

MANAGEMENT OF OBESITY IN THE ELDERLY: TOO MUCH AND TOO LATE?

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Introduction

The prevalence of obesity is increasing globally. This with the aging population structure accounts for the increased prevalence of chronic diseases associated with obesity. For example, the number of people with diabetes in the world is projected to reach 300 million before 2025. Through childhood, adolescence, and adult life, obesity prevalence increases with age. However, the elderly (aged 60 plus), have a lower prevalence and in the extreme elderly (aged 80 plus), it is only a third of that in middle life. Obesity in the elderly presents a distinct problem. As at younger ages, it is associated with chronic diseases, and with functional and cognitive decline. However, the prevalence of being underweight is also a high and is itself a marker for poor health and functional decline. The ideal body weight and composition for elderly populations has yet to be defined. Weight management should be a target for certain elderly individuals whose health is at risk. However, in the elderly is important to maintain an optimal body composition as well as weight. Elderly individuals with weight-related diseases such as type 2 diabetes represent an obvious target for weight management. It is, in practice, difficult to identify elderly patients who would benefit from weight management programmes. The various components of the metabolic syndrome (MS) become more common with aging. Drugs to decrease cardiovascular risk and to treat diabetes and the other chronic diseases of aging have improved in recent years. The elderly are frequently prescribed complex drug regimens with which they often comply poorly, derive little benefit, and experience a high risk of adverse reactions and drug interactions. Although it is clear that obesity should be treated in high-risk elderly patients, pharmacotherapy and surgery do not have an evidence base specific to the elderly. There is emerging evidence to guide us with dietary and exercise therapy (1, 2). This review attempts to define the situations in which management of obesity is indicated, and to summarise what is known, and what is emerging, about the various treatment options.

The Scope of the Problem

The projected increased prevalence of overweight and obesity in the elderly (60 plus) in the United States between 2000 and 2010 is from 32.0% to 37.4%, reflecting an increase

from 14.6 million to 20.9 million (3). The general prevalence of obesity, particularly abdominal obesity, has increased steadily in recent years – Figure 1 (4). Obesity is the most important modifiable risk factor after smoking, and may be overtaking smoking as a determinant of poor health. It is said that over 300,000 deaths annually in the United States are directly attributable to obesity. The impact of obesity on health and mortality risk is hard to estimate precisely because of the complex interplay with other factors, the lack of definition as to what constitutes obesity in the elderly, and the fact that most studies focus on BMI as an index of excess weight (5). Being either underweight or obese increases risk of death, but being modestly overweight may not increase risk for the elderly (6).

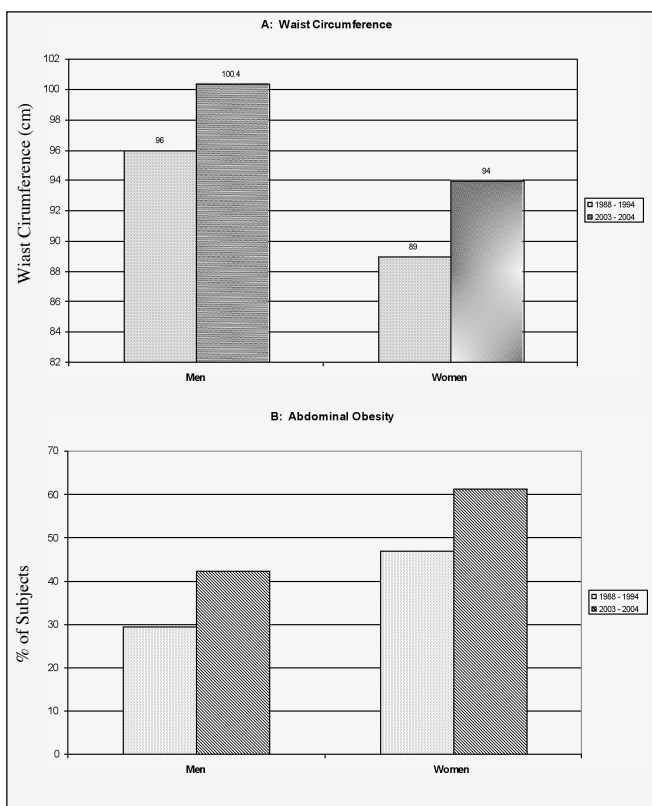
Evidence suggests that obesity prevalence continues to increase in the young and in men, although it may have reached a plateau in women (7). At least 32% of adults in the United States are obese, with extreme obesity (BMI \geq 40 kg/m²) affecting 2.8% of men and 6.9% of women. Obesity affects 30% of white non-Hispanic US citizens, 37% of Hispanic subjects and 45% of the black population (7). Diabetes is more than twice as likely to occur in Hispanic or Black Americans compared with Caucasians. The prevalence of diagnosed diabetes has increased from 5.1% to 6.5% (8). Prevalence of undiagnosed diabetes (2.8%) and impaired fasting glucose have remained static.

Expenditure on healthcare for obese individuals is likely to increase markedly. Costs are difficult to estimate for a number of reasons: The relative contributions of obesity and aging are hard to gauge; Expenditure on healthcare is increasing as new treatments become available, the evidence base favouring their use expands, and public expectations increase; it is not clear what the most appropriate clinical measures and reference ranges are for the elderly. The direct costs of managing people with obesity are particularly high in those with severe obesity (BMI \geq 40 kg/m²), accounting for over \$11 billion annually in the US (9).

There is strong evidence that increased BMI is associated with risk of death. However, low BMI is also a risk, presumably because of the association with diseases which influence life expectancy (10-12). Both decreased energy expenditure (13) and increased body mass (10, 12) have been correlated with increased mortality. In the Physicians' Health Study, (10) over 85,000 males were followed up for five years, during which there were 2,856 deaths. Those who never

smoked but had BMI > 30 kg/m² were at 70% increased risk of death. Both all-cause and cardiovascular mortality showed a clear relationship with BMI. Similarly, in a study of over 1.2 million Koreans, increased BMI was linked with increased mortality (12). Janssen and Mark (14) performed a meta-analysis of 28 studies and reported that overweight (but not obese) elderly subjects were not at increased risk, and that those who were only modestly obese had only slightly increased risk.

Figure 1
Increasing Prevalence of Abdominal Obesity



Data are from the National Health and Nutrition Examination Survey (NHANES) (4). A shows the increase in waist circumference from 1988-1994 to 2003-2004. B shows the increase in the prevalence of abdominal obesity.

Metabolic Syndrome (MS), Diabetes and Cardiovascular Risk

The precise definition of MS has been controversial. Currently, two definitions are widely used: The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) definition (2001) defines MS as any three from abdominal obesity (waist circumference \geq 102 cm for men or \geq 88 cm for women), increased triglycerides, decreased HDL-cholesterol, hypertension, or fasting plasma glucose \geq 6.1 mmol/l. The International Diabetes Federation (IDF) definition

(2005) is based on waist circumference \geq 94 cm for men or \geq 80 cm for women, plus any two of increased triglycerides, decreased HDL-cholesterol, hypertension, or fasting plasma glucose \geq 5.6 mmol/l. However defined, MS is highly prevalent among the elderly (15-17). He et al. (15) reported a prevalence of 19.6% among men and 39.2% among women using the ATPIII. The corresponding figures using the IDF definition were 34.8% and 54.1%. Similar high prevalence has been reported in recent Swedish (18) and Italian (16) studies. As expected, the prevalence of MS factors is higher amongst those with diabetes (16).

MS is strongly associated with cardiovascular (CV) disease, (19, 20) including stroke (21) and peripheral vascular disease (22) in the elderly. Not surprisingly, MS predicts death, (23) although mortality prediction may not be so reliable in the elderly unless combined with other biological markers (e.g.cytokines) (24). Obesity itself is strongly correlated with decreased physical activity and function, with both increased fat and decreased muscle (sarcopenia) making independent contributions (25-28). Chronic inflammation and changes in adipokines may mediate the link between increased fat and functional decline (29). Higher CV risk profile is itself a predictor of functional decline (30, 31). The relationship between MS and impaired function may be apparent from early old age with simple measures such as gait speed, (32, 33) even in the absence of vascular events (34).

Increased body mass, particularly fat, strongly correlates with decreased quality of life in elderly men (35) and elderly women, (36) even after correcting for co-morbidities (37). Physical variables are particularly affected (38). There is a strong relationship between impaired quality of life and the functional decline (28, 34). The prevalence of MS components, except diabetes has decreased in the past four decades (39). MS variables are strongly predictive of type 2 diabetes in the elderly, (40) with both body mass and insulin resistance exerting overlapping but also independent influences (40, 41) Diabetes, diagnosed and undiagnosed, affects 9.3% of the US adult population and is a major determinant of quality of life (42) and disability (43). It seems self evident that prevention and effective management of diabetes should be one of the major goals of managing obesity.

Other Consequences of Obesity in the Elderly

Predisposition to a wide range of disease states is increased in the overweight or obese – Table 1. These should not be neglected when assessing the impact of obesity, and in planning social and medical management. After CV disease, cancer is the most common cause of death. Mortality from cancer increases with BMI (12, 44). It was estimated that the equivalent of 14% of cancers in men and 20% in women in the US could be attributed to obesity (44). A particular link between obesity and colorectal neoplasia has been documented in recent years (45). Obesity and diabetes are independent risk

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factors, (46) and the inflammation and other metabolic changes may contribute. Low levels of exercise may also directly contribute: In the study by Larsson et al., (46) the hazard ratio for colorectal cancer was 0.57, comparing those who exercised for > 60 minutes per day with those who exercised for < 10 minutes.

Loss of muscle mass directly contributes to impaired function and mobility, (47) but through loss of muscle tone and joint protection, may also directly contribute to development of osteoarthritis (OA). Knee OA is more strongly associated with obesity than is hip OA (48, 49). In the Rotterdam study, (49) BMI of ≥ 27 kg/m² was associated with odds ratio of 3.3 for development of knee OA, and odds ratio of 3.2 for its progression. Decreased respiratory function also accompanies obesity, and is related to total BMI and abdominal obesity, (50) as well as with inflammatory markers (51). There is also a high incidence of obstructive sleep apnoea hypopnoea syndrome (OSAHS) in the elderly. Obesity and diabetes are contributory factors in many patients with OSAHS (52). Urinary symptoms are also very common in obese subjects, even without diabetes. In the Health, Aging and Body Composition study (53) urge and stress incontinence were increased in obese subjects. Nocturia may predispose to decreased quality of life through loss of sleep, and also to worsening obesity through increased nocturnal and daytime eating (54).

Dental disease is often overlooked as a cause of morbidity. Tooth loss, periodontal disease and poor masticatory performance can all cause under-nutrition, and attenuate the relationship between previous obesity and chronic disease. Tooth loss and periodontal disease, through low-grade systemic inflammation, have been linked with diabetes and CV risk. Gastro-oesophageal reflux disease (GORD) is common generally, and more likely to occur in the overweight or obese. Rey et al. (55) reported that a weight gain of < 5 kg increased OR of GORD by 1.5, while an weight increase > 5 kg was associated with an OR of 3.0. Non-alcoholic fatty liver disease (NAFLD) is increasingly recognised with obesity. This is often asymptomatic, and may only be recognised because of increased liver enzymes (56). NAFLD is, however, an important condition as it may lead to cirrhosis and hepatocellular carcinoma. Also, there is a strong association between NAFLD and the risk factors that constitute MS (57). Weight loss, however achieved, improves biochemical and histological features of NAFLD and consequently improves insulin resistance and dyslipidaemia. Specific trial data with NAFLD as a therapeutic target are somewhat lacking (58).

Table 1
Health Consequences of Obesity in the Elderly

Metabolic syndrome	Ischaemic heart disease
Type 2 diabetes	Stroke
	Peripheral vascular disease
Increased cancer risk	
Visual failure – diabetic retinopathy, cataract, macular degeneration	
Functional decline	Impaired quality of life
Cognitive decline	Social isolation
Anxiety, depression	
Poor respiratory function	Obstructive sleep apnoea
Osteoarthritis	
Gastro-oesophageal reflux	Non-alcoholic fatty liver disease
Urinary symptoms	Endocrine disorders

Age-related macular degeneration (AMD) is an important cause of visual deterioration with aging. AMD may not be more common in overweight or obese subjects, but progression of the condition is more rapid in those with higher body mass (59, 60). A recent study from the Women's Health Initiative (61) has demonstrated that high CV risk is associated with advanced AMD, with smoking, high BMI and hypertension being particularly important. There may be an interaction between obesity and genetic factors, including variations in the complement factor H (CFH) in determining susceptibility to progression of AMD (62, 63) Systemic inflammation (increased levels of IL-6 and CRP) is also related both to obesity and progression of AMD (64). Extreme obesity has also been identified as a possible risk factor for cataract (65).

MS is a recognised risk factor for cognitive decline and dementia, particularly in elderly women (66, 67). This risk extends to patients with diabetes (68) where both hypo- and hyper- glycaemia may contribute to impaired mental functioning. Cognitive decline is highly predicative of functional decline (69). The Health, Aging and Body Composition study (70) confirmed a strong association between mental and physical decline. A recent meta-analysis (71) suggested that high BMI was an independent risk factor for dementia, although other authors (72) have proposed a protective effect of obesity because of increased exposure to endogenous oestrogen.

In relatively low-risk and independently functioning individuals, primary management of obesity seems reasonable, particularly if there is potential for favourable change in diet and exercise. In patients at moderate to high risk e.g. those with poorly controlled diabetes or established vascular disease, specific management of their disease states is appropriate with weight management as a secondary goal. At the extreme end of the aging spectrum, frailty syndrome (not always directly related to chronological age) is characterised by weakness, exhaustion, slowness, and low levels of activity. Development of this syndrome is accelerated in subjects with pre-existing obesity (73, 74) It may be difficult to offer anything more than supportive care in such cases.

Body Composition and Biochemical Changes with Aging

Obesity in aging is accompanied by increasing mass and altered distribution of fat, along with decreased muscle mass and function. Sarcopenia predisposes to decreased performance in activities of daily living, (75) increased physical disability, (47) and development of the frailty syndrome (76). Loss of muscle mass also correlates with decreased bone quality, presumably because of decreased mechanical stresses (77). On the other hand, loss of muscle mass may protect against development of CV risk factors in elderly obese subjects (78). The issue is not simply loss of muscle tissue with consequent weakness of muscle groups, but other qualities of muscle such as fatigability may be affected, and may not be entirely reversed by treatments which preserve or restore muscle mass (79, 80). It is clearly important that measures to treat obesity in the elderly decrease fat mass while preserving muscle mass. Skeletal muscle mass is an important determinant of basal metabolic rate. Resting energy expenditure of typically 3.5 ml/min/kg may overestimate the energy expenditure of elderly subjects, irrespective of body composition (81, 82).

Fat mass not only increases with age but the distribution changes with increased accumulation in the abdominal and subscapular depots (83). Increased abdominal fat correlates strongly with MS and other CV risk factors, while peripheral adiposity in the typical female distribution may be protective (84). General adiposity of the elderly population has increased in recent years because of social changes and differences in dietary and other habits (85). Nonetheless, the level of adiposity associated with increased risk to health may be higher in the elderly than in younger age groups (86). Along with increased fat deposition in traditional fat depots, those with obesity develop ectopic fat deposition including in the liver leading to NAFLD and within muscle leading to insulin resistance (87).

Adipokines are hormones produced in adipose tissue, and which mediate interactions with other tissues. Adipokine measurements have not, to date, proved useful in routine clinical practice. As with younger subjects, circulating leptin levels increase in the elderly in relation to fat mass, and increased levels correlate with the presence of MS (88). Leptin is involved in regulating appetite but also in other processes including inflammation and bone turnover (89). Resistin is also increased in obesity, including in the elderly, and correlates with MS (90). In younger subjects ghrelin, an orexigenic mediator, levels decrease with obesity. This relationship is attenuated in the elderly (91). Low levels of adiponectin occur in elderly obese subjects (92, 93) and are associated with risk of diabetes and CV disease. Higher levels in the extreme elderly have suggested that the hormone may have a role in regulating longevity (94). While the association of low adiponectin with CV risk is established, (95) its role as an independent predictor of events has been questioned (96). Leptin and adiponectin levels return towards normal when elderly obese subjects undergo exercise training, (97) suggesting that they could be

used as surrogate markers for treatment response.

Many chronic disease states are accelerated by low-grade inflammation. In the elderly, inflammatory markers are increased with abdominal obesity, (98) metabolic syndrome, (99) or type 2 diabetes (100). In these high-risk groups, increased inflammatory markers (e.g. C-reactive protein or interleukin-6) are highly predictive of functional decline (100, 101). The association with other disease states make it not surprising that inflammatory markers are often increased in those who are nearing the end of life (102). As with adipokines, inflammatory markers have not yet been used routinely to indicate high-risk from obesity or to monitor treatment response.

Hormonal Changes and the Prospects for Endocrine Treatment

A number of endocrine changes take place in midlife and the ensuing years. Many of these tend to occur at an earlier age in the obese and may be more exaggerated. Collectively, we term these changes Obesity-related Endocrinopathy (ORE) - Table 1. Important alterations occur in secretion of sex steroids, the growth hormone/IGF-I axis, thyroid hormones, cortisol and in the regulation of calcium.

The most obvious endocrine change is the female menopause, which typically occurs around age 52. Women now spend up to 40% of their life in an oestrogen deficient state. It should not be assumed that all hormone changes around the menopause are related to oestrogen withdrawal and could, therefore, be reversed by oestrogen replacement. A number of recent sequential studies have clarified the changes in body composition and metabolism which accompany the menopause, but the influence of hormone replacement therapy has varied in different studies (103, 104). Following menopause there is an increase in fat mass with a shift towards upper body obesity, a decrease in lean body mass and skeletal mass. The Study of Women's Health across the Nation (SWAN) has documented changes in body composition over six years in the absence of hormone replacement therapy (HRT) (105). Total fat mass increased by 6.0 kg with a 5.7 cm increase in waist circumference, while skeletal mass decreased by 0.23 kg. Average weight gain was 9.0 kg, corresponding to a 1.2 kg/m² increase in BMI. Decreased muscle mass may be an important determinant of skeletal loss while increased central obesity leads to increased leptin and free androgen index (77, 106-108). Increased fat and loss of muscle, along with co-morbidities associated with obesity, are strong markers for disability and diminished quality of life (28, 36). Increased central fat mass may make an important contribution to oestrogen status by conversion from circulating androgens, and that this may protect against cognitive decline (109). Eating frequency is a determinant of overall energy intake but appears not to greatly influence adiposity in pre-menopausal women but correlates with adiposity in post-menopausal women (110).

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Table 2
Obesity-related Endocrinopathy (ORE)

Decreased oestrogen (women) Low SHBG	Decreased testosterone (men) Decreased DHEA (men and women)
Low growth hormone (GH)	Low insulin-like growth factor-1 (IGF-1)
Increased prolactin Changes in thyroid hormones (see text)	
Low vitamin D High Cortisol	Secondary hyperparathyroidism

HRT protects from loss of skeletal mass following the menopause for as long as it is taken. However, concerns about the increased breast cancer risk, and doubts about benefit in CV protection have led to recommendations that HRT is limited to those experiencing menopausal symptoms and that prolonged use be avoided where possible. Data from the Women's Health Initiative study suggested that combined HRT protected from loss of lean body mass following menopause, although it was doubtful whether the magnitude of this protection was likely to be of major significance (111). This confirms another recent report (112) that HRT did not protect against menopause-induced changes in body composition or muscle function. Additionally, it is likely that HRT leads to a slight, but significant, decrease in insulin sensitivity (113, 114).

Recent studies confirm that aging men have gradually decreasing levels of free and total testosterone, and that these changes relate to altered health, functioning, and quality of life (115, 116). Decreasing levels of testosterone with aging coincide with increasing fat mass (particularly abdominal) in aging men (117, 118). Changes in leptin and adiponectin levels with obesity correlate strongly with decreased testosterone levels, particularly in men (93, 119-121). Overall, androgens tend to be associated with predominantly lipolytic states while the effect of oestrogen on adipose tissue is mainly lipogenic. For both men and women, the ratio of androgen to oestrogen relates more closely to adiposity than levels of the individual hormones (120). Loss of muscle with aging also correlates with decreasing testosterone, but this is not the sole determinant (122). Low androgen status, which may be a consequence, as well as a cause, of obesity increases risk of developing MS or type 2 diabetes (119, 123).

The relationship between obesity and androgen status in aging women is not so clear cut. While total testosterone tends to decrease with age, this may be due to decreased SHBG secondary to oestrogen withdrawal, and free testosterone may remain relatively stable (124). Testosterone levels are lower in individuals who have undergone oophorectomy and in those taking pharmacological doses of steroids. The significance of decreasing testosterone as a determinant of changes in body composition with aging has been questioned (28, 122, 124). Testosterone level is probably only a weak determinant of physical functioning in elderly women (125). There is a clear

relationship between low testosterone status and decreased libido and sexual function in women. SHBG is lower, and free testosterone higher, in women with abdominal obesity, insulin resistance and metabolic syndrome (106, 126, 127). As in men, this may be effect rather than a causative relationship.

Androgen replacement prevents or reverses some of the changes in body composition and features of MS that develop with aging in men (128). Although some studies support the benefits of low-dose testosterone, most have been fairly limited and of short duration. A more prolonged and extensive study, (129) did not show any benefit. Potential side effects include increased risk of breast cancer, prostatic disorders and altered liver function. At present, androgen replacement should be reserved for those with clear-cut symptoms of hypogonadism, preferably with an established diagnosis, and the treatment should be carefully monitored (130). Some of this variability in symptoms and treatment response may relate to the CAG repeat polymorphism in the androgen receptor (AR) gene (131). Androgen replacement is more beneficial when combined with other treatments: Exercise not only increases the testosterone level achieved with replacement, but the combination but also enhances physical and social functioning (132). The combination of testosterone and growth hormone replacement has been reported to have beneficial effects on protein turnover, lipid profile, and fat mass (133, 134).

Dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) are the most abundant circulating adrenal steroids in humans, and levels decline progressively with age. DHEA exerts peripheral effects through conversion in tissues to either androgens or oestrogens, and may also have direct effects. The decline in DHEA with aging has been related to increased risk of obesity, type 2 diabetes, CV disease, neurodegenerative diseases, as well as to general physical and cognitive decline. Relative androgen deficiency contributes to sarcopenia, and may limit the response to exercise programmes. Villareal et al. (135) found no effect of six months of DHEA supplementation on muscle performance or on muscle bulk assessed by MRI. However, in a subsequent four months of treatment where DHEA was continued along with a muscle-building exercise programme, both performance and muscle bulk were increased. These improvements were accompanied by increased IGF-I levels. Decreases in both circulating DHEA and IGF-I have been reported in frail elderly individuals, (136) and decreases in these two hormones may correlate with low grade inflammation as evidenced by increased IL-6.

The Massachusetts Male Aging Study (MMAS) examined the relationship between measures of obesity and sex steroid levels in 942 men examined in 1985 – 1987, and during follow-up until 1995 – 1997 (117). Obesity was defined as BMI greater than 30 kg/m², waist circumference greater than 100 cm, or waist-hip ratio greater than 0.95. All three measures were associated with progressive decrease in testosterone (total and free) and SHBG. Central adiposity was particularly related to decreased DHEAS. The relationship between the latter and

risk of MS is uncertain (119). A recent two-year trial of DHEA supplementation (137) in elderly men and women failed to show any improvements in insulin secretion or sensitivity or in postprandial glucose. Increased fat mass, decreased muscle mass and performance, as well as the presence of comorbidities are undoubtedly associated with decreased quality of life, but recent studies suggest that levels of DHEA(S) or IGF-1 may not be determinants (36, 129). In the study by Nair et al., (129) there was no beneficial effect of DHEA replacement on body composition, aerobic performance, muscle strength or insulin sensitivity in either men or women. Recent studies, therefore, suggest that routine supplementation of DHEA is not warranted even though many of the changes in body composition and other parameters that accompany aging are paralleled by declining levels of DHEA.

SHBG is down-regulated by insulin, and low levels in hyperinsulinaemic states may be useful marker for MS, (138) and increasing SHBG levels could be a useful therapeutic target (127). Low SHBG is strongly associated with MS variables in older men, (117, 119, 123) as well as in younger, non-obese men (139). Low SHBG occurs in women with polycystic ovarian syndrome (PCOS) and in those with isolated MS (140, 141). A number of studies have documented the inverse relationship between circulating SHBG and obesity/MS in postmenopausal women (106, 125, 126, 142). The relationship between SHBG and features of MS holds good in cohorts from different ethnic groups (143, 144). SHBG levels are partly genetically determined. The (TAAAA)_n polymorphism in the SHBG gene has been linked with PCOS, (145) women with PCOS having a larger number of repeats and lower SHBG. More recently, the Pro12Ala polymorphism in the PPAR- γ 2 gene has been linked with susceptibility to MS as well as with SHBG levels (146). Individuals with the Ala12 Ala genotype had higher SHBG and lower incidence of MS compared with those with Pro12Ala or Pro12Pro genotypes. Furthermore, amongst those with the latter two genotypes, SHBG was particularly low in those who had MS.

The gradual decline in activity of the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis with aging has been termed the somatopause. It is physiological and does not indicate development of clinical hypopituitarism. Symptoms include decreased muscle strength, decreased cardiovascular performance, impaired sense of well being, and decreased cognition. Numerous relatively short term studies have demonstrated improvement in these symptoms with GH. However, recombinant human GH is expensive and can cause side effects (peripheral oedema, joint pains, carpal tunnel syndrome) and theoretically might accelerate development of malignancies. It is not, therefore, recommended for routine use, (147-149) except in patients with proven hypopituitarism where there is sustained benefit (150). Low-dose GH has been advocated, particularly with testosterone treatment, to improve protein metabolism (133) and body composition (134) in the elderly. Studies with positron emission tomography (PET) and

functional MRI have respectively shown improved cerebral blood flow (151) and cerebral function (152) with GH replacement. A recent meta-analysis (153) of 13 studies confirmed the association between low IGF-1 and cognitive impairment. Low IGF-1 is also involved in loss of lean body mass (121) and development of frailty, (136) but not with features of MS (127).

Increased circulating prolactin has been correlated with high BMI, (126) abdominal obesity, (154) and insulin resistance (155). High prolactin may help explain the relationship between obesity and breast cancer. The metabolic effects may be mediated through prolactin receptors on adipocytes, leading to decreased adiponectin (156, 157). Increased platelet aggregation (158) and increased inflammation (159) in obesity may also be related to hyperprolactinaemia. Levels of prolactin decrease with weight loss, (160) and preliminary data suggest that lowering prolactin with dopamine agonists leads to lower levels of inflammation (159) and weight loss (161). Increased free thyroxine (fT4) and reverse triiodothyronine (rT3) with decreased triiodothyronine (T3) may occur with decreased physical functioning during aging, while lower fT4 correlates with longer survival (162). These differences almost certainly reflect changes in thyroid hormone metabolism, perhaps mediated by TNF- α , rather than changes in underlying thyroid status. They do not therefore merit treatment to alter circulating thyroid hormone changes. The decrease in metabolic rate with aging is not mediated by changes in thyroid hormones (163). Hyperparathyroidism has been shown to be associated with increased body weight and fat mass (164). Low vitamin D status is also common, (165) and could contribute to development of secondary hyperparathyroidism. It is not clear whether hyperparathyroidism leads to obesity or vice versa and these changes are only partially reversed if the patients lose weight (86). Renal impairment is common with aging, especially with diabetes, and may contribute to low vitamin D and high PTH. Bone changes secondary to renal disease with increased calcium mobilisation contribute to vascular calcification which is a marker for developing atherosclerosis (72, 166)

Increased circulating cortisol occurs in patients with central obesity, insulin resistance and MS (167, 168). This may be due to increased activity of the pituitary-adrenal axis because of stress or to increased generation of cortisol from the biologically inactive hormone cortisone by 11- β -hydroxysteroid dehydrogenase type 1 (11- β -HSD1). Cortisol levels are particularly high in patients with diabetes, where there is a correlation with the presence of vascular complications (169). High cortisol has been linked with cognitive decline, (170) and with the development of dementia (171). Inhibitors of 11- β -HSD1 have been developed and may assist with the management of obesity and insulin resistance by decreasing bioavailable glucocorticoid (172, 173)

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Activity and Exercise

Sarcopenic obesity leads to functional decline and is related to co-morbidities and decreased life expectancy. The Health, Aging and Body Composition Study (174) investigated > 3,000 subjects aged 70 – 79 years, and showed that habitual activity was a major determinant of physical functioning. In young and old subjects, obesity is more common in those who have lower levels of habitual activity. Obesity is 2-3 times more common in elderly people who walk < 30 minutes per day compared with those who have a higher level of regular activity (175). Additionally, low levels of exercise strongly correlate with impaired performance in activities of daily living. By contrast, elderly subjects who perform high-intensity exercise have decreased fat mass, increased skeletal mass, and perform better in activities of daily living (175). Relationship between energy expenditure during the active period of the day and fat mass has been confirmed recently (176). Muscle fat oxidation is increased during exercise, leading to mobilisation of fat. Sequential changes in body composition of elderly subjects over a three-year period have been studied by Raguso et al. (177). Even when total body weight is unchanged, fat-free soft tissue and skeletal mass characteristically decrease, and individuals with high in leisure time activity are not protected. Activity level is lower in those with lower life expectancy. Menini et al. (13) studied 302 subjects aged 70 - 82 years followed for six years, measuring total energy expenditure (TEE, with doubly labelled water), resting metabolic rate and diet-induced thermogenesis (RMR and DIT, by indirect calorimetry). Free-living energy expenditure (FLEE) was calculated from TEE and RMR, and reported to be higher in patients still living at the end of the follow-up period. The presence of chronic diseases such as diabetes and cardiovascular disease may themselves influence activity level, energy expenditure, and life expectancy.

Although metabolic changes of aging and obesity relate to low levels of habitual activity, a higher intensity of activity than that typified by activities of daily living is required to reverse the changes. In elderly subjects, exercise interventions increased expression of skeletal muscle glucose transporter (GLUT4) and decreased intramuscular triglyceride; (178) Muscular strength, energy expenditure (resting and during exercise), and maximal oxygen consumption, along with flexibility and range of movement of various joints are all increased by programmes of exercise (97, 179). At the same time, leptin levels decrease, and adiponectin levels increase. These changes may contribute to altered feeding behaviour and decreased risk of diabetes. The low-grade inflammatory changes which accompany obesity are also reversed: Bautmans et al. (180) reported decreased circulating TNF- α and IL-6 and decreased expression of heat shock protein-70 (Hsp-70) in circulating monocytes. Exercise induces oxidative stress in muscle. This stress is decreased and circulating homocysteine increased with exercise training (181).

Short-term exercise interventions in the elderly have benefits including increasing lean body mass; and decreasing fat mass; decreasing waist circumference, insulin resistance, circulating triglycerides, and blood pressure (182-184). Weight loss induced by regular exercise has also been linked with functional improvement in frail elderly subjects (185). In a small trial conducted by Weiss et al., (186) weight loss by either calorie restriction or by exercise improved insulin sensitivity, while a control group who were simply given healthy living advice showed no change. Recent work confirms that exercise interventions have to be of relatively high intensity to improve insulin sensitivity and glucose disposal (187, 188). For example, in the study by Thomas et al., (187) Tai Chi did not lead to improved insulin sensitivity. That is not to say that relatively low intensity (in terms of energy expenditure) regimens such as yoga and Tai Chi do not have health benefits, which include effects on mood and mental function, improved sense of well-being, increased suppleness and improved muscle tone. The interventions which are most likely to increase energy expenditure, improve physical performance, and to enhance insulin sensitivity are those that increase muscle mass (189). Skeletal muscle has a metabolic rate which is approximately eight times that of other lean tissues in the body. Even a modest increase in muscle mass can improve energy expenditure. Furthermore, endurance or resistance exercises can improve metabolic status without influencing overall body weight. This may be due to improved insulin action and decreased systemic inflammation, perhaps related to lower intramuscular levels of triglyceride. Interventions should target the major muscle groups of the body and perhaps a combination of endurance exercise for lower limbs and resistance exercise for upper limbs is ideal (184).

The regimen used has to be tailored to the ability and preference of the patient while being of sufficient intensity for benefit to accrue. In practice, this balance is hard to gauge. Evans et al. (190) suggest that increasing energy expenditure by 400 kcal per day leads to decreased fat mass and improved insulin sensitivity in subjects aged 77 – 87 years. An increase in energy expenditure of this order is often hard to achieve, particularly in very elderly subjects. Another issue is compliance and the duration of treatment. While the benefits of exercise on energy expenditure and body composition in the elderly have been demonstrated, it is equally apparent that these are rapidly lost when the subject becomes detrained (97, 179, 191). Longer term strategies are required. Translating the findings of short-term intervention studies into long-term programmes is difficult practically and likely to be costly. Successful and economically viable programmes are likely to be delivered to groups of subjects and to be community-based. More intensive short programmes to induce weight loss or to improve glucose tolerance or CV risk profile may need to be interspersed. As with pharmacological interventions, we need to consider weight loss and weight maintenance phases separately.

Improved compliance will involve provision of a variety of interventions. For example, aquatic training provides a good mixture of resistance and aerobic exercise and increases muscular performance, lean body mass, and exercise capacity (192). The aim of short-term interventions should be to improve the mass and function of key muscle groups, and to promote loss of fat, particularly from abdominal depots. Where possible, simple measures of success of these interventions should be employed (fasting glucose and lipids, inflammatory markers, anthropomorphic measures, and measures of performance and well-being). Maintenance of benefit requires encouragement of habitual activity and energy expenditure. Use of biofeedback devices such as a pedometer may help. Design of living environments to encourage walking activity within the individual's capabilities may also be important (193). Activity and exercise are of central importance in managing the high-risk overweight or obese elderly patient. Assessment of current exercise and planning increased exercise should never be neglected. As well as improving measures of health, the patient may benefit from improved sense of well-being and decreased reliance on drugs. Ideally, tailored programmes of exercise should be designed with a qualified and suitably experienced exercise physiologist.

Diet

While the role of nutrition therapy in weight management in the elderly is paramount, the optimum approach or approaches have yet to be determined, and there is little in the way of supporting evidence. Even modest weight loss may improve body fat content, fat distribution, adipokine profile, and MS variables (194, 195). However, severe calorie restriction, or repeated attempts at dieting with weight regain, may worsen muscle loss and thus hasten functional decline (196). Concurrent exercise will help to preserve muscle mass. Ideally, a calorie deficit of 200 – 500 kcal per day should be achieved by a combination of diet and exercise. Restriction of calorie intake should focus on the fat and carbohydrate components of the diet. The effectiveness of very low fat diets has been questioned in recent years, partly because they are poorly tolerated. Moderate restriction of carbohydrate is reasonable in patients who are hyperglycaemic. A tailored approach taking into account the patient's preferences and eating habits is needed, (197) and more likely to achieve realistic outcomes. Severe dietary restriction is stressful, increases cortisol secretion and may thus worsen some of the features of the features of the obesity/sarcopenia syndrome (198).

Many elderly patients consume less than the recommended daily protein intake of 0.8 grams/kilogram body weight per day. Poor appetite, dental problems and economic considerations may contribute. As in younger subjects (199), the response to exercise in the elderly may be optimal with increased protein intake above the recommended daily intake (200). Endurance exercise increases the need for dietary protein while muscle

gain with resistance exercise is increased with higher protein intake. Daily protein intake of up to 1.6 grams/kilogram body weight is reasonable. Improved insulin sensitivity with exercise inhibits protein breakdown. Decreased protein breakdown has been documented with amino acid supplementation, (201, 202) and this should be considered in stressful situations which might lead to a catabolic state such as surgery on intercurrent illness (203). Wholegrain foods improve insulin sensitivity and cardiovascular risk profile, and elderly subjects should be encouraged to consume these foods regularly as part of a controlled diet (203). The importance of micronutrient components of the diet should not be underestimated. Deficiency of vitamins B6 and B12 as well as selenium have been associated with functional decline, (204) and low levels of magnesium increase risk of insulin resistance and cardiac disease.

Drugs and Bariatric Surgery

While pharmacotherapy is never the first line treatment for obesity, modern drugs have a place in some elderly patients with obesity. Available agents are summarised in Table 3. Orlistat, sibutramine and rimonabant are now widely used and considered safe. The amphetamine derivative phentermine is still used in some countries. Its use should be short-term (up to three months) and under close supervision. Interaction with other centrally-acting drugs, central side effects and adverse effects on pulse rate and blood pressure limit its use in the elderly. Greater understanding of adipocyte biology and the pathways that regulate food intake is leading to development of novel approaches (205). An example is inhibition of the renin angiotensin system, widely used in CV event protection. Angiotensin converting enzyme inhibitors may improve body composition and retard functional decline in the elderly (206, 207). With current evidence examining endpoints such as diabetes prevention, lifestyle interventions are at least as effective as drug treatments (208).

Orlistat, a derivative of a bacterial product (lipstatin), inhibits multiple gastrointestinal lipases, thus decreasing dietary fat absorption by up to one third. Very little is absorbed systemically, and side effects are limited to the gastrointestinal tract (oily stool, flatulence, increased defecation, faecal incontinence). Use is not necessarily confined to the short term but long-term effects can be modest. The recent study by Richelsen et al. (209) perhaps points the way to optimal use of orlistat. Patients who successfully lost weight with a very low calorie diet were randomised to either orlistat or placebo. Those taking orlistat were more likely to maintain their weight, and there was a lower incidence of diabetes in the treated group. Weight loss with orlistat has been associated with lower levels of inflammatory and oxidative markers, and improved features of non-alcoholic fatty liver disease (210, 211). Because of the theoretical risk of fat-soluble vitamin malabsorption, patients taking orlistat are often recommended to take a multivitamin

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supplement. This seems prudent in the elderly.

Sibutramine is a centrally-acting inhibitor of serotonin and noradrenaline reuptake. It increases satiety and decreases food intake. Side effects occur in up to 10% of patients and include headache, insomnia, dry mouth, rhinitis and constipation. Use for up to one year is recommended and, like orlistat, the optimal use may be in weight maintenance after initial weight loss. When used for three months or twelve months, typical weight loss is around 3 kg and 4.5 kg respectively (212). Use beyond one year is not generally recommended, particularly in the elderly. Both orlistat and sibutramine are effective but, predictably, there is often rebound weight gain when they are discontinued (213). The effects of sibutramine on cardiovascular risk profile are mixed with modest improvements in lipids and insulin sensitivity but increased pulse rate and blood pressure (up to 5 mm systolic). It should not be used in patients with uncontrolled hypertension. The recent Hypertension Obesity Sibutramine (HOS) study has shown that hypertension management with ACE inhibitors ± calcium channel blockers is preferable to a regimen based on beta-blockers and diuretics (214). Recent studies suggest that weight loss with sibutramine improves quality of life, (215) and decreases symptoms of sleep apnoea (216).

Table 3
Drug Treatments for Obesity

	Orlistat	Sibutramine	Rimonabant
Mechanism	Lipase inhibitor	5-HT and N Reuptake inhibitor	CB-1 antagonist
Action	Peripheral	Central	Central + Peripheral
Recommended Duration *	Up to 4 years	Up to 1 year	1 year
Dose	120 mg TDS	10 or 125 mg OD	20 mg OD
Side effects	> 30%	10%	5%
	Oily stool	Headache	Depression
	Faecal incontinence	Insomnia	Anxiety
	Flatulence	Rhinitis	Nausea
	↑ Defecation	Constipation	Dizziness
		Dry mouth	
Drug interactions	+	+++	++
Lipids	↓	↓↓	↓↓↓
Diabetes	↓↓	↔	↓↓
Blood pressure	↓	↑	↔
Suitable for the elderly	++	+	Probably

* Duration of treatment based on available evidence.

Rimonabant is an antagonist at the cannabinoid-1 (CB-1) receptor. Agonists to this receptor (e.g. cannabis) commonly stimulate appetite. Endogenous cannabinoids are involved in regulation of appetite and CB-1 antagonists decrease appetite. Large studies in Europe (217) and in North America (218) confirm that the drug used over one year decreases body weight and waist circumference, improves dyslipidaemia and insulin

sensitivity, but has limited effect on blood pressure. Typical weight loss over one year is 3.4 kg with the 5 mg dose and 6.6 kg with the 20 mg dose. The latter is now used in clinical practice. Side effects are relatively common (up to 5%) and include depression, anxiety, nausea and dizziness. More recent trials confirm significant improvements in lipid profile (219), and in glycaemic control in patients with diabetes (220). Some of these improvements may be due to peripheral as well as central effects of the drug. CB-1 receptors have recently been demonstrated on adipocytes and may mediate some of the effects of a high-fat diet inducing adipocyte hypertrophy (221). Rimonabant has only recently become available in many countries, and clinical experience with the drug is limited. The balance of evidence suggests that, like other anti-obesity drugs, it is moderately effective when combined with a hypocaloric diet, although the drop-out rate in studies is a cause for concern (222).

The utility of drug treatments for obesity in the elderly is limited by the efficacy of available treatments, the fact that they are only recommended for short to medium term use after which there may be rebound weight gain, and the lack of specific evidence relating to the elderly. There are only limited data to suggest that they improve overall body composition and protect against adverse clinical outcomes. Bariatric surgery is becoming safer and more widely available, and is indicated for patients who do not necessarily have morbid obesity but are otherwise at risk from their excess body weight (223). It is undoubtedly more effective than available medical treatments in decreasing body weight. Other reported benefits include improvements in sleep disturbances, gastro-oesophageal symptoms, diabetes and other MS variables, respiratory function, mobility and quality of life. There is growing experience of bariatric surgery in the elderly and clear evidence that it may be of benefit for carefully selected patients (224, 225).

Conclusions

Obesity, insulin resistance and metabolic syndrome are common in the elderly and influence health status and life expectancy. These are targets for clinical intervention, as in the younger age group, but care needs to be taken as over-enthusiastic attempts by medical practitioners to regulate body weight of their patients in later life are not always welcome and do not always improve function or outcome. For some patients, monitoring and vigorous management of individual conditions associated with obesity is appropriate. For others, management of the underlying problem – excess body fat with decreased muscle mass – is more appropriate. Inflammatory markers, endocrine changes and adipokines may all be useful in identifying high-risk individuals and in monitoring the effect of interventions.

It should go without saying that diet and exercise are the cornerstones of management. Lack of evidence precludes firm

and proscriptive dietary recommendations. Modest restriction of calories from fat and carbohydrate seems appropriate, along with ensuring that there is adequate protein intake. The latter may enhance the benefits of exercise which go beyond simple weight management and include improved functional status. A combination of lower body endurance and upper body resistance training appears to be particularly beneficial for the elderly. Among potential hormonal treatments, current evidence does not favour routine growth hormone, IGF-1, androgen or oestrogen replacement, except in proven clinical deficiency states. However, endocrine treatment may augment the response to exercise. Lowering prolactin and decreasing glucocorticoid excess are manoeuvres with therapeutic potential. Drug treatments and surgery for obesity should rarely be in the first line of management, but there is every reason to believe, and emerging evidence, that they are as effective in the elderly. Demographic changes along with the complexity of disease states and physiological changes with aging and obesity are opening up a new area of medicine which transcends current specialty and professional boundaries. Appropriate and effective management of obesity and its complications in the elderly has considerable potential to improve the quantity and quality of life for many people.

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