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FRAILTY, OSTEOPOROSIS AND HIP FRACTURE: CAUSES, CONSEQUENCES AND THERAPEUTIC PERSPECTIVES

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Abstract: *Objective:* The aim of this review of the literature is to report the factors which both contribute to the frailty syndrome and increase hip fracture risk in the elderly. This work is the fruit of common reflection by geriatricians, endocrinologists, gynecologists and rheumatologists, and seeks to stress the importance of detection and management of the various components of frailty in elderly subjects who are followed and treated for osteoporosis. It also sets out to heighten awareness of the need for management of osteoporosis in the frail elderly. *Design:* The current literature on frailty and its links with hip fracture was reviewed and discussed by the group. *Results:* The factors and mechanisms which are common to both osteoporosis and frailty (falls, weight loss, sarcopenia, low physical activity, cognitive decline, depression, hormones such as testosterone, estrogens, insulin-like growth factor-I (IGF-I), growth hormone (GH), vitamin D and pro-inflammatory cytokines) were identified. The obstacles to access to diagnosis and treatment of osteoporosis in the frail elderly population and common therapeutic pathways for osteoporosis and frailty were discussed. *Conclusion:* Future research including frail subjects would improve our understanding of how management of frailty can can contribute to lower the incidence of fractures. In parallel, more systematic management of osteoporosis should reduce the risk of becoming frail in the elderly population.

The term frailty is used by physicians caring for elderly persons to describe a patient at high risk of becoming dependent, of comorbid illnesses, admission to an institution and mortality. This term often reflects a physician's subjective perception of the patient's state of vulnerability. For some authors, frailty expresses an acceleration in the aging processes (1). For others, frailty is a pathological state that has its own pathophysiological mechanisms which are distinct from those of advancing age (2). Although the clinical reality of the concept of frailty is recognized by the whole scientific community, there is no generally accepted definition. Nevertheless, the central element defining frailty is a state of great vulnerability of an aged subject when confronted by a stressor. The causes appear to be varied and to differ in importance according to the individuals. Frailty is thought to be related to multiple deficiencies (Figure 1) which interact between themselves and lead to a decrease in physiological reserves (3-5).

Typically, frail patients lack strength, tire easily, are generally inactive and move slowly. They have little appetite and have recently lost weight. Their morale is poor and their cognitive functions are in decline. These symptoms are present in varying degrees. Although often found in association, frailty is distinct from comorbid illnesses, which are above all factors that hasten the frail subject's transition into disability (Figure 2). In practice, the concept of frailty can provide an explanation for the considerable differences in tolerance of stress between one aged subject and another. At the same age, and faced by the stress of pulmonary disease, bereavement, a fall or admission to hospital, the outcome will be much more unfavorable in the frail than in the robust elderly subject.

Identification of the clinical characteristics of the frailty syndrome (Figure 1) has been the theme of several expert meetings (6-9). Decreased strength, a feeling of tiredness, involuntary weight loss, slowness and inactivity appear as the key domains, to which various teams add social isolation and comorbid conditions, among which depression and cognitive deficiencies are proposed. Although all these factors are recognized as determinant in the frailty syndrome, adoption of a practical clinical definition is still difficult (6,8,10-13). In 2001, Fried et al. proposed an operational approach to the phenotype of frailty (Figure 3). Although there is no consensus, the majority of contemporary studies are based on these criteria or their adaptation.

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Figure 1

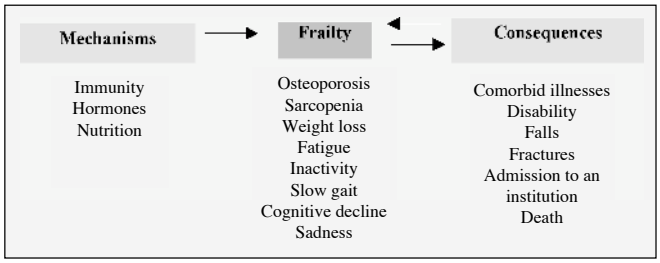
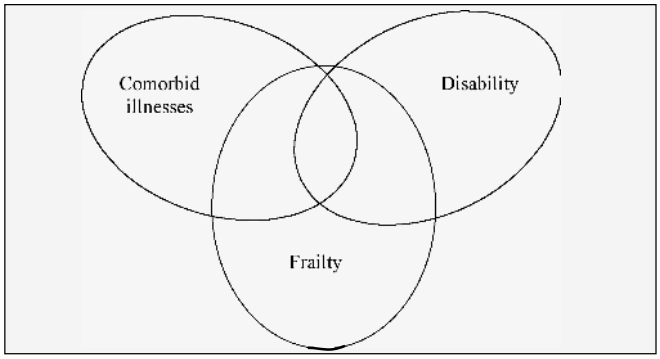


Figure 2
Relations between frailty, disability and comorbid illnesses



Adapted from Fried et al. (5)

Figure 3
Criteria of frailty proposed by Fried et al., 2001 (5)

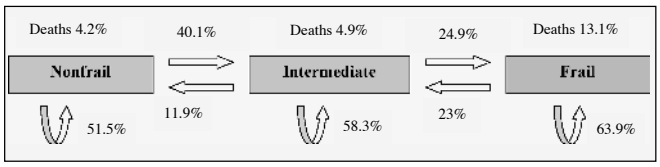
1 – Weight loss
-5% body weight/year
2 – Subjective fatigue
CES-D Depression Scale
3 – Physical activity
Minnesota Leisure Time Activity (MLTA) scale
4 – Walking speed
Walking speed over 4.5 meters
5 –Muscle strength
Grip strength

3 criteria or more = Frail
1 or 2 criteria = Intermediate
0 = Nonfrail

The growing interest in the concept of frailty is related to its reversible nature (Figure 4, (12)). While frailty is highly predictive of a certain number of adverse events, it is also amenable to interventions. Early detection and early, often simple measures for management of frailty can prevent transition into disability. Once disability has set in, on the other hand, it is rarely reversible in spite of difficult and costly interventions.

In the absence of a generally accepted definition, it is difficult to judge the exact prevalence of the frailty syndrome. Depending on the criteria of frailty used, its prevalence may vary three-fold (14). The prevalence of frailty also depends on the characteristics of the population studied. All studies agree in emphasizing the importance of the public health problem that it represents (Table 1).

Figure 4
Outcome at 18 months of subjects classified by the criteria of Fried et al.



Adapted from Gill et al., 2006 (12)

The literal meaning of the Anglo-Saxon term also signifies that the frail subject « breaks easily ». Exposed to the stress of a fall, he or she has a high risk of fracture, and thus of transition to disability, institutionalization, comorbid illnesses and death. The osteoporotic subject therefore seems to be, in the geriatric sense, a frail subject. Paradoxically, no current definition of frailty includes bone mineral density (BMD) (7). Various authors have however highlighted the frequent association between osteoporosis and frailty (15). Osteoporosis appears to be a good marker of frailty. It is a sign of vulnerability.

Hip fracture is the major complication confronting elderly subjects and this too is a major public health problem. Frail subjects seem to be particularly exposed to this complication, which may be predicted a few years beforehand by a so-called « sentinel » fracture of the wrist (16). The incidence of hip fracture rises from 1.6 per 1 000 at the age of 65 years to 35.4 per 1 000 at the age of 95 years (17). Mortality ranges from 35% at 12 months (18) to 10% at 2 years (19) depending on the cohorts. Of those patients who do not die, the majority never regain their earlier functional performances (20,21). Hip fracture exposes the aged subject to pain, depression, reduced physical activity, weight loss and hypercatabolism. During hip fracture, the aged subject often transitions to disability.

The notion that the frail subject is at particular risk of hip fracture is a recent one (22). Yet frailty and its accompanying mechanisms such as inactivity, decreased strength and weight loss are associated conditions known to hasten the onset of osteoporosis (23) and increase the likelihood of falls and fractures. Independently of BMD, recent works have shown that frailty is a major risk factor for falls (OR=2.41, 95 CI%, 1.93-3.01) (22). The number of falls is in itself a major risk factor for hip fracture, independently of BMD (24). As the frail subject is at risk both of osteoporosis and above all of falls, he or she presents all the prerequisites for hip fracture. Ensrud et al. have shown that their fracture risk was higher than that of nonfrail elderly subjects of the same age (OR=1.70, 95% CI, 1.35-2.15) (22).

It is important to understand the links between frailty, osteoporosis and hip fracture as the therapeutic approaches may be different or complementary. The efficacy, cost and adverse effects of a purely pharmacological approach aiming to increase BMD or of a multidisciplinary approach aimed at countering the factors associated with frailty (malnutrition, inactivity, weakness…) may be very different in a frail or a

robust aged population (25). Faced with these issues, it is for example necessary to determine in aged persons the influence which may be imputed to decreased BMD in the occurrence of a fracture as compared with other fracture risk factors (25) such as falls and their multiple causes.

At the present time, few elderly subjects have the benefit of a diagnostic and therapeutic approach aimed at estimating their hip fracture risk. Approaching osteoporosis through the frailty syndrome would not only encourage access to investigation and treatment of osteoporosis but would also give frail subjects the benefit of a therapeutic approach adapted to their health status.

Screening and management of selected factors associated with frailty would certainly have a major impact on hip fracture risk by limiting the risk of falls, disability and decreased BMD and by opening up access to the diagnosis and treatment of osteoporosis.

The aim of this review of the literature is to report on the factors which both contribute to the frailty syndrome and increase hip fracture risk in the elderly. By emphasizing the complementary nature of geriatric and rheumatological management, this work, which is the fruit of common reflection by a group of geriatricians, endocrinologists, gynecologists and rheumatologists, aims to increase awareness of the importance of detection and management of the various components of frailty in elderly subjects who are followed and treated for osteoporosis. It also sets out to heighten awareness of the need for management of osteoporosis in the frail elderly.

Factors and mechanisms common to osteoporosis and frailty

Falls

Various reviews underline the highly heterogeneous nature of fracture risk factors in the aged, differing between individuals (26, 27). In frail subjects, several factors expose them to multiple falls (28). The data of the literature suggest, moreover, that fracture risk is related to the high frequency of falls rather to low BMD.

In an institutional setting, the high incidence of falls is the determining factor in the onset of hip fractures, more than low BMD (29). Fracture risk is greatest when a high risk of falls and low BMD are present concurrently. Risk of hip fracture is nearly 25 times higher in elderly women with a history of both a recent fall and osteoporosis than in those with neither a fall nor decreased BMD (30). Frail subjects who associate factors contributing to a decrease in BMD and multiple falls thus seem to be particularly exposed to hip fracture (Figure 3). This explains why the fracture risk is higher in a frail elderly population (30-32).

At the present time, the part played by falls and low BMD in

Table 1
Prevalence of the frailty syndrome according to the populations and criteria used in some studies of frailty

Name of study	Population	Criteria of frailty	Frail (%)	References
Osteoporotic Fractures in Men Research Group	5993 men aged 65 or older living at home	Sarcopenia, fatigue, weakness, low activity, slow walking speed	4	Cawthon et al. 2007 (161)
Comparison of studies	309 cardiology inpatients aged 70 or older	Fried et al. versus Rockwood et al.	27 versus 63	Purser et al. 2007 (162)
InCHIANTI study	827 subjects aged 65 or older living at home	Fried et al. adapted	6.5	Ble et al. 2006 (163)
Precipitating Events Project	754 subjects aged 70 or older living at home	Fried et al. adapted	25.7	Gill et al. 2006 (12)
Women's Health Initiative Observational Study	40 654 women aged 65 – 79 living at home	Fried et al. adapted	16.3	Woods et al. 2005 (164)
Hispanic Established Population Epidemiological Study of the Elderly	621 subjects aged over 70 living at home	Fried et al. adapted	20	Ottenbacher et al. 2005 (165)
Canadian Study of Health and Aging	9008 subjects aged 65 or older living at home	Physical activity, disability, cognition	4.4% of subjects aged over 85 very frail	Rockwood et al. 2004 (166)
EPIDOS study	7574 women aged over 75 living at home	One or more IADL disability	32	Nourhashémi et al. 2001 (167)
Cardiovascular Health Study	5317 subjects aged 65 or older living at home	Fried et al.	6.9	Fried et al. 2001 (5)

the occurrence of fractures in the frail population has not been defined. Its determination is however of practical interest, for the therapeutic approach is not the same. In the EPIDOS study, the relationship between BMD and hip fracture rate decreased with age (33). The Study of Osteoporotic Fractures (SOF) (34) made similar findings. In the European Prospective Osteoporosis Study, BMD was less predictive of hip fracture risk than was an increased rate of falls (35). In the Fracture Risk Epidemiological in the Elderly (FREE) Study, fall frequency was the determinant factor in fracture risk (29). A study of nursing home residents by Greenspan et al. demonstrated that fracture risk was more strongly correlated with fall characteristics (OR 5.7; 95% CI 1.7-13; p=0.003) and impaired mobility (OR 3.5; 95% CI 1.1-11; p=0.04) than with low BMD (OR 1.9; 95% CI 1.1-3.2; p=0.02) (25). In another population of 3 886 women aged over 80, selected for their high fall risk, the group treated with risedronate did not experience fewer hip fractures (34).

It should be noted, moreover, that fracture risk may be higher in frail subjects than in ill subjects who are already dependent and have impaired balance. This paradox may be explained by the higher frequency of falls in frail subjects than in already dependent subjects (36). Dependent subjects may take less risks and engage in less at-risk activities than frail subjects.

Weight loss

Among predictors of weight loss, reduced protein and energy intake is a factor of osteoporosis and of frailty. Weight loss is a criterion of frailty in the elderly subject (37). Reduced food intake, in particular of protein, hastens transition to frailty and also osteoporosis (38). Changes in femoral neck BMD accompany weight changes in postmenopausal women (39). BMD is also associated with markers of nutritional status such as serum albumin (40-42). These relations explain why subjects with hip fracture generally have lower body weight than subjects of the same age without fracture (43).

In 1995, Cummings et al. already reported from the findings of the Study of Osteoporotic Fractures (SOF) that weight loss was an independent and reversible risk factor of fracture (44). In both men and women, weight loss increases fracture risk (45, 46). Some studies have suggested that the threshold of 10% weight loss increases fracture risk two-fold (RR=1.8; 95% CI 1.04-3,3). Importantly, a 10% gain of body weight has a protective effect (45).

It is however difficult to know whether fracture risk is increased because of a thinner fatty layer which poorly absorbs impact energy, or whether low body weight reflects low bone density and quality as well as poor nutritional status. Some studies have reported an association between low body mass index (BMI = weight/height^2) and increased hip fracture risk (47), and have suggested that fracture risk is related to the severity of the impact of the injury, which is greater if the patient is tall.

Sarcopenia

Among the important changes in body composition which are associated with aging, sarcopenia is one of the major domains which characterize frailty. The term sarcopenia was initially introduced by Rosenberg in 1989 and applied to the progressive wasting of muscle mass during aging (48). The present definition of sarcopenia comprises reduced muscle strength, mass and quality. Sarcopenia is an important field of research in geriatrics as it is considered to be bear considerable responsibility for functional limitations and motor dependency in elderly persons.

Subjects who have difficulty in carrying out certain motor tasks such as chair rises or standing for a long while without fatigue have a higher risk of hip fracture (44). Impaired mobility is a fracture risk factor in the elderly population (25) in addition to low BMD and a high fall risk. Lack of strength (49,50), slow gait speed (24), and poor balance are conditions which reflect the patient's frailty and are predictive of fractures (51).

Muscle mass declines by about 1 to 2% per year after the age of 50 (52). Strength declines by 1.5% per year between the ages of 50 and 60 then by 3% per year subsequently (55-56). There is no consensual definition of sarcopenia. However, it is estimated that about 20% of men aged 70 to 75 and about 50% of subjects aged over 80 have sarcopenia. Among women, 25 to 40% in the same age ranges are sarcopenic. Janssen et al. reported that 35% of elderly subjects were moderately and 10% severely sarcopenic (57). For Melton et al., 6 to 15% of subjects aged over 65 are affected (58). In the EPIDOS cohort of home-dwelling women aged over 70, about 10% are sarcopenic (59). Whatever the study, however, all describe very great disparity between individuals of the same age.

Sarcopenic subjects are also those who have lower BMD and a higher risk of falls (58,60,61). Among postmenopausal women, 25% of osteopenic women and about 50% of osteoporotic women are sarcopenic (62). This association between low muscle mass and low BMD has been reported in various studies (63-68).

Decreased BMD could be due in part to decreased bone stress associated with the reduced physical activity observed in elderly persons (69). The decrease in physical activities and in particular resistance activities promote muscle wasting, which is itself associated with the decrease in BMD. Inactivity is also associated with impaired balance and reduced coordination and suppleness, which all contribute to the risk of falls.

Cognitive decline and depression

Cognitive decline is often considered as a characteristic factor of the frailty syndrome and a fall risk factor. Falls are very frequent in patients with impaired higher functions (70-72). Prospective studies have reported that falls were twice as frequent as in subjects of the same age without cognitive impairment. These falls explain why 3 to 7 times more hip fractures are observed in patients with Alzheimer's disease,

even in the earlier stages of the illness (70, 73). Fall mechanisms, more than low BMD, are the cause (73).

Cognitive decline may contribute to the relation between the frailty syndrome and fractures. Frail subjects with poor functional performances (slow walking speed) are also at risk of cognitive decline. Recently, Wang and collaborators (74), in a prospective study of 2 288 participants, showed that motor performances were predictors of dementia and of Alzheimer's disease in particular. A possible hypothesis is that poor motor performances reflect a low level of physical fitness, which is in itself associated with the risk of dementia (75). These findings support the notion that the decline of functional performances such as walking or balance precede cognitive decline, also a predictor of falls (76).

Hormones

It is now widely recognized that frailty reflects deficiencies of various systems, among them dysregulations of the endocrine system and overexpression of pro-inflammatory cytokines (Figure 1). These mechanisms are common to both frailty and osteoporosis.

Decreased testosterone is often cited as an important factor of frailty in aging men (13). In the elderly subject the andropause is associated with muscle mass and could be implicated in the decrease of BMD. However, the majority of epidemiological studies do not support this association between serum testosterone levels and BMD (77,78) and the few interventional studies do not report an increase in BMD in hypogonadal men treated with testosterone (79). The marked decrease in estrogens during the menopausal period and the rise in cortisol observed during aging also contribute to modify body composition to the detriment of muscle mass.

Insulin-like growth factor-I (IGF-I) and growth hormone (GH) also decline with age (52) and these two hormones could be risk factors for frailty (via sarcopenia) and osteoporosis. GH treatment decreases fat mass and increases lean mass and BMD (80,81). In elderly women, a positive association has been reported between GH levels and BMD (82). GH may also have a direct modulating effect on vitamin D receptors (83).

However, the effect of GH on strength remains debated (84-89) as the increase in muscle mass appears to be related to sodium and fluid retention. Its side effects also restrict its use. At the present time and in spite of the probable relations between GH, IGF-I, muscle mass and bone tissue, the benefits of GH remain to be demonstrated, on muscle as well as on bone.

During the last 15 years, numerous works have reported the role of pro-inflammatory cytokines such as IL-6 in the development of sarcopenia (90). The rise in IL-6 could also be implicated in other disorders which are frequent during aging, among them osteoporosis (91).

Lastly, the importance of vitamin D deficiency and probably of secondary hyperparathyroidism has been widely debated in the scientific literature. Vitamin D status and inactivity play a decisive role in the risk of osteoporosis and of falls (92,93). They will be discussed in the section on treatment.

Prevention and treatment

Access to diagnosis and treatment of osteoporosis

In the absence of a consensual definition of frailty, the proportion of frail elderly subjects who have osteoporosis and who receive treatment is not known at the present time. However, it is probable that few frail elderly patients have the advantage of pharmacological treatment for osteoporosis. Our knowledge of subjects beyond the frailty syndrome such as residents of institutions, who are generally dependent, highlights the lack of diagnosis and treatment of osteoporosis (94, 95). In 2007 and in spite of awareness-raising campaigns on osteoporosis, the great majority of subjects who have had an osteoporotic fracture are not treated for the disease (96). Only one in two institutionalized osteoporotic subjects receive calcium and/or vitamin D supplements (97). In spite of national recommendations (95, 98), only 18% of patients with fractures are given vitamin and calcium supplements (99). This is a regrettable situation, since on the other hand we know the devastating consequences of hip fractures on the quality of life, morbidity and mortality of the most vulnerable aged subjects (32).

In 2004, a group of experts listed the barriers to access to osteoporosis treatments (95) of elderly subjects living in institutions. The characteristics of the frail subject differ from those of institutionalized subjects. However, the reasons put forward are certainly very similar to those which restrict the prescription of a treatment for osteoporosis in frail subjects. These reasons are not based on any rationale. The inutility of a long-term treatment, on account of the patients' low life expectancy, is sometimes mentioned. However, according to the criteria of Fried et al. (5), the mortality at 18 months of frail subjects is 13.5% (12), whereas the benefit of treatment is already significant at 6 months (93). The idea generally held by geriatricians is that non-pharmacological and in particular nutritional management take precedence at this age. However, this does not exclude recourse to medication. Observance is a major problem in the treatment of osteoporosis (100) but has no reason to be poorer in the frail elderly. Tolerance of treatment is usually good. Lastly, polypharmacy, which is often cited to avoid adding another item to an already lengthy prescription, must above all be discussed in terms of risk/benefit ratio. It is estimated that the risks related to untreated osteoporosis exceed those related to treatment (95).

Another barrier to osteoporosis management is the question of access to bone density measurement by dual energy X-ray absorptiometry (DXA). DXA is the gold standard complementary investigation to establish the diagnosis of osteoporosis. At the present time there is no clinical test or evaluation scale which can replace it. A subject with a T-score more than 2.5 standard deviations below that of a young

reference population at the lumbar spine or femoral neck is considered as osteoporotic. DXA is simple to perform, reliable, reproducible and without risk. Ultrasound of the calcaneum can be used to estimate fracture risk but at the present time it is in no way an investigation which could replace DXA measurement. Moreover, no therapeutic trial has been carried out in populations selected in this manner. The sensitivity of ultrasound in the selection of osteoporotic subjects aged over 65 was only 61%, which greatly diminishes its value both in research and in clinical practice (101).

The majority of studies on osteoporosis presume that subjects lost to follow-up are comparable to the rest of the cohort. In fact, they are often frail subjects with restricted mobility. These frail subjects introduce significant bias resulting in underestimation of BMD decrease in the cohort (102). The difficulty of following frail patients generally leads investigators to exclude the most vulnerable subjects from clinical research studies. It is therefore often difficult for practitioners to recognize in the current literature on osteoporosis the frail elderly subjects they have in their care.

We consider, however, that frail subjects particularly exposed to the risk of falls, osteoporosis and so of fractures certainly form a target population which could benefit both from more systematic screening for osteoporosis and from pharmacological treatment of the condition. In the absence of contemporary data specifically concerning this population, these recommendations will need to be validated by future research studies.

Common therapeutic pathways for osteoporosis and frailty

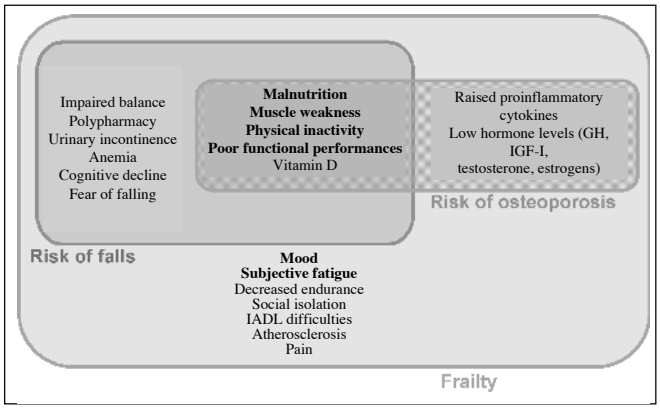
As far as we are aware, there are no specific recommendations on management of osteoporosis in the frail elderly. National recommendations on diagnostic and therapeutic procedures for osteoporosis in institutionalized patients have been issued in Quebec and in the United States. These recommendations concern elderly subjects who are already dependent. However, they stress the value of the usual therapeutic regimens and also that of non-pharmacological management (95, 98).

The frailty syndrome, falls and osteoporosis share common determining factors (Figure 5) that contribute to the occurrence of hip fracture. In frail subjects, management of factors such as weight loss, inactivity, decreased muscle strength and fatigue in association with treatments aiming to increase BMD are rarely seen as a priority in clinical practice.

Non-pharmacological treatment

Numerous studies have shown that non-pharmacological management of elderly subjects, even in institutions, would make it possible to reduce the number of falls and especially of fractures (103).

Figure 5
Usual factors of frailty, falls and osteoporosis



* Short Physical Performance Battery (SPPB), proposed consensual walking speed

Physical activity

Physical activity can have three main beneficial effects in prevention of hip fracture in frail subjects: increased BMD, improved strength and better balance, effectively reducing the risk of falls.

Increased BMD

Throughout life, bone and muscle adapt to the mechanical strains to which they are subjected. Regular physical activity increases not only muscle mass but also bone mass (104). Observational findings all corroborate the association between an active life and high BMD. However, interventional studies, probably because of their insufficient duration, do not always confirm the cause-to-effect relation between subjection of bone to mechanical stress and the increase in BMD. This emphasizes above all the importance of long-term management.

The mechanical stress exercised by muscle groups on bone structures generate in response an increase in BMD. Various works have reported a positive correlation between muscle mass or strength and BMD (63, 66, 67). Athletes or former athletes have higher BMD than inactive subjects (105). However, bone response only occurs in the site involved and is not a systemic phenomenon. The increase of muscle mass is associated with bone of larger diameter and thicker cortical bone (78, 106), probably due to increased periosteal apposition (107, 108). These anatomic changes in bone are associated with greater resistance to compression, which is often the mechanism implicated in fractures (long bones, radius, vertebrae) (67).

However, even if most randomized studies have demonstrated that participation in physical activity could increase BMD in elderly subjects (109,110), some found no significant differences (111) and the great majority of works included healthy subjects without frailty syndrome. Only one study investigated the effects of a physical exercise program on

BMD in 112 frail subjects defined by poor endurance, poor functional performances and difficulties in one ADL or two IADL (112). After a physical activity program lasting 9 months and including resistance exercises, endurance, suppleness and balance training, BMD was similar to that of a group following a low-intensity exercise program (112). It appears that an adequate threshold of bone stress, and thus of intensity of physical exercise, must be reached in order to stimulate bone formation (113). Some works also suggest that the threshold of mechanical stimulation required to promote BMD increase is higher with lower estrogen levels (114). At the present time, the modalities of the physical activity regimen of frail elderly subjects which would make it possible to increase BMD are yet to be defined and the benefits of physical activity on the bones of frail elderly subjects remain to be demonstrated (112).

Improving strength and balance to reduce fall risk

Increasing activity appears to be a simple and effective means of countering fall risk factors such as muscle weakness, functional limitations or fatigue, all of which are associated with frailty. Specific training can improve strength, balance and coordination (115, 116) and contribute to resumption of an active life by reducing fear of falling (117). For more than twenty years, various teams have shown that an intervention focusing on the practice of a physical activity reduced hip fracture risk by about half (118, 119). Tai chi is probably the activity which has received most attention in this domain (116). Activity can also yield a positive effect in frail subjects (120), in whom such non-pharmacological management is particularly indicated. In these subjects at risk of falls, a realistic exercise program improves balance, strength, suppleness and endurance and reduces the number of falls (121, 122).

Body composition

Sarcopenia is a determining factor in frailty, and is often associated with osteoporosis and falls. The decrease in muscle mass is secondary to multiple factors, among them decreased protein and energy intake (122). In frail subjects, who are often malnourished, low protein intake slows the synthesis of muscle tissue and strength increase. Various works consider that in association with adequate energy intakes, the protein intakes of more than 1 g/kg/day which are traditionally recommended are a minimum, particularly in frail subjects, to minimize sarcopenia (123).

In subjects who are well, who are not malnourished, protein supplementation is not associated with an increase in muscle mass or in strength. Even in association with a physical activity program, most randomized studies on the effect of protein supplementation in the robust elderly yielded negative findings (see 124 for references).

Bone tissue is also dependent on nutritional status. Numerous works have reported inadequate calcium and vitamin D intakes in elderly subjects, in particular among the most vulnerable. Protein intake has also a decisive impact on bone quality. A recent review of the literature concluded that bone resorption decreased when protein supplements were given to osteoporotic subjects living at home (125).

These findings highlight the value of nutritional management, particularly in frail subjects. As far as we are aware, no study has specifically addressed the issue of the impact of long-term nutritional management of frail subjects on the risk of osteoporosis, falls and fractures.

Hip protectors

Hip protectors are a non-pharmacological approach which may be envisaged to reduce the fracture risk of falls. A recent literature review published in the BMJ suggested that hip protectors were effective in institutionalized subjects, which is the section of the aged population at highest risk of falls (126). A short time previously, a paper in the same journal concluded that hip protectors were ineffective (127). A study published in August 2007 in JAMA and carried out in over 1 000 residents in 37 nursing homes did not confirm a protective effect on fracture risk (128). Methodological differences (randomization by cluster, by patient, by hip) account for these conflicting results. It appears however that in institutionalized subjects at highest risk of falls hip protectors are a simple and useful option, whose main drawback is mediocre adherence. In the light of these findings, the frail elderly, most of whom live at home and have a lower fall risk than those in institutions, are probably not a target population which would beneft from wearing hip protectors.

Pharmacological treatment

Vitamin D

Vitamin D insufficiency is defined as a level less than 25 nmol/l (or <10 ng/ml) and deficiency as less than 12.5 nmol/l (or <5 ng/ml) (25 (OH)D measurement with organic extraction and high pressure liquid chromatography, HPLC). Differences in exposure to sunshine and in dietary intake of vitamin D, which complete endogenous production, explain why the prevalence of insufficiency and deficiency varies greatly between different populations. About 15% of the general adult population have vitamin D insufficiency (129,130). Vitamin D insufficiency affects 50% of women aged 65 or over in France (131). It is often complicated by osteomalacia and concerns 70 to 100% of the institutionalized population (132). In spite of these figures, few elderly persons have an adequate vitamin intake, particularly among the most frail elderly. Yet the value of vitamin D supplementation could be even greater in a less active population at high risk of falls (92). In an institutional setting, vitamin D (700 to 800 IU) in association with calcium slightly reduces hip fracture risk according to most authors (93,133). In a more independent elderly population, living at home, the most recent studies have not confirmed these results,

even in association with calcium (134,135). Fracture risk is the result of more or less frequent falls and a decrease in BMD. These divergent results could be explained by the preventive effect of vitamin D on fall frequency. It has in fact been shown that vitamin D reduces fall risk by about 20% and by up to 65% in women (92). As secondary prevention, in patients who have presented a femoral fracture, the association of calcium and vitamin D is no longer adequate, and specific treatment for osteoporosis is required (bisphosphonates or strontium ranelate).

The preventive effect of vitamin D on falls may be related to its effect on muscle. Various observational studies have reported an association between low vitamin D levels and low muscle mass, muscle weakness, impaired balance and increased fall risk (78,93,136-138). Visser et al. also showed in a longitudinal study that a low vitamin D level was a predictor of sarcopenia (139). The effect of vitamin D supplementation on muscle strength and fall frequency in elderly women is currently being evaluated in a randomized controlled study.

Low vitamin D is often associated with a high level of parathyroid hormone (PTH). Some studies also suggest that secondary hyperparathyroidism is a contributory factor of sarcopenia, independently of vitamin D levels (139,140), and is a risk factor for falls (141). Parathyroid hormone has however rarely been studied in the frail elderly population (142).

The dose and modalities of vitamin D administration are still debated. The dose of 800 IU/day of cholecalciferol is certainly more appropriate than the 400 IU previously recommended. However, this supplementation does not take account of individual disparities. The findings of the prospective OPRA study suggest that below the threshold serum level of 20 ng/ml of 25-hydroxy vitamin D, the fall risk increases significantly (143) and the optimal level to be reached is about 30 ng/ml.

Bisphosphonates and strontium ranelate

The value of bisphosphonates and strontium ranelate has been demonstrated in cohorts of osteoporotic subjects. There are no specific data on frail subjects. With regard to dependent subjects, a symposium of experts concluded that pharmacological treatment of osteoporosis was justified even in this population (95). Only one study of bisphosphonates has been carried out in an institutional setting, where fall risk is known to be high. This work did not enable a conclusion to be drawn because the series was too small (144). Only analyses of findings in the most aged subjects in existing cohorts, which certainly contain the largest proportion of frail subjects, make it possible to study the effect of pharmacological treatment in the frail elderly. In women aged 70 to 80 years with known osteoporosis, risedronate reduced hip fracture risk by 40% (34). In an analysis of a subgroup of osteoporotic subjects aged over 80 years in the TROPOS and SOTI studies, strontium ranelate also significantly reduced the risk of vertebral and non-vertebral fractures (145). A yearly infusion of zoledronic acid within 90 days after an osteoporotic hip fracture also reduced the incidence of new fractures and mortality (19). These few data suggest that in frail subjects, fracture risk can be reduced by pharmacological management. These arguments support the value of primary or secondary therapeutic management.

Estrogens

The Women's Health Initiative (WHI) has demonstrated the benefits and the limitations of hormone replacement therapy (HRT) (146). Estrogens are thus not usually envisaged as a treatment of osteoporosis in the frail elderly population. Very few studies have observed the effect of estrogens on bone mineral density in frail elderly subjects. The existing studies have however reported increased BMD of the lumbar spine (+4%) and hip (+2%) (147). This effect may be enhanced if the subjects follow an exercise program, whether they are postmenopausal women (148) or women who already present criteria of frailty (114). This additive effect of exercise and HRT seems, however, to affect only trabecular vertebral bone (114, 148).

Other works have also demonstrated the beneficial effect of estrogens on muscle mass and strength (114). A review of the literature has recently been published on the effects of estrogens on body composition and strength (149). Estrogens may increase muscle strength but may have no effect on muscle mass. Hormone replacement therapy may have a direct action on nuclear receptors of muscle fiber and increase vitamin D levels (150,151). However, these results relate to menopausal women and are not confirmed in subjects aged over 60 (149).

Selective estrogen receptor modulators (SERMs) are another alternative treatment which has been very little studied in frail subjects. A study using SERMs in institutionalized patients did not however report a decreased number of hip fractures in treated subjects even though their BMD increased (152). Moreover, little is known of the safety of SERMs in the elderly population.

Androgens

Various anabolic molecules can be envisaged to increase muscle mass in frail subjects.

About 20% of men aged over 60 and 50% of men aged over 80 are considered to be hypogonadal. Testosterone concentration declines by 110 ng/dL on average every 10 years (153). At the present time, studies of the effects of testosterone on muscle mass and strength in elderly subjects have yielded divergent results. Muscle mass increases in young subjects taking supraphysiologic doses and carrying out resistance exercises (154). Such doses cannot however be envisaged in elderly subjects because of the adverse effects, in particular the risk of prostate cancer. Some studies have reported a modest increase in muscle mass but the majority found no increase in strength (see 124 for references). The increase in strength

reported in some studies is markedly lower than the increase in strength which may be expected through a resistance exercise program. In view of this, use of testosterone is not recommended in the elderly at the present time. The DHEAge study also reported no beneficial effect on muscle mass or strength (155). Other molecules with an anabolic effect such as 7 alpha-methyl-19-nortesterone (MENT or trestolone), selective androgen receptor modulators (SARMs) or teriparatide, but which do not have the adverse effects of testosterone, are being experimented.

Numerous questions remain as to the value and safety of GH in elderly subjects. In subjects with GH deficiency secondary to hypopituitarism, GH supplementation increases muscle mass (84) through increased production of IGF-I and of form 3 of its carrier protein (IGFBP-3). This effect is dependent on the subject's nutritional status. Critically ill patients have low IGF-I levels in spite of high GH levels (156). GH supplementation after hip fracture in elderly subjects induces an elevation in serum levels of the hormone but the elevation is less as the severity of illness is greater (157). This peripheral resistance to GH is not observed in well subjects (158). As frail subjects would be those most likely to benefit from GH supplementation, this observation limits the potential scope of such treatment. In another respect, GH supplementation results in a higher mortality rate in malnourished elderly subjects (159). Numerous adverse effects have been reported in treated subjects (arthralgias, edema, adverse cardiovascular effects and increased insulin resistance), leading to numerous dropouts (89). At the present time, the data of the literature do not allow us to envisage this treatment in frail subjects.

Conclusion

The frail patient is at high risk of hip fracture. However, he has little access to organized fall prevention measures, nor to the diagnostic and therapeutic approach to osteoporosis. The concept of frailty opens up a different approach to hip fracture risk in the elderly. Prevention and care organization appear as pertinent perspectives in this population. The classic model in which each disorder is treated individually is poorly adapted to management of the frail subject. The therapeutic approach to osteoporosis directed at increasing BMD is necessary but probably inadequate in this population (160). The aim of treatment cannot be restricted to obtaining an increase in BMD. Fall prevention by improving muscle strength, balance, nutritional status and cognition are therapeutic means which should limit the incidence of fractures.

Further studies including frail subjects would improve our understanding of how management of frailty can have an impact on fractures. In parallel, more systematic management of osteoporosis should reduce the risk of becoming frail or of hastening the transition from frailty to disability in the elderly.

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