Caring the elderly diabetic patient with respect to concepts of successful aging and frailty

I Bourdel-Marchasson[1, 2], G Berrut[3]

SUMMARY

Successful aging and frailty are emerging constructs becoming necessary to define prevention and treatment goals in elderly subjects. Frailty corresponds to the stages between full autonomy or successful aging and irreversible functional dependency or pathological aging. However its definition is imprecise and potential clinical criteria are numerous and interrelated. Diabetes decreases the likelihood for successful aging and particularly increases the risk for functional dependency. One major end-point in the care of elderly diabetic subjects is to investigate the impact of blood glucose control on progression of disability. Geriatric intervention based on comprehensive geriatric assessment (CGA) in the frail elderly population has been shown effective to prevent the loss of autonomy and to improve quality of life, but seems ineffective on mortality. It is now recommended to screen elderly diabetic patients for frailty criteria. The effect of combined individualized diabetes care and CGA on the aging profile should be investigated.

Key-words: Disability · Frailty · Successful aging · Comprehensive geriatric assessment · Diabetes mellitus.

I Bourdel-Marchasson, G Berrut. Caring the elderly diabetic patient with respect to concepts of successful aging and frailty. Diabetes Metab, 2005;31:5S13-5S19

RÉSUMÉ

Le patient diabétique âgé, entre vieillissement réussi et fragilité

Dans le domaine du vieillissement, les concepts de vieillissement réussi, de fragilité émergent en réponse au besoin de construire des stratégies de prévention et de traitement chez les personnes âgées. La fragilité représente les états intermédiaires entre vieillissement réussi avec autonomie fonctionnelle complète et dépendance irréversible ou encore vieillissement pathologique. Cependant, les critères utilisés sont nombreux, le plus souvent reliés entre eux et ne permettent pas d'aboutir à une définition univoque de la fragilité. Le diabète diminue les chances de vieillissement réussi et en particulier augmente les limitations fonctionnelles. Un objectif majeur de la prise en charge des patients diabétiques âgés serait d'étudier l'impact du contrôle glycémique sur la progression du handicap. Une intervention gériatrique bâtie sur la base de l'évaluation gérontologique standardisée (EGS) chez des personnes fragiles a montré son efficacité dans la prévention de la perte d'autonomie et l'amélioration de la qualité de vie, mais semble sans effet sur la mortalité. Il est maintenant recommandé de dépister les critères cliniques de fragilité chez les personnes âgées diabétiques. Les effets de la prise en charge individualisée du diabète, combinée à celle de l'EGS sur le profil de vieillissement des diabétiques, devraient être étudiés.

Mots-clés : Handicap · Fragilité · Vieillissement réussi · Évaluation gérontologique standardisée · Diabète sucré.

[1] Département de Gériatrie, Hôpital Xavier-Arnozan, CHU de Bordeaux, F-33604 Pessac Cedex, France.
[2] UMR 5536 CNRS/Université Victor-Segalen Bordeaux 2, F-33000 Bordeaux, France.
[3] Département de Médecine Interne et de Gérontologie Clinique, CHU d'Angers, F-49933 Angers, France.

Address correspondence:
I Bourdel-Marchasson, Centre de Gériatrie Henri-Choussat,
Hôpital Xavier-Arnozan, CHU de Bordeaux, F-33604 Pessac Cedex, France.
isabelle.bourdel-marchasson@chu-bordeaux.fr

Successful aging and frailty are two recent constructs with as many definitions as there are authors. This reflects the vitality of thought and discussions about an important concern: quality of aging. Diabetes, a chronic disease frequent in the older than 65 yr population, interferes with the aging process and quality-of-life. We aimed to describe the different constructs of aging and their implications in the prevention and therapeutic strategies for elderly diabetic patients.

Successful aging

Rowe and Kahn have distinguished three categories of aging: usual or normal aging, in subjects whose health and functional status is in accordance with physiological aging, successful aging in subjects who have no limitations and no chronic disease, and pathological aging, in subjects with life-threatening chronic diseases or disability generally with subsequent functional dependency [1]. Thinking about what could be successful aging is another way to think prevention, and gives a goal in treating chronic diseases in the elderly population. The proportion of totally unrestricted subjects decreases sharply with age and in 1990, the percentage of French community-living subjects older than 85y without any limitation for performing heavy tasks was 10.9% in women and 14.3% in men, contrasting with percentages of 33.9% in women and 55.0% in men in the 65-74y age class [2]. Heavy tasks were "heavy work in the house", "walk about half a mile" and "walk up and down a flight of stairs". Thus, in old-old people (over 85y), very few subjects could be considered as "successfully aged", limiting the point of this concept. Thus constructing health-aging promotion should be based on the point of view of aged people.

Only one quarter of North American elderly people interviewed on their perception regarding successful aging thought living a long time was important, and only half cited being able to work after usual retirement age [3]. In contrast, almost 90% of them highlighted the importance of being free from chronic disease, living independently (physically) and remaining engaged in social life until close to death. The mean age of these people was close to 80y and they were representative of community-living elderly subjects. Representations of dignity in the elderly echo these considerations. For elderly British subjects, dignity included the respect of identity and human rights, and capacities for independence and autonomy [4]. Loss of autonomy, either physical or mental, exposes the elderly persons to the feeling they are a burden, which they feel is incompatible with dignity. However, some functionally dependent subjects felt that coping with loss of autonomy had allowed them to maintain their dignity [4]. Loss of basic daily living autonomy (ADL) was present in 34.8% of women and in 22.6% of men in a cohort of old-old (> 85y) French community-living subjects [2]. The ADL scales investigate personal autonomy for bathing, dressing, feeding, transferring, locomotion at home and continence. Surprisingly, only 12.1% of women and 14.3% of men in the same cohort rated their health as poor. Furthermore, only 6.8% of women and 13.1% of men felt worse in comparison to other people of the same age. Elderly subjects seem to cope better with chronic diseases than younger subjects. Mental-health scores recorded in subjects with six different chronic diseases (arthritis, diabetes, cancer, renal disease or dermatological disorders), showed higher scores associated with advancing age and poorer scores in subjects with depression or impaired functional status [5]. In comparison to younger subjects, old people may have substantially different expectations about aging. The study of very-old subjects is interesting from this point of view: among the 20% of centenarians found to be in good health with full autonomy and normal cognition, none had maintained social activities [6].

Frailty

Loss of physical, social or psychological autonomy appears to correspond to a transition state between successful and pathological aging, the latter usually associated with ADL dependency and institutionalization. Frailty represents the state(s) between the two conditions: full autonomy and irreversible dependence or death. Increased risk for adverse outcomes such as disability, morbidity, hospitalization, institutionalization or death describe frailty [7]. As underlined in the review by Hamerman, frailty is not a defined clinical entity, but represents a constellation of many conditions [8]. Vulnerability, is a construct, similar to that of frailty, which emphasizes the age-associated loss of homeostasis [7]. Frailty also depicts a state of lacking reserve. A sudden event such as a fall, leading to an unbalanced physical and mental state, reveals the frailty of elderly subjects, who are unable to cope with this new situation. The challenge of care for frail elderly subjects is thus to prevent or to render reversible their loss of autonomy. In a cohort of elderly French community dwellers, one-year recovery of ADL autonomy has been described in 44.7%, while death followed in 16.7%. In this cohort, normal baseline cognitive status was associated with higher rate of autonomy recovery [9]. Thus the issue of frailty definition could be targeting preventive actions for the preservation of functional autonomy.

Clinical criteria

Clinical and probably biological criteria are needed to establish the clinical diagnosis of frailty. The choice of clinical criteria of frailty is usually based on the observation of an associated increased risk of adverse outcomes. Numerous models have been described which cannot be extensively described here *(Table I)*. Mitnitski *et al.* recorded no less than 38 binary variables including symptoms (e.g. hearing problems), disabilities (e.g. help in preparing meals) and deficits (e.g. high blood pressure, glaucoma, diabetes, stroke) [10]. The consequences of these deficits vary from discomfort to dis-

Table I
Clinical criteria for frailty [from ref. 7, 8, 10-12, 15, 19, 23-26, 28, 30].

Category	Criteria
Age	Continuous effect after 65y
Sex	Male sex
Diseases	Stroke
	Chronic and disabling illness
	Cancer
	Diabetes
Dependency	Need for help in preparing meal, shopping, housework
	Impaired mobility
	Slow gait speed
Geriatric conditions	Delirium
	Malnutrition
	Fall
	Incontinence
	Pressure sores
	Susceptibility to adverse drug effect
	Sensory problems
Mental status	Depression
	Alzheimer disease
	Other dementia
Care	Restraints
	Bed-rest
General	Poor subjective health
Social	Socio-economic problems
	Familial problems

abilities and are included in a frailty index. Such a complex index is however not very useful in clinical practice. Winograd *et al.* [11] included the diagnosis of chronic disabling diseases among frailty criteria. This could include diabetes. Cancer is another frequent diagnosis associated with frailty [10]. However, typically, the frail subject is likely to present an association of chronic diseases, rather than one specific disease. Adverse drug reactions increasing risk for hospital admission have been also proposed as a clinical criterion for frailty [12].

Alzheimer's disease and dementia of other types, are the most important risk factors for development of disability [13]. Thus, at any stage of the disease the patient is at risk for adverse outcome, malnutrition and functional dependency, and could be considered as frail. At hospital admission frail patients frequently cumulate most of the geriatric conditions including fall, behavioral and social problems, disability, urinary incontinence, malnutrition and a high rate of adverse drug events [14] in addition to an increased risk for delirium [15]. Delirium occurring during hospital stay is associated with increased risk of incomplete functional recovery [16] and increased risk for institutionalization [15]. Delirium is also associated with an increased risk for diagnosis of dementia within two years [17]. Thus mental disorders are a target point in assessing older individuals with the aim to prevent disability and further deterioration of cognition.

Depressive symptoms are particularly frequent in older subjects and usually associated with disability, malnutrition, and social problems [18]. It has been shown that depression is associated with lower muscle strength independently of nutritional status [19]. Depressive subjects seem to be at increasing risk for falls [20], which is another criterion of frailty. Thus, any statistical evaluation of the association between depression and frailty depends on the model used for the analysis. Assessment of depression seems however to be a useful way to detect frail subjects. Self-rated health considers the subject's psychology, experience, and well being. Self-assessment of health is recognized as a strong predictor of mortality, independently of morbidity, depression and disability [21]. It is also correlated with disability and depression [2] and associated with change in functional status [22]. Thus, it could be considered as another good criterion of frailty [23].

According to most authors, malnutrition and muscle weakness are pivotal criteria of frailty [7, 8, 11, 24-26]. Indeed, their impact on physical function and quality-of-life are obvious and malnutrition is strongly associated with risk of falls [27]. Hospitalized elderly subjects with caloric intake lower than 600 Kcal/d or with a diagnosis of fall are at increased risk for institutionalization [15]. Slow gait speed has also been used as a frailty criterion [28, 29]. A cohort of 754 elderly people was followed each month for a 6-year period and assessed for four ADL items (bathing, dressing, transferring and walking) [30]. Slow gait speed was used to define frailty and the impairment of one ADL activity was called mild disability. The rates of transition between "no disability" to "mild" or "severe" disability were four times higher in frail subjects than in the non-frail subjects. Similarly the rates of transition from "mild" or "severe" disability to "no disability" were two to four times higher in non-frail subjects than in frail ones. Furthermore, death as the issue of severe disability episodes occurred twice as often in non-frail subjects, suggesting that diseases causing disability are more often life-threatening in non-frail people. However, slow gait speed is a limited definition for frailty. Disuse due to hospitalization or bed rest are associated with decreased muscle strength [31] and decrease in gait speed [32]. Among the criteria used to define malnutrition, the association between disuse and weight loss appear to be a better predictor of functional decline than disuse associated with low BMI (< 23.5 kg/m^2) or with caloric intake lower than 1,800 Kcal/d [33]. On the other hand, compared to usual care, nutritional support and exercise can increase muscle strength and decrease functional dependency in elderly patients recovering from an acute illness [31, 34, 35]. Obese elderly subjects are not protected against frailty, due to unfa-

vorable body composition with high fat mass and lower percentage of fat free mass and decreased muscle quality (lower ratio of strength to muscle mass) [36, 37]. Furthermore, in elderly patients, it is difficult to obtain a decrease in fat mass without a decrease in muscle mass. Exercise was shown to be efficient to prevent muscle mass decrease during energy restriction in elderly obese women [38].

Clinical criteria for frailty recognition are thus numerous and generally interrelated. As an example, we have shown that very low energy intake, delirium, stroke and fall were independent risk factors for institutionalization in hospitalized subjects, but that ADL dependency and previously known cognitive disorders, although very frequently present in this population, were not [15].

The frail elderly subject is likely to be old, cognitively impaired, depressed, and undernourished, with one or more chronic disease, a low level of physical activity, at risk for fall and with social difficulties.

Biological criteria *(Table II)*

Several attempts have been made to find biological markers of frailty. Such biological markers have to be a link between clinical conditions and lacking reserves. The example of dehydroepiandrosterone sulfate (DHEAS) is illustrative of this attempt to find a biological marker of "unsuccessful aging" and a target for preventive interventions. Low blood levels of DHEAS have been associated with low quality-of-life, impaired health and excess of 4-year mortality [39]. However, double-blind supplementation trials had shown no benefit of such long-term treatment on physical function (muscle and bone), sexual or general well being despite normalization of DHEAS blood concentrations [40-43]. On the other hand, no relationship between the 8-year course of DHEAS level and functional, psychological, and mental status was observed in the PAQUID cohort [44].

The hypothesis of a genetic predisposition to unsuccessful aging and then to frailty comes readily to mind, and ApoE4 phenotype has been proposed as a frailty profile of apolipoprotein E gene expression, based on the low rate of ApoE4 carriers among healthy centenarians compared to a 40y-adult population [45]. However, in a longitudinal study, ApoE4 carriers were not at higher risk for functional decline than others [46].

Table II
Biological criteria for frailty [from ref. 45-47, 50-53, 64].

ApoE4 carriers (controversial)
Plasma osmolarity (> 300 mosm/l) (controversial)
Serum albumin < 38 g/l (controversial)
Increased C-reactive protein
Increased IL-6
Low total cholesterol (controversial)

Abnormal high plasma osmolarity, apart from acute disease, may reflect dysregulation in fluid homeostasis and has been considered as an index of frailty [47]. Osmolarity was calculated using Na (mEq/l), K (mEq/l) and blood glucose (mmol/l) and not BUN (blood urea nitrogen) and was equal to (Na + K) x 2 + blood glucose. Osmolarity higher than 300 mOsmol/l was associated with an increased 4-year risk of dependency for heavy tasks, instrumental (phone use, budget management, transportation, medication management, housekeeping) or basic activities of daily living [47]. This relation was similar for the normoglycaemic subgroup and the whole population. However, we have previously shown that hyperosmolarity syndromes, with or without high blood glucose, were predicted by prevalent high level of functional dependency [48]. These latter subjects were likely to be in the subgroup of irreversible dependency. Thus, hyperosmolarity could be considered as a marker of unsuccessful aging, frailty or irreversible dependency.

Serum albumin could be a candidate as a biological marker for frailty. Serum albumin is a strong predictor of mortality, the risk beginning with plasma concentration lower than 38 g/l in elderly community dwellings [49]. However there are no data exploring the predictive value of serum albumin on functional outcome. A transversal study in a similar population has shown that increased C-reactive protein blood concentration is associated with frailty, with a mean value of 5.5 mg/l in frail subjects compared to 2.7 mg/l in others [50]. Furthermore, a high level of interleukin-6 (IL-6) was associated with higher rate of decreased muscle mass [51] and in another study with higher rate of 3-year functional decline and loss of muscle strength [52].

Low level of total cholesterol and HDL cholesterol is associated with increased mortality in elderly people [53]. Adjustment to clinical indices of frailty decreased the attributed risk for mortality while elevated cholesterol was associated to an increased risk of coronary mortality. Furthermore, lipoproteins are involved in the anti-infectious defenses and low levels could expose frail subjects to increased mortality [54]. Thus cholesterol determination can not *per se* be considered as a marker of frailty, but should be interpreted with reference to geriatric assessment.

The place for comprehensive geriatric assessment in health promotion

Comprehensive geriatric assessment (CGA) is a useful tool in prevention strategies [55]. It consists in a systematic evaluation of cognition, mood, gait and risk of fall, functional autonomy, nutrition, bladder continence, medications and morbidity, social support and self-reported health and quality-of-life. This requires specific scales, a medical examination and a clinical and social procedure targeted on the results of this assessment. This evaluation drives medical, psychological and social interventions including, for example in case of fall, anti-osteoporotic treatment, physiotherapy, psychological

support, treatment revision, and home care interventions. Such an approach helps in improving functional autonomy in older frail subjects, could reduce the rate of mortality, hospitalization, institutionalization and adverse drug-effects and could improve cognitive functioning [56]. In a randomized trial, CGA driving home intervention was effective for functional autonomy recovery, but without effect on survival [57]. It has also been shown as an effective tool in the management of elderly patients with cancer. Associated to a relevant staging of cancer at diagnosis, CGA permits an optimal prevention of loss of autonomy and is helpful in maintaining quality-of-life [58].

Diabetes, a risk factor for frailty

Diabetes is a constantly present diagnosis in studies investigating successful aging. Diabetes was less frequent in centenarians (5%) than in the 65-85y age class (13.6%) in an Italian study [6]. Indeed, diabetes increases mortality in elderly subjects [59] and in one study this increased risk persisted even in very old age [60]. The resulting prevalence could decrease in the oldest. However, successful aging is more than surviving.

Among chronic diseases, prevalent diabetes was the most powerful factor in decreasing the likelihood of subsequent 6-year successful aging with odds of 0.10 (95% CI: 0.01-0.79) [61]. In this article, remaining free from functional dependency or physical activity restriction was defined the successful aging, but the relation between diabetes and incident disability was not described. In the *Cardiovascular Health Study*, including about 6,000 subjects older than 65y, about 3,000 were considered to have successfully aged using more restrictive criteria (no cardiovascular disease, no cancer, no chronic obstructive pulmonary disease, no impairment in ADL autonomy and normal cognition) [62]. In this population, known diabetes was present in 5.3% of women and in 7.5% of men. Newly diagnosed diabetes on the basis of elevated fasting blood glucose according to ADA *(American Diabetes Association)* criteria was present in 5.9% of women and in 7.8% of men. Age was the most powerful predictor of unsuccessful aging: the odds ratio (OR) in subjects older than 85y was 0.27 (95% CI: 0.21-0.37). The negative effect of diabetes was similar in known diabetes and in newly diagnosed diabetes (respectively OR 0.77, 95% CI: 0.65-0.95 and OR 0.78, 95% CI: 0.66-0.93). Unfortunately, there were no data on blood glucose control in this population and the analysis did not explore the risk factors of unsuccessful aging within this group.

In transversal studies, diabetes is associated with higher rate of disability [63, 64], depression, and poor subjective health [65]. In this issue of *Diabetes & Metabolism*, the associations of diabetes with cognitive impairment, depression, stroke and dementia are discussed [66]. The extent of excess risk of disability associated with diabetes decreased after adjustment for possible confounding factors such as peripheral arterial disease, depression, peripheral nerve function, visual impairment, hypertension, obesity, stroke and cardiovascular diseases but remained significant [64]. Other studies have shown that cardiovascular and other prevalent complications of diabetes do not fully mediate the disability associated with diabetes [63, 67]. Diabetes impaired each level of functional autonomy: autonomy for heavy tasks, instrumental autonomy and ADL autonomy [65, 67]. In subjects older than 75y and followed for 9 years, diabetes was associated with an increased risk of gait disturbance due to parkinsonian-like symptoms [68], this association was not explained by stroke or dementia. In older women, diabetes has been shown to increase the risk of 12-year incident loss of autonomy for heavy tasks with a relative risk (RR) of 2.05 (95% CI: 1.77-2.37) [69]. After adjustment on variables which were each predictive of disability: age, education level, BMI, marital status, diagnosed cardiovascular diseases, depression, cognitive level, arthritis and visual impairment, RR for disability was 1.42 (95% CI: 1.23-1.65). Diabetes duration was not predictive for loss of autonomy in this population, but there was a strong interaction between age and diabetes. Similar results has been shown in the *Women Health and Aging Study* [70]. In a subgroup of these women, the adjustment on HbA1c values decreased the excess risk attributable to diabetes, which was no longer significant. However, the efficiency of blood glucose control in the prevention of disability has never been investigated.

Comprehensive geriatric assessment in diabetic patients

Following the example of geriatric oncology, elderly diabetic patients should benefit from CGA associated with the usual diabetes care [71]. Two major issues of diabetes care in elderly have to be addressed.

– The first question, is the impact of blood glucose control in the prevention of the loss of autonomy associated with diabetes. This question concerns all elderly patients after 65y. Epidemiological observational studies could further describe the progression of disability with reference to blood glucose control and co-morbidity in the different age groups. An interventional survey comparing the effect of different thresholds for HbA1c on the disability process would be helpful to target individualized therapeutic goals and follow up in elderly diabetic patients.

– The second question, is to determine which elderly diabetic subjects will benefit from CGA. Ineffectiveness of CGA has been reported as due to inadequate targeting: both independent subjects and those too impaired do not benefit from CGA [72]. Recent guidelines proposed to systematically screen subjects older than 65y for depression, pain, injurious falls, cognitive impairment, polypharmacy and bladder incontinence [71]. In this list, nutritional and functional evaluations were lacking and should be added. Randomized trials, on the effectiveness of CGA in screened diabetic subjects on their subsequent autonomy and quality of life, should be implemented.

Referring to CGA, the care of elderly diabetic people is likely to better address the concerns of the patients, such as preserving social and functional autonomy [73].

References

1. Rowe JW, Kahn RL. Human aging: usual and successful. Science 1987;237:143-9.
2. Barberger-Gateau P, Chaslerie A, Dartigues JF, Commenges D, Gagnon M, Salamon R. Health measures correlates in a French elderly community population: the PAQUID study. J Gerontol 1992;47: S88-95.
3. Phelan EA, Anderson LA, LaCroix AZ, Larson EB. Older adults' views of "successful aging"-how do they compare with researchers' definitions? J Am Geriatr Soc 2004;52:211-6.
4. Woolhead G, Calnan M, Dieppe P, Tadd W. Dignity in older age: what do older people in the United Kingdom think? Age Ageing 2004;33:165-70.
5. Cassileth BR, Lusk EJ, Strouse TB, *et al.* Psychosocial status in chronic illness. A comparative analysis of six diagnostic groups. N Engl J Med 1984;311:506-11.
6. Motta M, Bennati E, Ferlito L, Malaguarnera M, Motta L. Successful aging in centenarians: myths and reality. Arch Gerontol Geriatr 2005; 40:241-51.
7. Hogan DB, MacKnight C, Bergman H. Models, definitions, and criteria of frailty. Aging Clin Exp Res 2003; 15:1-29.
8. Hamerman D. Toward an understanding of frailty. Ann Intern Med 1999;130:945-50.
9. Sauvel C, Barberger-Gateau P, Dequae L, Letenneur L, Dartigues JF. Facteurs associés à l'évolution à un an de l'autonomie fonctionnelle des personnes âgées vivant à leur domicile. Rev Epidemiol Santé Publ, 1994;42:13-23.
10. Mitnitski AB, Mogilner AJ, MacKnight C, Rockwood K. The mortality rate as a function of accumulated deficits in a frailty index. Mech Ageing Dev 2002;123:1457-60.
11. Winograd CH, Gerety MB, Chung M, Goldstein MK, Dominguez F Jr,Vallone R. Screening for frailty: criteria and predictors of outcomes. J Am Geriatr Soc 1991;39:778-84.
12. Onder G, Pedone C, Landi F, *et al.* Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). J Am Geriatr Soc 2002;50: 1962-8.
13. Barberger-Gateau P, Fabrigoule C, Amieva H, Helmer C, Dartigues JF. The disablement process: a conceptual framework for dementia-associated disability. Dement Geriatr Cogn Disord 2002;13:60-6.
14. Nourhashemi F, Andrieu S, Sastres N, *et al.* Descriptive analysis of emergency hospital admissions of patients with Alzheimer disease. Alzheimer Dis Assoc Disord 2001;15:21-5.
15. Bourdel-Marchasson I, Vincent S, Germain C, *et al.* Delirium symptoms and low dietary intake in older inpatients are independent predictors of institutionalization: a 1-year prospective population-based study. J Gerontol A Biol Sci Med Sci 2004;59:350-4.
16. Andrew MK, Freter SH, Rockwood K. Incomplete functional recovery after delirium in elderly people: a prospective cohort study. BMC Geriatr 2005;5:5.
17. Rockwood K, Cosway S, Carver D, Jarrett P, Stadnyk K, Fisk J. The risk of dementia and death after delirium. Age Ageing 1999;28:551-6.
18. Katz IR. Depression and frailty: the need for multidisciplinary research. Am J Geriatr Psychiatry 2004;12:1-6.
19. Bassey EJ. Longitudinal changes in selected physical capabilities: muscle strength, flexibility and body size. Age Ageing 1998;27 (Suppl 3): 12-6.
20. Buchner DM, Cress ME, Esselman PC, *et al.* Factors associated with changes in gait speed in older adults. J Gerontol A Biol Sci Med Sci 1996;51:M297-M302.
21. Helmer C, Barberger-Gateau P, Letenneur L, Dartigues JF. Subjective health and mortality in French elderly women and men. J Gerontol B Psychol Sci Soc Sci 1999;54:S84-92.
22. Idler EL, Kasl SV. Self-ratings of health: do they also predict change in functional ability? J Gerontol B Psychol Sci Soc Sci 1995;50:S344-53.
23. Lyness JM, King DA, Conwell Y, *et al.* Self-rated health, depression, and one-year health outcomes in older primary care patients. Am J Geriatr Psychiatry 2004;12:110-3.
24. Carlson JE, Zocchi KA, Bettencourt DM, *et al.* Measuring frailty in the hospitalized elderly: concept of functional homeostasis. Am J Phys Med Rehabil 1998;77:252-7.
25. Rockwood K, Howlett SE, MacKnight C, *et al.* Prevalence, attributes, and outcomes of fitness and frailty in community-dwelling older adults: report from the Canadian study of health and aging. J Gerontol A Biol Sci Med Sci 2004;59:1310-7.
26. Vanitallie TB. Frailty in the elderly: contributions of sarcopenia and visceral protein depletion. Metabolism 2003;52:22-6.
27. Vellas B, Baumgartner RN, Wayne SJ, *et al.* Relationship between malnutrition and falls in the elderly. Nutrition 1992;8:105-8.
28. Gill TM, Williams CS, Tinetti ME. Assessing risk for the onset of functional dependence among older adults: the role of physical performance. J Am Geriatr Soc 1995;43:603-9.
29. Hardy SE, Gill TM. Recovery from disability among community-dwelling older persons. JAMA 2004;291:1596-602.
30. Hardy SE, Dubin JA, Holford TR, Gill TM. Transitions between states of disability and independence among older persons. Am J Epidemiol 2005;161:575-84.
31. Bourdel-Marchasson I, Joseph PA, Dehail P, *et al.* Functional and metabolic early changes in calf muscle occurring during nutritional repletion in malnourished elderly patients. Am J Clin Nutr 2001;73: 832-8.
32. Gill TM, Allore H, Guo Z. The deleterious effects of bed rest among community-living older persons. J Gerontol A Biol Sci Med Sci 2004; 59:755-61.
33. Chin APMJ, Dekker JM, Feskens EJ, Schouten EG, Kromhout D. How to select a frail elderly population? A comparison of three working definitions. J Clin Epidemiol 1999;52:1015-21.
34. Melin AL, Bygren LO. Efficacy of the rehabilitation of elderly primary health care patients after short-stay hospital treatment. Med Care 1992;30:1004-15.
35. Sullivan DH, Wall PT, Bariola JR, Bopp MM, Frost YM. Progressive resistance muscle strength training of hospitalized frail elderly. Am J Phys Med Rehabil 2001;80:503-9.
36. Davison KK, Ford ES, Cogswell ME, Dietz WH. Percentage of body fat and body mass index are associated with mobility limitations in people aged 70 and older from NHANES III. J Am Geriatr Soc 2002; 50:1802-9.
37. Villareal DT, Banks M, Siener C, Sinacore DR, Klein S. Physical frailty and body composition in obese elderly men and women. Obes Res 2004;12:913-20.
38. Ross R, Pedwell H, Rissanen J. Effects of energy restriction and exercise on skeletal muscle and adipose tissue in women as measured by magnetic resonance imaging. Am J Clin Nutr 1995;61:1179-85.
39. Berr C, Lafont S, Debuire B, Dartigues JF, Baulieu EE. Relationships of dehydroepiandrosterone sulfate in the elderly with functional, psychological, and mental status, and short-term mortality: a French community-based study. Proc Natl Acad Sci USA 1996;93:13410-5.
40. Flynn MA, Weaver-Osterholtz D, Sharpe-Timms KL, Allen S, Krause G. Dehydroepiandrosterone replacement in aging humans. J Clin Endocrinol Metab 1999;84:1527-33.

41. van Niekerk JK, Huppert FA, Herbert J. Salivary cortisol and DHEA: association with measures of cognition and well-being in normal older men, and effects of three months of DHEA supplementation. Psychoneuroendocrinology 2001;26:591-612.
42. Kahn AJ, Halloran B, Wolkowitz O, Brizendine L. Dehydroepiandrosterone supplementation and bone turnover in middle-aged to elderly men. J Clin Endocrinol Metab 2002;87:1544-9.
43. Percheron G, Hogrel JY, Denot-Ledunois S, *et al.* Effect of 1-year oral administration of dehydroepiandrosterone to 60- to 80-year-old individuals on muscle function and cross-sectional area: a double-blind placebo-controlled trial. Arch Intern Med 2003;163:720-7.
44. Mazat L, Lafont S, Berr C, *et al.* Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: relationship to gender, subjective health, smoking habits, and 10-year mortality. Proc Natl Acad Sci USA 2001;98:8145-50.
45. Gerdes LU, Jeune B, Ranberg KA, Nybo H, Vaupel JW. Estimation of apolipoprotein E genotype-specific relative mortality risks from the distribution of genotypes in centenarians and middle-aged men: apolipoprotein E gene is a "frailty gene", not a "longevity gene". Genet Epidemiol 2000;19:202-10.
46. Blazer DG, Fillenbaum G, Burchett B. The APOE-E4 allele and the risk of functional decline in a community sample of African American and white older adults. J Gerontol A Biol Sci Med Sci 2001;56: M785-9.
47. Stookey JD, Purser JL, Pieper CF, Cohen HJ. Plasma hypertonicity: another marker of frailty? J Am Geriatr Soc 2004;52:1313-20.
48. Bourdel-Marchasson I, Proux S, Dehail P, *et al.* One-year incidence of hyperosmolar states and prognosis in a geriatric acute care unit. Gerontology 2004;50:171-6.
49. Volpato S, Leveille SG, Corti MC, Harris TB, Guralnik JM. The value of serum albumin and high-density lipoprotein cholesterol in defining mortality risk in older persons with low serum cholesterol. J Am Geriatr Soc 2001;49:1142-7.
50. Walston J, McBurnie MA, Newman A, *et al.* Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med 2002;162:2333-41.
51. Payette H, Roubenoff R, Jacques PF, *et al.* Insulin-like growth factor-1 and interleukin 6 predict sarcopenia in very old community-living men and women: the Framingham Heart Study. J Am Geriatr Soc 2003;51:1237-43.
52. Ferrucci L, Penninx BW, Volpato S, *et al.* Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. J Am Geriatr Soc 2002;50:1947-54.
53. Corti MC, Guralnik JM, Salive ME, *et al.* Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. Ann Intern Med 1997;126:753-60.
54. Vreugdenhil AC, Snoek AM, van 't Veer C, Greve JW, Buurman WA. LPS-binding protein circulates in association with apoB-containing lipoproteins and enhances endotoxin-LDL/VLDL interaction. J Clin Invest 2001;107:225-34.
55. Rainfray M, Bourdel-Marchasson I, Dehail P, Richard-Harston S. L'évaluation gérontologique : un outil de prévention des situations à risque chez les personnes âgées. Ann Med Interne 2002;153:397-402.
56. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet 1993;342:1032-6.
57. Nikolaus T, Specht-Leible N, Bach M, Oster P, Schlierf G. A randomized trial of comprehensive geriatric assessment and home intervention in the care of hospitalized patients. Age Ageing 1999;28: 543-50.
58. Terret C. Management and geriatric assessment of cancer in the elderly. Expert Rev Anticancer Ther 2004;4:469-75.
59. Bourdel-Marchasson I, Dubroca B, Decamps A, Richard-Harston S, Emeriau JP, Dartigues JF. Five-year mortality in elderly French subjects from the PAQUID epidemiologival survey: the burden of diabetes. Diabet Med 1998;15:830-5.
60. Bertoni AG, Kirk JK, Goff DC, Jr,Wagenknecht LE. Excess mortality related to diabetes mellitus in elderly Medicare beneficiaries. Ann Epidemiol 2004;14:362-7.
61. Strawbridge WJ, Cohen RD, Shema SJ, Kaplan GA. Successful aging: predictors and associated activities. Am J Epidemiol 1996;144: 135-41.
62. Newman AB, Arnold AM, Naydeck BL, *et al.* "Successful aging": effect of subclinical cardiovascular disease. Arch Intern Med 2003; 163:2315-22.
63. Maggi S, Noale M, Gallina P, *et al.* Physical disability among older Italians with diabetes. The ILSA study. Diabetologia 2004;47: 1957-62.
64. Volpato S, Blaum C, Resnick H, Ferrucci L, Fried LP, Guralnik JM. Comorbidities and impairments explaining the association between diabetes and lower extremity disability: The Women's Health and Aging Study. Diabetes Care 2002;25:678-83.
65. Bourdel-Marchasson I, Dubroca B, Manciet G, Decamps A, Emeriau JP, Dartigues JF. Prevalence of diabetes and effect on quality of life in older French living in the community: the PAQUID Epidemiological Survey. J Am Geriatr Soc 1997;45:295-301.
66. Bauduceau B, Bourdel-Marchasson I, Brocker P, Taillia H. The brain of the elderly diabetic patient. Diabetes Metab 2005;31:5S90-5S95.
67. Maty SC, Fried LP, Volpato S, Williamson J, Brancati FL, Blaum CS. Patterns of disability related to diabetes mellitus in older women. J Gerontol A Biol Sci Med Sci 2004;59:148-53.
68. Arvanitakis Z, Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and progression of rigidity and gait disturbance in older persons. Neurology 2004;63:996-1001.
69. Gregg EW, Mangione CM, Cauley JA, *et al.* Diabetes and incidence of functional disability in older women. Diabetes Care 2002;25:61-7.
70. Volpato S, Ferrucci L, Blaum C, *et al.* Progression of lower-extremity disability in women with diabetes. Diabetes Care 2002;26:70-5.
71. Brown AF, Mangione CM, Saliba D, Sarkisian CA. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc 2003;51:S265-80.
72. Winograd CH, Gerety MB, Brown E, Kolodny V. Targeting the hospitalized elderly for geriatric consultation. J Am Geriatr Soc 1988;36: 1113-9.
73. Huang ES, Gorawara-Bhat R,Chin MH. Self-reported goals of older patients with type 2 diabetes mellitus. J Am Geriatr Soc 2005;53:306-11.