due to falls occur in adults over 65 years. Only one-half of older adults hospitalized due to falls will be alive after 1 year. By 2030, 280,000 Americans will die annually from falls.¹⁵

Loss of balance causes falls, so balance measures are used to identify people who are more susceptible. Kejonen et al.¹⁶ found significant correlations between poor balance and high BMI in women but not men, once again suggesting that muscle weakness is a mediator of poor balance and falls. Jadelis et al.¹⁷ found that for older adults with a BMI above 30 kg/m² and a given amount of knee strength, the more obese, the worse the balance, suggesting that obesity, independent of strength, is a risk factor for poor balance and falls.

Not without reason, then, obesity is related to a fear of falling and injury risk.^{18;19} Austin et al.¹⁸ followed 1,282 community-dwelling women aged 70–85 for 3 years and found that obesity was independently associated with fear of falling at baseline and with the onset of this fear in women who were symptom-free at baseline. In a sample of over 42,000 adults, the odds of sustaining an injury were greater among those with excess weight. As BMI category increased from overweight (25.0 kg/m² ≤ BMI ≤ 29.9 kg/m²) to class III obesity (BMI ≥ 40.0 kg/m²), the odds of sustaining an injury, including those related to falls, rose from 15% to 48%.¹⁹

Obese adults make adjustments to help stabilize their larger mass and reduce fall risk. DeVita et al.²⁰ compared obese and lean adults and noted that the obese group increased ankle torque during walking but showed no difference in knee or hip torque. Specifically, the ankle plantar flexors act eccentrically to control the forward motion of the leg throughout stance, to stabilize body mass, and at toe-off to assist in propulsion. Their greater mass requires more ankle plantar flexor torque to perform these tasks.

Obese people try to reduce the load on their knees by shortening their stride and reducing knee extensor torque. In an obese cohort, the greater the BMI, the shorter the stride and the lower the knee-joint extensor/flexor torque, actually shifting from an overall extensor torque to a dominant flexor torque at high BMIs. This switch results in the hamstrings, rather than the

quadriceps, providing knee stability. In lean subjects, no relationship exists among BMI, stride length, and knee torques, indicating that lower BMI values have little effect on gait.²⁰

Liu and Nigg²¹ examined the effects of rigid and soft tissue mass on impact forces during running. They termed the soft tissue mass *wobbling mass*. Their spring-damper-mass model consisted of upper- and lower-body rigid and wobbling masses. A computer simulation found that upper-body wobbling mass had no effect on impact forces but strongly influenced the propulsive peak. As upper-body wobbling mass increased, vertical force propulsive peaks increased, suggesting that obese individuals exert greater forces during gait due to their greater wobbling mass.

Empirical data support Liu and Nigg's model. Messier et al.²² found a strong positive association between BMI and peak ground reaction forces ($r = 0.76$, $p = 0.0001$) in older adults with knee OA. A study by Browning and Kram²³ found that obese people exerted 60% greater vertical ground reaction forces compared to normal weight people (Figure 2).

Abnormal gait is characteristic of obese people. Messier et al.²⁴ found that a severely overweight population walked with bilaterally abducted forefeet, or a stance that was 276% more toed-out than that of a normal weight group. Chodera and Levell²⁵ suggested that the feet have different functions, with the more abducted forefoot responsible for balance and the less abducted foot responsible for direction. In severely obese people, the amount of abduction is significantly greater in both feet relative to a normal weight control group, suggesting that balance is more important than direction.²⁴

In addition to greater forefoot angles, severely obese people have more rearfoot motion: typically, greater touchdown angle, more pronation range of motion, and faster pronation. This excessive rearfoot motion may cause injury and discomfort and negatively affect mobility.

Plantar fasciitis and heel pain are commonly associated with obesity. In a case-controlled study, obese subjects were 5 times more likely to have heel pain than their nonobese counterparts, with an odds ratio of 5.6.²⁶ Similarly, obese men and women exert greater plantar pressure while both standing and walking.^{27–31} Hills et al. found a significant correlation ($r = 0.81$) between midfoot peak pressure and BMI²⁸ (Figures 1A & 1B). Gravante et al.³² found greater midfoot weight-bearing area in obese men and women versus a control. The additional pressure on the medial longitudinal arch could have a detrimental effect on the plantar ligaments, causing them to collapse. Considering that the medial longitudinal arch is critical in distributing loads to both the rearfoot and forefoot, it is not surprising that foot ailments are common among the obese.

In summary, obese adults exert greater forces than normal weight adults during gait. As obesity worsens they try to minimize these loads by shortening their stride. However, adjusting gait mechanics without reducing body weight does not eliminate obesity's detrimental effects on the lower extremities.

What role obesity plays in the degenerative process is unclear. The multiphasic nature of articular cartilage permits it to withstand compressive stresses as high as 20 MPa, or 3000 lb/in².³³ A densely woven collagen fibrillar network, water (normally < 80% by wet weight), and ionic species of Na⁺, Ca⁺⁺, and Cl[–] provide a unique combination of material properties that prevents such high loads from crushing the tissue. Cartilage has little permeability, resulting in large interstitial fluid pressures inside the tissue during compression. This pressurized fluid accounts for most of the load-bearing capability and protects proteoglycans and chondrocytes from dangerously high stresses and strains. Moderate running increases cartilage matrix synthesis and may have a protective effect on the joint.^{34,35} Peak knee-joint compressive forces in humans during long-distance running range between 10–14 times body

weight.³⁶ In spite of these high forces, most studies have shown no relationship between running and OA.³⁷ Compressive loads during walking are less than half those found during running.³⁸ Hence, obesity's cumulative effect on knee-joint loads during daily activities must play the critical role in the disease process.

Obesity and Inflammation

Obesity is typified by nutrient excess and insulin resistance, which are closely related to the excessive pro-inflammatory cytokine production seen in chronic inflammation.³⁹ Nutrient excess produces reactive oxygen species, resulting in oxidative stress that damages cells and triggers an inflammatory response. The increased inflammation blocks the protective action of insulin, which normally stimulates target cells to take up nutrients. Unfortunately, as excessive nutrients are consumed, neighboring cells and tissues that remain insulin-sensitive are placed at risk. As insulin resistance progresses, inflammation is exacerbated, initiating a cycle of excessive nutrient intake/insulin resistance/ inflammation.⁴⁰ In some cells, nutrient excess impairs endoplasmic reticulum function and accelerates the accumulation of fatty acid derivatives that also promote inflammation.³⁹

The broad inflammatory response characteristic of obesity was first demonstrated by Hotamisligil et al.⁴¹ in 1993. They showed that the inflammatory cytokine tumor necrosis factor alpha (TNF- α) was overexpressed 5 to 10 fold in obese compared to lean mice. TNF- α activates signal transduction cascades that result in insulin resistance. The inflammatory response appears to be triggered and to reside predominantly in adipose tissue, which secretes a variety of hormones known collectively as *adipokines*. Deregulation of these proteins is associated with excessive weight gain, an inflammatory state, and a variety of chronic diseases, including knee OA.⁴²

Inflammation and OA

Since obese individuals have higher concentrations of inflammatory markers, inflammation may contribute to functional limitation and disease progression in those with OA. Besides direct effects on the joint, inflammatory mediators can affect muscle function and lower the pain threshold. Recent studies confirm that low-grade inflammation plays a pathophysiological role in OA. One of our earlier studies showed that the inflammatory cytokine interleukin-1 beta (IL-1 β), believed to mediate joint inflammation and cartilage degradation in OA, was present in the joint fluids of OA patients.⁴³ Likewise, an inflammatory component associated with OA can be detected in the circulation since serum concentrations of inflammatory markers, such as cytokines (interleukin-6, IL-6; TNF- α) and the acute-phase reactant C-reactive protein (CRP), are higher in people with knee or hip OA.^{44–46} Longitudinal studies demonstrate that high serum levels of CRP and TNF- α predict increased radiographic progression of knee OA as long as 5 years later.^{45;47;48} Moreover, a few studies, including one by our group,⁴⁹ associate OA severity and the resulting impaired physical function with higher inflammatory markers in the blood.^{50;51} Thus, severity, mobility, pain, stiffness, and radiographic progression are at least partly mediated by an OA patient's level of chronic inflammation. Diffusion of cytokines from the synovial fluid into the cartilage could contribute to the cartilage matrix loss observed in OA by stimulating chondrocyte catabolic activity and inhibiting anabolic activity. The adipokine leptin increases TGF- β synthesis within the joint; TGF- β is a known stimulator of osteophyte formation.⁵² Weight loss lowers serum leptin levels in OA subjects and is related to improved function.⁵³

No experimental studies in humans show that weight loss prevents knee OA. However, Felson et al.⁴ demonstrated that a 5.1 kg loss over 10 years decreased the odds of developing knee OA by over 50% in an observational study. Hartz et al.⁵⁴ suggested that the strong link between obesity and knee OA is related to the additional mechanical stress on the knees. It follows that

weight loss should relieve this mechanical stress, improving function and reducing pain in the affected knee. In a case-controlled study, the odds ratio for knee OA prevalence with a BMI ≥ 30 kg/m² was 6.8 compared to a reference group with a BMI between 20.0–24.9 kg/m². The authors predicted that 24% of surgical procedures for knee OA could be avoided by controlling obesity.³ Inflammation and joint loads are important mechanisms in osteoarthritis disease pathogenesis; however, their exact roles in the process and their association with obesity remain unclear.

Managing body weight

Given the important influence obesity has in OA pathogenesis, intervening on this modifiable risk is a critically important public health goal. This said, Wadden et al.^{55;56} noted that obese individuals have difficulty achieving permanent weight loss. Successful weight-loss and maintenance programs involve attention to a number of factors including behavioral change strategies, extended treatment, increased hours of intervention contact, adherence to a rigorous diet, exercise, and inclusion of significant others.^{57;58} Wing improved weight loss with increased treatment duration and intensity.⁵⁹ While maintaining weight loss is challenging, individual attention to coping strategies and increased intervention efforts during the maintenance phase have produced success. Approximately 80% of clients on moderate calorie restriction will remain in treatment for 20 weeks, and approximately 50% will lose 9.1 kg or more. An average weekly loss of 0.4 to 0.5 kg, with an average 33% regained 1 year after treatment is expected.

Maintaining weight loss seems to require rigorous follow-up contacts. Perri et al.⁶⁰ showed that participants in a 20-week behavioral therapy program, followed by an 18-week maintenance program with bi-weekly contact, maintained a 13.15 kg loss. Esposito et al.⁶¹ produced a 14.7% loss over a 2-year period in women following a moderate energy-restricted diet of 1300 kcals/day for year 1 and 1500 kcals/day for year 2. This intervention employed education, individualized goal setting, self-monitoring, and a structured exercise program. In the longest (3 years) and largest (n = 1032) study to date, Svetkey et al.⁶² found that participants randomized to a personal contact intervention regained less weight during the 30-month maintenance phase that followed the 6-month loss period than participants in an interactive technology intervention or a self-directed control group. Personal contact appears to be a vital component of successful, long-term dietary weight-loss programs.

The long-term effectiveness of low-fat and low-carbohydrate diets is currently under debate. Meta-analyses have found them no more effective than a low-calorie diet in reducing weight and improving cardiovascular risk factors.^{63;64} Increasingly popular meal-replacement diet drinks have been studied as a complement to reduced-calorie diets. Heymsfield⁶⁵ performed meta- and pooled analyses of six clinical trials that compared partial meal replacement to reduced-calorie diet plans and found greater weight loss, reduced risk factors, and a lower drop-out rate with the partial meal-replacement plan, but the small number of trials limited conclusions.

Weight loss reduces risk factors for symptomatic knee OA and lowers pro-inflammatory cytokines and adipokines thought to play a role in cartilage degradation. Our Arthritis, Diet, and Activity Promotion Trial (ADAPT)⁶⁶ diet groups achieved 5% weight loss over 18 months using a reduced-calorie diet with behavioral strategies, and the Physical Activity, Inflammation, and Body Composition Trial (PACT) pilot study achieved a 9% weight loss over 6 months in obese older adults with knee OA by combining a partial meal-replacement plan with accepted behavioral strategies.⁶⁷ Using a similar cohort and an intensive low-energy diet that achieved an 11% weight loss, Christensen et al.⁶⁸ found a 3-fold improvement in WOMAC function over an 8-week period compared to a control diet group who lost 4% of

their body weight. Cognitive strategies were used to promote behavior change. A recent meta-analysis of 35 potential trials identified only four that met the authors' inclusion criteria. From these four studies, they concluded that weight loss in knee OA patients significantly reduces disability and that a weight loss of at least 10% would result in a moderate-to-large clinical effect.⁶⁹ Christensen et al. concluded that weight loss should be the first-choice therapy for obese adults with knee OA.⁶⁸

Randomized clinical trials (RCTs) that examined weight loss in adults over 65 years reported no difference in mortality compared to groups that did not lose weight.^{70;71} Diehr et al.⁷² suggested that for the aged population, quality of life and years of healthy life may be more appropriate outcomes. These measures have important public health implications for morbidity and daily living activities. Moreover, for older adults with knee OA, pain reduction and improved mobility are important outcomes.

Loss of bone and muscle mass is a problem in weight-loss programs for older adults. Weight loss is associated with decreased bone-mineral density,^{73;74} increased bone turnover,⁷⁴ and increased fracture rates.^{75;76} Fiatarone Singh⁷⁷ noted that combining hypocaloric diets with aerobic exercise in older adults resulted in loss of lean mass, which resistance training tended to offset. Janssen et al.⁷⁸ found no lean tissue loss when diet was combined with resistance or aerobic training in premenopausal women. In contrast, Wang et al.⁷⁹ found that a 6-month weight-loss intervention that incorporated partial meal replacements and aerobic and resistance exercises for older obese adults with knee OA resulted in an 8.1% weight loss of which 19.9% was lean mass. However, the exercise training improved knee-extensor strength 37% compared to a 1% loss of strength in a weight-stable control group. These results show that intentional weight loss, when combined with aerobic and resistance exercise training, improves knee-extensor strength despite loss of lean body mass.

Exercise Interventions

Although OA patients commonly avoid activity, physical exercise is an effective nonpharmacologic treatment. Several studies have shown that pain, physical function, and walking distance improve an average of 26%, 31%, and 15%, respectively, with short-term exercise.^{80;81} Furthermore, long-term walking and resistance-training programs have made significant, if modest, improvements in self-reported function (1–11%), slowing the decline in physical function commonly seen in this disabled population (Figure 3).^{82–84} Participants in the Fitness Arthritis in Seniors Trial (FAST) who were randomized to either 18-month aerobic or resistance-training interventions showed a dose response to exercise, with higher compliance yielding better function, less pain, and longer 6-minute walking distance and similar gains being found in both groups compared to an attention control group.⁸² Recently, the exercise group in our ADAPT trial showed statistically significant and clinically relevant (16%) long-term gains in mobility, effectively slowing the impairment common in the older OA population.⁶⁶

Exercise interventions in older adults with knee OA, however, tend to help them to maintain their weight more than to lose it. The exercise-only group in ADAPT lost 3.5 kg, or 3.7% of their baseline body weight, after 18 months of intervention compared to 5.2 kg (5.7%) and 4.6 kg (4.9%) for the diet-plus-exercise and diet-only groups, respectively.⁶⁶ In the ADAPT pilot study, a 6-month exercise program resulted in a 1.8 kg weight loss, whereas the exercise-and-diet group lost 8.5 kg.⁴³ In summary, long-term exercise programs in this disabled population improve mobility and pain and are effective in maintaining body weight.

Conceptual Basis and Delivery of the Lifestyle Intervention

The reciprocal interaction of personal factors (e.g., beliefs and values), social influence (e.g., support and strain), and physical environment (e.g., structure and access to resources) can improve weight loss and fitness by modifying both eating and physical activity behaviors.⁸⁵ Our clinical trial protocols (FAST, ADAPT, and, currently, Intensive Diet and Exercise for Arthritis [IDEA]) evolved from social cognitive theory, group dynamics literature, and over 15 years' experience in clinical trial research.

Social cognitive theory is based on three constructs: self-efficacy expectations, outcome expectations, and incentives. Self-efficacy expectations arise from individuals' beliefs that they can act to satisfy the demands of a situation. Such beliefs are determined by prior behavior, physical symptoms (e.g., pain, fatigue), appetite, affect, and social/environmental factors.⁸⁵ The physical activity literature studies them to predict the ability to perform functional tasks or physical challenges of varying difficulty,^{86–88} and both the physical activity and eating behavior literatures have examined them under various environmental, social, and emotional stressors. Because self-regulation is important to successful behavior change, our clinical trials use goal setting and self-monitoring.^{89,90}

Outcome expectations refer to the anticipated costs and benefits of a behavior. People are more likely to try if the perceived consequences have a favorable cost/benefit ratio.⁸⁹ Some people simply do not know the negative health effects of being overweight/obese and sedentary or are unduly optimistic about their own fate. They often become discouraged when lifestyle interventions, first, do not meet their unrealistic expectations about how much weight they can lose; second, cause pain and fatigue; or third, prohibit a valued food.

Incentives refer to the value that people associate with outcomes.⁸⁹ In our weight-loss clinical trials, the nutrition interventionist personalizes the protocol by learning how much participants value controlling their physical disability and/or reducing their weight; the dissatisfaction differential between the goal and the current weight; and the commitment to competing behaviors, such as responsibilities to families or friends. In the IDEA trial, we train our diet and exercise interventionists in social cognitive behavioral strategies, reinforced by discussion of success stories. They review participant programs with our health psychologist bi-weekly, developing strategies to use with participants who are finding it difficult to adhere.

The Future of Behavioral Weight-loss Interventions

OARSI guidelines recommend a combination of nonpharmacological and pharmacological interventions for the treatment of knee OA.⁹¹ In addition to the challenges presented by any weight-loss intervention, the knee OA population's typical age and chronic pain create barriers. Nevertheless, dietary weight-loss trials demonstrate significant improvements in pain and function with only a 5% loss, especially if exercise is included as part of the intervention. Weight loss reduces inflammation and joint loads, but no evidence indicates that it alters disease progression. A meta-analysis of previous weight-loss interventions suggests that at least 10% is necessary for a large clinical effect, but such results lasting longer than 1 year are rare. The ongoing IDEA clinical trial will determine if a 10–15% weight loss over 18 months either slows or stops OA disease progression. We hypothesize that a weight loss of this magnitude—2 to 3 times that achieved in previous long-term OA weight-loss trials—will reduce inflammation and knee-joint loads sufficiently to retard joint destruction and to improve function and pain far beyond what has previously been attained.

Translating Trial Results to Clinical Practice

The National Institutes of Health (NIH) have identified research on intervention approaches that incorporate primary care practice as a high priority.⁹² Patients generally believe that their primary care physician should have a role in weight management.⁹³ A recent study found that only 42% of obese adults who had visited their healthcare professional during a 12-month span were advised to lose weight.⁹⁴ More disturbing, when either diet or exercise was discussed, a median of 0.7 minutes (42 seconds) was spent on this pressing and pervasive public health concern.⁹⁵

Integrating the primary care physician and nurse into weight-loss intervention trials has met with modest success. Ashley et al.⁹⁶ enrolled 113 overweight, premenopausal women in a 1-year weight-loss program. A primary care office intervention (meeting with the primary care physician or nurse) combined with partial meal replacements was compared to traditional dietitian-led groups with and without meal replacements. Over the course of 52 weeks, the dietitian-led group with meal replacements produced greater weight loss (9.1%) than the traditional dietitian group (4.1%) and the primary-care-plus-meal-replacement group (4.3%). However, all three groups were successful in achieving and maintaining weight loss.

An evidence-based, weight-management model was implemented in 47 clinical practices involving 1,256 obese patients⁹⁷. It involved four phases: setting priorities, setting guidelines, measuring performance, and improving performance. Both general practice physicians and practice nurses were recruited at each clinical site. The weight-loss target was 5–10% of baseline weight. Preliminary results indicated that one-third of all patients had a clinically relevant loss of more than 5% of baseline body weight at 12-month follow-up. Of the 58 general practices that began the trial, 15 dropped out, primarily due to lack of resources and time. The authors concluded that a primary care weight-management model can be used as part of a multistrategic approach to manage obesity in the community.

Clinical trial results can only be integrated into clinical practice if it is financially viable. We recommend that primary care physicians and rheumatologists urge their obese patients to enroll in a comprehensive weight-loss and exercise programs run by a nurse, dietitian, or physician assistant in collaboration with an ACSM-certified exercise specialist. However for such a program to be successful, several barriers must be addressed, including lack of reimbursement, lack of training, time constraints during normal office hours, and physicians' perceptions that these behavioral interventions are generally unsuccessful.⁹⁴

Conclusion

Obesity plays an important role through both mechanical forces and inflammation in predisposing to OA development. Interventions designed to promote dietary weight loss and exercise in obese persons with OA have demonstrated clinically significant improvements in symptoms and disease risk factors. Dissemination of these pivotal research findings into clinical practice is facing a number of obstacles that health care practitioners can become more involved in removing to facilitate addressing this pervasive, but modifiable public health problem.

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Figure 1.

A: Peak pressure during walking

B: Mid-foot peak pressure

From: Hills et al. *Int J Obes Relat Med Disord*, 2001

Figure 2.
Obese exert 60% more force than normal weight individuals.
From: Browning and Kram, MSSE. 2007

Figure 3.
Disability versus time
From: Ettinger et al., JAMA 1997