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Sarcopenia, hypermetabolism, and aging

Sarkopenie, Hyperkatabolismus und Altern

Summary Sarcopenia is a constant in aging. Observed over long periods, it can reach 1% per year. But it is such a tenuous phenomenon that it cannot be observed over short periods at steady state. The aging phenomenon mainly hits fibers, Type II but on aged muscle thin, normal, and hypertrophic fibers cohabit with sclerosis and fat increases.

Sarcopenia is difficult to study, due to the lack of simple clinical, biochemical, or imaging measures. Anthropometric data are largely dependent on water content. DEXA gives better information on appendicular muscle loss. Measures of strength analyze functional outcomes of sarcopenia.

Sarcopenia appears largely multifactorial. Hormonal changes, e.g., drop in growth hormone, menopause, and andropause, explain impaired protein synthesis. Disuse (sedentary, bed rest) may explain chronical protein lysis.

But the main factors for muscle lysis imply life events and occurring diseases.

Cytokines (IL6, TNF alpha) and stress hormones (cortisol) induce quick protein lysis in muscle. Rapid and intensive successive aggressions during life cannot be compensated by slowed synthesis.

Harmful consequences of sarcopenia explain many disabilities of old age: loss of strength, inducing itself loss of mobility, falls, equilibrium disorders, poor ADL; loss of nutritional reserves (protein and glycogen) impairing capacities of immune response. Muscle loss spoils vital functions as respiration.

Treatment remains rather limited to resistance exercise. Although, these results are thin, they are the only ones to be validated in all the elderly even the frail or the old. However it is not efficient during the evolution of an inflammatory process. The powerful action of cytokine and cortisol on muscular hypermetabolism must be incited for early treatment of any infectious or inflammatory event. Nutritional supplementation has no efficiency in the absence of malnutrition and without exercise.

Although mobility impairments mainly due to sarcopenia are the first cause of disablement in the elderly, we lack information on etiology, evolution, and measurement of sarcopenia. We also lack controlled therapeutical studies.

Key words Muscle loss – metabolism – consequences – unanswered questions

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Zusammenfassung Sarkopenie – d. h. der alternsgängige Verlust von Muskelmasse und Muskelkraft – ist eine Konstante des Alterns. Über längere Zeitspannen beobachtet, kann sie etwa 1% pro Jahr ausmachen. Sie verläuft aber so schleichend, daß man sie bei kurzen Beobachtungszeiten nicht erkennen kann.

Dieser Prozeß betrifft vorwiegend Typ-II-Muskelfasern. Dennoch findet man in alter Muskulatur neben dünnen atrophischen auch normale und hypertrophische Fasern mit Sklerose und vermehrtem Fettgehalt.

Sarkopenie ist schwierig zu objektivieren, denn es fehlt an entsprechenden einfachen klinischen, biochemischen und bildgebenden Verfahren. Anthropometrische Daten hängen im weiten Bereich vom Wassergehalt des Gewebes ab. DEXA vermittelt hier bessere Informationen. Messungen der Muskelkraft untersuchen primär die funktionellen Folgen der Sarkopenie.

Sarkopenie imponiert als ein multifaktorielles Geschehen. Hormonale Änderungen – nämlich Abnahme des Wachstumshormons. Meno- und And-

ropause – erklären eine verschlechterte Proteinsynthese. Inaktivität verschiedener Ursachen kann eine chronische Proteolyse erklären. Aber die Hauptfaktoren des Muskelschwundes liegen in Lebensereignissen und in abgelaufenen Krankheiten.

Zytokine (IL 6 TNF-alpha) und Streßhormone (Cortisol) bewirken eine schnelle Proteolyse im Muskel. Rasche und wiederholte intensive Störungen können infolge einer verminderten Proteinsynthese nicht kompensiert werden.

Die negativen Auswirkungen der Sarkopenie erklären viele Nachteile des Alterns: Verlust von Kraft – die zu einem Mobilitätsverlust führt –, Stürze, Gleichgewichtsstörungen, Verminderung der ADL, Verlust von Protein und Glykogen mit negativen Rückwirkungen auf die Immunkompetenz. Muskelabbau kann außerdem vitale Funktionen wie z. B. die Atmung negativ beeinflussen.

Behandlung durch konsequentes Training bleibt wenig wirksam. Dennoch sind diese Ereignisse die einzigen bisher als sicher wirksam geltenden Maßnahmen bei allen Älteren, sogar bei Gebrechlichen und Hochbetagten. Sie helfen aber nicht bei Infektionen oder Entzündungen. Und die intensive Wirkung von Zytokinen und Cholesterol auf den muskulären Hyperkatabolismus muß zu einer möglichst frühen Behandlung von jeglichen Infekten oder Entzündungen anspornen.

Eine ausgewogenere Ernährung bleibt bei Fehlen von Mangelernährung und ohne konsequentes Training ohne Effekt.

Obgleich Mobilitätsstörungen als Folge von Sarkopenie die erste Ursache der Behinderungen im Alter sind, fehlen uns Kenntnisse über deren Ätiologie, Entwicklung oder Meßbarkeit. Und es mangelt auch noch an kontrollierten therapeutischen Studien.

Schlüsselwörter Muskelschwund – Stoffwechsel – Konsequenzen – offene Fragen

Introduction

Muscle loss is the most constant marker of aging (1, 2). This loss is common to all mammals. The decline of muscle mass reaches 40 % from 20 to 70 y (3), parallel with the decline of muscle strength: 30–50 % from 30 to 80 y (4). This decline concerns mainly postural muscles either in experimental animals (rats) or in man. Even in older athletes who are physically active, this decline is present (5).

No other organ shows such an age-linked deterioration. In spite of its importance and its universality, this deficiency is the least studied phenomenon of aging.

We have no satisfactory answers on the main questions concerning age associated muscle loss: is this loss avoidable? Can it be reversible? What is the quota of muscle lost in age associated symptoms and disabilities? What is the role of different etiological factors for aging itself, disease, malnutrition, or disuse?

Different aspects of muscle loss

Semantic classifications have been discussed. Sarcopenia was suggested (6, 7) as the age specific loss of muscle mass and muscle strength. Each year after 50 y a loss of about 1 % of muscle mass (8) and 1% of muscle strength is observed, but the loss begins after 25 years of age. This regular, slow phenomenon could be directly age related. But, if it is a constant phenomenon, its speed differs greatly in individuals. It is too slow and tenuous to be observed in an experimental longitudinal survey over a few years. There is no data to demonstrate clearly that it is a regular process relying only on time.

Roubenoff (6) suggested to keep the word “wasting” for unintentional loss of weight, with decrease of fat mass, but also of fat free mass, as observed in starvation at any age or in the geriatric failure to thrive (9). But how are we to distinguish difference between age related sarcopenia and wasting due to inadequate diet, so common in the elderly?

Roubenoff (7) also made the proposition to keep the word “cachexia” for the cytokine mediated loss of body cell mass, as observed in intensive care medicine. This cachexia is a frequent situation in geriatrics due to Senile Systemic Inflammatory Response Syndrome (10, 11). In cachexia, muscular water infiltration associated with water retention will mask muscle mass loss. However after recovery from the inflammatory process, how can we differentiate residual muscle loss from age related sarcopenia? During the life cycle, with such definitions, the association of “cachexia” and “wasting” with sarcopenia is unavoidable and we can keep the word “sarcopenia” for the different aspects of age related muscle loss.

Age related sarcopenia is associated with modification of muscle constitution (12, 13). The number of fibers II b (glycolytic) and II a (oxydo-glycolytic) are decreased, but the number of fibers I (oxidative) remain the same. So in biopsies a relative increase of density of fibers I (related with endurance) appears. Another modification is the increase of thin fibers and atrophic fibers. Normal fibers remain and hypertrophied fibers result likely from comensatory mechanisms (14). So the heterogeneity of fibers is one of the main modifications due to age. As there is no renewal of muscle fibers, exercise can only increase hypertrophic fibers.

Collagen fibrosis is observed between fibers. The fat content of muscle increases during aging, but we have no data on fat content of the muscle in very old individuals. These modifications are accompanied by loss of muscle mass and loss of

strength. But there is large heterogeneity between muscles both in man and rats. Postural muscles, as quadriceps, are more concerned. So it cannot be accepted without proof that "sarcopenia" is only related to the aging process, and not also with metabolic or disuse resistance processes.

Metabolism and physiology of aging muscle

Myofibrillar proteins are in permanent renewal (15, 16). During growth, synthesis predominates on lysis. During aging, that is during adulthood, lysis predominates in synthesis. But this reversion of metabolism after maturation can be observed only over long periods. This very tenuous phenomenon is not perceptible over a one year period (decrease of 1% per year over 20 y) (1). For instance, the postprandial synthesis is the same in young and old. So it is impossible to say if sarcopenia is a continuous phenomenon, or if it is a result of periods of lysis, equilibrium, and compensatory synthesis. The end outcome of muscular loss may be due to the absence of renewal of muscular fibers. A loss fiber cannot be always compensated by the hypertrophy of another one. Succession of accelerated lysis (inflammation, inactivity) and incomplete repairs is more likely than a very slow, regular chronic process. The natural evolution over long periods remains muscle loss (16).

The role of muscle is to give mobility. Muscular strength is the tool of efficiency for the muscle. Strength is a function of muscular mass, but also of its metabolism, mainly its capacity to generate ATP and to hydrolyze ATP (17, 18). The glucolytic routes are altered through the decrease of fiber II b. The oxidative capacity could be altered by reduced blood flow. So any decrease of blood flow reduces muscular strength; poor capillarization, immobility, arthritis are direct factors for low strength and sarcopenia. In active elderly, the muscular capillarization is the same as in the young and better than in sedentary elderly (19, 20).

Measure of muscle loss (21)

Clinical knowledge on age related sarcopenia is poor in spite of the fact that skeletal muscle is the largest organ in the body. This is mainly due to the difficulties for measuring sarcopenia. There is no accepted, universal, simple method to score sarcopenia.

Clinical methods

Clinical examination gives pertinent information, but not measures (as concave aspects of anterior face of thighs). Anthropometry (22) (triceps thickness, middle-arm circumference is biased by water content). A functional aspect of muscle loss may be appreciated by hand-grip strength measure, walking speed test, and knee extension strength (23). These elementary functional mobility tests are not used enough in daily clinical geriatric practice; in fact there is only very limited information on these in the 80 y.o. (24).

Imagery and physical methods

- *Computerized tomography* (CT) gives a precise assessment of muscle mass.
- *Dual energy X-ray absorptiometry* (DEXA) (25) is likely the more precise, the less invasive way to estimate muscle mass. This method also allows one to follow evolution of the global muscle mass. However, it is a better tool for investigating muscle mass in malnutrition, as the main protein reserve of the organism, than to measure muscle function.
- *Muscle echography* is an interesting new method. It has been used to follow day by day cachexia in intensive care units. It can be used also in geriatrics to follow aging associated sarcopenia, inflammatory cachexia (muscle infiltrated by water), and wasting due to starvation (26). Another advantage of muscle echography is the possibility of using it at the patient's bed.
- *Bioelectrical impedance*. This noninvasive method determines the relative proportion of fat to lean tissue, that is mainly muscle (22).
- *Biochemistry*. There is no simple blood test to measure muscle mass; however creatine excretion is related to muscle mass. 3-Methyl histidine excretion is also a classical marker.
- *Diverse research methods* have been described: biopsy, kalium distribution (27), infrared spectography (28). They cannot be used in clinical practice. The more powerful and quite noninvasive tool is magnetic resonance spectography. This imagery can give morphological, biochemical, and precise metabolic data (29).

Baumgartner proposed defining sarcopenia as appendicular skeletal mass (kg) (needs DEXA evaluation)/height (meters $\times$ 2). Age sarcopenia is defined by a ratio two standard deviations beneath that of young controls (25).

Mechanisms of sarcopenia in the elderly

Sarcopenia is the result of intricate external and internal factors.

Internal factors

Among the internal factors, we must consider:
- *Genetics*. We cannot compare the elderly with their parents, only with their children. Muscle mass of an octogenarian is re-

lated to the muscle mass the subject had when he was twenty years old. This mass has seen a life lasting decrease. As a young adult the future octogenarian inherited the muscle mass from the genome and added, or not, exercise built muscle mass to this "basic" muscle.

• *Hormonal factors.* Insulin is a strong inhibitor of proteolysis. In day to day regulation, insulin action is the same in young and old.

• *Growth hormone* (GH). Decline of muscle mass parallels the decline of growth hormone secretion (30, 31). Growth hormone effects are mediated by insulin growth factor (IGF1) (32). Experimentally, overexpression of the IGF1 gene protects against sarcopenia (33). A local production of IgF1 and IGF-BP1, IGF-BP6 is observed in muscle (32). Then, a synthesis promoting role is likely but age variations are not yet proven. If the GH control of muscle mass is obvious, it is not sufficient or direct. GH alone does not restore muscle synthesis in men (29).

• *Sexual hormones.* Estrogens decrease proteolysis. Estrogens are also included in regulatory loops. Lack of estrogen increases action of cytokines (see below) (34). Substitutive hormonal treatment during menopause partially protects from sarcopenia (34). Testosterone (35) is a strong protector against proteolysis. Testosterone decrease with age is not constant; however when this decrease appears, sex hormones binding to globulines increase (3).

• *Cortisol* has a double role during aging. It is mainly a factor of proteolysis in the young, but of decreased proteosynthesis in the old (18). Both factors lead to sarcopenia. Corticosterone produced in sepsis and inflammation induces rapid muscle catabolism and potentializes TNF alpha actions (7, 36).

• *DHEA* is decreased in the elderly, in function of their activity (18). It seems to act in muscle mass. However, does it have direct action on muscle, or is its action mediated by gonadal hormones (35)? Or are high DHEA-S levels and maintained muscle mass both related with activity? Thus, hormonal clocks may play a role in age related sarcopenia, but hormonal factors are also important factors for disease associated "cachexia". Hormonal changes are influenced by life events (such as biological stress) and are powerful actors of hypermetabolism and muscle mass consumption.

• *Immunological aging.* Increase of IL6 is a classical manifestation of aging. This cytokine acts as a factor of hypermetabolism and proteolysis (cf infra).

• *Neurological factors.* A relative loss of motor neurons with age has been observed. When a muscle fiber is no longer innervated any more, atrophy happens, and the fiber disappears (37). However, the reverse is also a factor of neurological aging. The loss or the deactivation of sensitive proprioceptive fibers in the muscle (inactivity) provokes alteration of the spatial position sense. Thus, multifactorial internal factors may contribute to induce age related sarcopenia.

External factors

• *Role of diseases.* During life, different diseases interfere with muscle mass through various mechanisms: nutrition, clinostatism and rest, cytokines, hormonal secretions; these factors can also act independently without patent illness. Even if the period of action is short, not every muscle fiber loss can be reverted. Voluntary exercise of readaptation may lead only to a compensatory hypertrophy of some fibers.

• *Nutrition.* Classically, muscle metabolism needs protein intake following the recommended dietary allowances (RDA) (38). In fact only very severe protein deficiency may decrease muscle mass, muscle protein synthesis, and muscle repairs (6), if there is no caloric restriction: only severe starvation may lower muscle mass. However, the elderly need more protein than the young for proteosynthesis (39), then for muscle synthesis. But as muscle mass is reduced, the RDA remains the same. Some amino acids (ex: alpha cetoglutarate) may increase muscle protein synthesis. During the normal aging process, sarcopenia inversely correlates (2, 6) with fat mass (which also decreases with severe starvation). Under nutrition does not seem a main factor in "physiological" aging sarcopenia. Better activity correlates with better appetite and food intake: muscle activity protects from undernutrition (40).

• *Cytokines.* Mainly chronic diseases (10, 11) are associated with a high production of cytokines as heart failure, bed rest, diabetes, any tissue resorption, sepsis, ischemia, etc. Among disorders of aging, the main data about cytokines concern IL6 which shows a large increase in these pathological circumstances (41) and to a lesser extent TNF alpha, a potent factor (36) of muscular proteolysis and anorexia.

A biochemical syndrome due to cytokine (IL1, IL6, TNF alpha) hypersecretion has been described as "systemic inflammatory response syndrome" (SIRS) (10, 11). This frequent condition, due to sepsis from cell destruction or suffering, associates clinical symptoms (fever, polypnea, tachycardia, low blood pressure) and biological symptoms (low albumin, high CRP, neutrophilia, etc.) (42). Rapid muscle loss (masked by water retention) appears as a constant symptom of this syndrome. SIRS in a less active form is a frequent condition in the elderly (11). In the elderly, low albumin and/or high CRP are good markers of IL6 and TNF alpha production (43, 44), and so of active muscle loss and cachexia.

• *Clinostatism.* Experimental absence of gravity (space flight or bedridden status) induces muscle loss different of age related sarcopenia; type I fibers are also decreased (14). In sedentary humans, bed rest is a factor of muscle loss (14). Muscle needs to contract against a resistance. After long duration bed rest, only exercise against resistance may restore strength and muscle mass (45, 46).

The mechanisms of muscle loss due to inactivity are not perfectly understood and are probably multifactorial. Absence of feedback may accelerate the loss of neuronal motor plates

(14, 37). The mechanichal constraint seems to be necessary for good functioning of the muscle (cf space medicine). Thus, any muscular inactivity leads to muscle loss. Furthermore, inactivity seems associated with higher cytokine production and increase of muscle catabolism. So a vicious circle appears: decrease of activity leads to the loss of muscle strength and mass, which induces a reduction of activity. May sarcopenia only worsen?

• *Muscle injury.* Muscle injury is easier on a muscle made frail by disuse, disease, or excessive use (5). Muscle injury and partial repair (fibrosis, motor neuron loss, fiber loss, and compensatory hypertrophy of remaining fibers) also belong here.

Consequences of sarcopenia

Sarcopenia is one of the main age associated disabilities (47). More centenarians have gait disorders than cognitive disorders.

• *Strength.* The most direct consequence of sarcopenia is the loss of muscular strength (48–50), likely the earliest and the most common handicap due to aging. Strength loss induces gait disorders, falls (48, 51), and decreased activities of daily life (ADL) (52).

• *Equilibrium.* Muscle loss due to muscle rest without mechanical constraint induces a loss of proprioceptive sensibility and alters spatial representation of the body (51). So-called post-fall syndrome is largely explained by this sensitive deficiency, a "side effect" of sarcopenia.

• *Bone metabolism.* Bone metabolism and density are functions of muscular insertions and muscular mechanical constraint (53). Sarcopenia participates significantly in senile osteoporosis. Physical inactivity worsen bone loss, severe osteoporosis, and fractural risk. Muscle strength and mobility (linked to sarcopenia) appear to be good predictors for survival of 75–84 y.o. people (54).

• *Fractures.* Hip fracture risk is more closely associated with reduced muscle strength and mass than with body mass or fat (55).

• *Vital functions.* The Diaphragm is not protected against sarcopenia. Hiatal hernia due to weakness of diaphragm muscle is probably the more prevalent digestive disorder of the elderly. But when diaphragm and other respiratory muscles are unable to answer increased O_2 needs, this leads to respiratory failure (2). Also defecation needs contraction of diaphragm and abdominal wall muscles. Sarcopenia is a factor for transit disorders in the elderly. Fever and shivering are the ways for organisms to increase body temperature, a factor for struggling against infectious germs. In the elderly with sarcopenia, the normal febrile answer cannot be obtained, due to lack of muscle reserves (56).

• *Blood flow.* Peripheral arteriolar flow depends on blood needs of peripheral tissues. Inactivity, immobilization, or any absence of use of muscle may decrease capillary and arteriolar circulation (19, 20). Sarcopenia and immobilization are risk factors for critical ischemia in the elderly with arteriosclerosis. These small arteries are very sensitive to any lowering of peripheral blood flow.

• *Nutrition.* Muscles represent the main protein and glycogen reserves of the body, the main component of lean mass. Consequently, the sarcopenic elderly lose functional reserves of amino acids and of glycogen. This is a factor for decreased basal metabolism (56) and decreased glucose tolerance (57). But the main outcome is the inability to cope with a new disease. Under a critical level of sarcopenia, the elderly cannot mobilize any more amino acids and glucose to synthesize the tools of an inflammatory response (2, 7). We do not know how to calculate this critical degree of sarcopenia.

• *Biological markers.* Sarcopenia induces false values for creatinine clearance, even taking in account the classical age correction formulae (as Cockroft formula). In very sarcopenic patients with low protein intake, classical formulae overestimate renal clearance. In contrast in elderly with good muscular mass and high protein intake, clearance is underestimated. Clinically relevant is that sarcopenic patients are more exposed to renal iatrogenic risks.

Unanswered questions on sarcopenia

Sarcopenia explains numerous age associated disorders, mainly limited mobility and lack of nutritional reserves. These consequences severely impair the quality of life of all elderly.

In recent years the knowledge about sarcopenia has increased greatly, but as always, better knowledge pointed out new questions:

• Is there a feedback mechanism from muscle to GH?

• Are muscular growth factors only hormonal?

• May muscle satellite cells be used for muscle regeneration?

• We know only a little about the cytokine activities on proteolysis and glycogenolysis, but what are the regulatory feedback loops?

• Why the discrepancies between different muscles in aging and why are postural muscles more affected? Is it due to aging or to age associated disuse (excess of clinostatism)?

• Why is there such a difference between cardiomyocytes (hypertrophy) and appendicular muscle myocytes (atrophy: is atrophy due to age inactivity and hypertrophy to age associated compensatory mechanisms)?

• What threshold of strength is critical for function? How can it be scored?

• What threshold of muscle mass loss is critical for life?

• Is the decrease of muscle protein synthesis pre- or post-transcriptional? This may give directions for therapy.

We lack clinical longitudinal studies in sarcopenia; we also lack reproducible clinical, biological or image markers for sarcopenia.

The present knowledge on sarcopenia in the elderly is not sufficient to establish a validated nosologic classification of sarcopenia. Only this nosography may permit the validation of therapeutical protocols. The most constant and common consequence of aging remains largely a "terra incognita".

What we can do?

Therapeutical approaches remain limited to a small number of studies on limited cohorts, with controversial results.

Physical exercise

The benefits of exercise are well proven, but in fact very limited. Endurance exercise (3) increases aerobic capacities, but has no effect on protein synthesis. It improves capillarization and oxidative capacities (58).

Resistant exercises increase strength (59) and volume (not number) of fibers II, has a very limited positive (60) effect on muscle mass (3, 8), is effective even in the frail elderly (61) and nonagenarians (62), and in disabled nursing home residents (1). Even simple walking (63) increases equilibrium and strength. But in all studies the effects are a function of intensity of exercise and are labile: they disappear if exercise is not pursued. Exercise in patients with an evolutive disease is always unsuccessful (1). It cannot be efficient in patients with cytokines production and hypermetabolism.

So if exercise seems a good way to maintain activity of daily living, mobility and some degree of fitness, is it not sufficient to preserve muscular mass nor to entirely restore it. The only validated therapeutics on which some consensus is observed is for preventive exercise.

Nutritional therapy

Elderly need more protein/kg than the young for metabolic equilibrium (64). However, protein supplementation is beneficial only if there is a large deficiency on protein intake (65). Protein supplementation alone does not increase muscle mass in sarcopenia (60). Protein supplementation, plus exercise, does not do significantly better than exercise (3). There is no data on creatine supplementation in the sarcopenic elderly. No athletic supplementation had been tested in the elderly. Thus, the nutritional track remains rather uncertain. The only proposition we can make is to please respect RDA for proteins in the elderly (healthy or diseased); they are the same as RDA for adults (65).

Drugs

There is not any validated data giving sufficient evidence on the treatement of sarcopenia in the elderly. However two tracks are being tested.

Hormonal therapy

Growth hormone (GH) increases muscle mass but not strength (it increases the water content of muscle). 30 % of the patients develop adverse effects (66, 67). So if GH does not seem to be the answer to all hopes, parallel ways are expertized: growth hormone releasing factors and association GH-IGF1 (30).

DHEA has been proposed as the panacea for prevention of aging. Among the results to confirm this, the increase of muscle mass has been reported. A randomized study is being held currently.

Gonadal hormones. Estrogen substitutive therapy is a logical treatment for preventing in women acceleration of muscle loss due to menopause. The main studies have not studied muscle until recently (34). Testosterone and androgens are an attractive and logical track in men with andropause (35), but we do not know how to avoid the prostatic risk. Treatment with derivates of progesterone have shown activities on treating cachexia of AIDS. There is no geriatric trial.

Hormonal therapy could be proposed in subjects showing a deficient or low level of circulating hormones. That is the case in menopause and in andropause. But it is difficult to define what is normal, or what are low levels of GH, IGF1 or DHEA-S in the elderly. Levels are not only associated with age but mainly with health and activity status. In the frail, diseased, malnutrished inactive elderly, hormonal levels of the GH-IGF1 axis or of DHEAE-S are "normally" lower than in the healthy elderly; what is first: the egg or the hen? Will hormonal supplementation be active if hormonal deficiency is a consequence?

Perhaps future studies will be made on the doping of athletes. When a product is sufficiently safe and efficient for athletes to build more muscle without side effects, it will be urgent to test it in elderly sarcopenia.

Anticytokines

Cytokines play a major role in sarcopenia, either physiological or pathological. However, anticytokines (anticytokines receptors (68), cytokines receptors, Thalidomide, Pentoxifylline, Etanercept) have not been used except on an experimental level in sarcopenia. Today no evidence supports any anti-oxydative therapy (69).

Today, the therapeutical consensus in sarcopenia in the el-

derly is rather limited: to do resistance and endurance exercise, to follow protein RDA, to treat as early as possible any inflammatory disease, and to limit bed rest. These are rather poor, but simple and inexpensive recommendations. If more elderly followed them, there would be fewer disabled elderly.

Conclusion

Regulation of muscle mass remains largely unknown. There is a preeminence of intermittent inflammatory and stress factors in muscle proteolysis (cytokines and cortisol). So we can expect circadian factors in muscle synthesis (GH, sex hormones, insulin) rather than a continuous phenomenon. This can lead to the following hypothesis: during life acute events the organism uses muscle as a reserve and consumes muscle mass. The repair phenomena take longer. The differential speed explains this long-term process of muscle loss. Inactivity and disuse slow recovery; action against resistance is needed for muscle metabolism.

The lack of knowledge needs to be corrected through more research: clinical, on measures of sarcopenia and on syndromes of hypermetabolism factors for accelerated muscular aging; epidemiological longitudinal studies on evolution of sarcopenia; and pathophysiological studies on hormonal inflammatory and clinostatic approaches of sarcopenia.

But the emergency remains the therapeutical approach. To give back mobility to frail elderly is to offer them a better quality of life. We must recall that sarcopenia and its consequences on mobility are the first health problem of aging before dementia. Dementia hits some of the elderly, but sarcopenia hits all of them.

References

1. Fiatrone MA, Evans WJ (1993) The etiology and reversibility of muscle dysfunction in the aged. J Gerontol 48 (suppl):77–83
2. Chumlea WC, Guo SS, Glaser RM, Vellas BJ (1997) Sarcopenia, function and health. Age and Nutrition 8:4–11
3. Rogers MA, Evans WJ (1993) Changes in skeletal muscle with aging: effects of exercie training. Exerc Sport Sci Rev 21:65–102
4. Frischknecht R (1998) Effect of training on muscle strength and motor function in the elderly. Reprod Nutr Dev 38:167–174
5. Faulkner JA, Brooks SV, Zerba E (1995) Muscle atrophy and weakness with aging contraction induced injury as an underlying mechanism. J Gerontol 50 A (suppl): 124–129
6. Roubenoff R (1999) The pathophysiology of wasting in the elderly. J Nutr 129 (suppl):256 S–259 S
7. Roubenoff R (1997) Inflammatory and hormonal mediators of cachexia. J Nutr 127 (Suppl):1014 S–1016 S
8. Tseng BS, Marsch DR, Hamilton MJ, Booth FW (1995) Strength and aerobic training attenuate muscle wasting. J Gerontol 50 A (suppl):113–119
9. Roubenoff R, Harus TB (1997) Failure to thrive, sarcopenia and functional decline in the elderly. Clin Ger Med 13:613–622
10. Rangel-Frausto S, Pittet D, Costigan M, et al (1995) The natural history of the systemic inflammatory response syndrome (SIRS). JAMA 273:117–123
11. Salvatore R, Meaume S, Weill-Engerer S, Raynaud A, Ramamonjisoa M, Lesourd B, Moulias R (1996) Hand grip dynamometry and its association to nutritional status and body composition in two populations; one hospitalized in a nutritional acute care unit (NACU), the other in a long term care ward (LTCW). Geriatria (suppl) VII, n° 5:178
12. Hortobagyi T, Zheng D, Weidner M, et al (1995) The influence of aging on muscle strength and muscle fibers characteristics. J Gerontol Biol Sci 50 A (suppl):B 399–B 406
13. Grimby G (1995) Muscle performance and structure on the elderly as studied cross sectionally and longitudinally. J Gerontol 50 A (suppl):17–22
14. Carlson BM (1995) Factors influency the repair and adaptation of muscles in aged individuals. J Gerontol 50 A (suppl):96–100
15. Nair KS (1995) Muscle protein turn over; methodological issues and the effect of aging. J Gerontol Biol Sci 50 (suppl): 107–112
16. Proctor DN, Balagopal P, Nair KS (1998) Age related sarcopenia in humans is associated with reduced synthetic rates of specific muscular proteins. J Nat 128 (suppl):351 S–355 S
17. Berthon P, Freyssenet D, Chatard JC, et al (1995) Mitochondrial ATP production rate in 55 to 73 years old men; effect of endurance training. Acta Physiol Scand 154:269–274
18. Balagopal P, Proctor D, Nair KS (1997) Sarcopenia and hormonal changes. Endocrinol 7:57–60
19. Chilibeck PD, Paterson DH, Cunningham DA, et al (1997) Muscle capillarization, O2 diffusion distance and VO2 kinetics in old and young individuals. J Appl Physiol 82:63–69
20. Hepple MT, Mackinnow JL, Goodman JM, et al (1997) Resistance and aerobic training in old men; effects on VO2 peak and the capillary supply to skeletal muscle. J Appl Physiol 82:1305–1310
21. Lukaski H (1997) Sarcopenia assessment of muscle mass. J Nutr 127 (suppl):994 S–997 S
22. Fogt ES, Bewll ST, Blackburn GL (1995) Nutrition assessment of the elderly in geriatric nutrition. In: Morley JP, Glick Z, Rubenstein LZ (eds) Geriatric Nutrition, 2nd edition. Raven Press, pp 51–62
23. Chumlea WC, Guo SS, Vellas B, Guigoz Y (1995) Techniques of assessing muscle mass and function (sarcopenia) for epidemiological studies of the elderly. J Gerontol 50 A:45–51
24. Baumgartner RN, Stauber PM, Mchug HD, Koehller KM, Garry PJ (1995) Cross sectional age differences in body composition in person 60+ years of age. J Gerontol Med Sci 50 A: M 507–M 316
25. Baumgartner RN, Koihler KM, Gallagher D, et al (1998) Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 147:755–763
26. Moulias S, Belaud-Rotureau MA, Raynaud A, Patat F, Pourcelot L (1998) Evaluation de la sarcopenie au cours du vieillissement normal et pathologique; interêt de l'échographie musculaire. Année Gérontologique 12:237–238
27. Kehayas JJ, Fiatarone MA, Zhuang H, Roubenoff R (1997) Total body potassium and body fat: relevance to aging. Am J Clin Nutr 66:904–910
28. Costes F, Barthelemy JC, Feasson L, et al (1996) Comparison of muscle near infra red spectroscopy and femoral blood gases during steady state exercise in humans. J Applied Physiol 80:1345–1350
29. Conley KE, Cres ME, Jubrias BN, et al (1995) From muscle properties to human performance using magnetic resonance. J Gerontol 50 A (suppl):35–40

30. Marcus R (1996) Should all older people be treated with growth hormones? Drug and Aging 8:1–4
31. Roubenoff R, Rall LC, Veldhius JD, et al (1998) The relationship between growth hormone kinetics and sarcopenia in post menopausal women. J Clin Endocrinol Metab 83:1502–1506
32. Borst SE, Lowewthal DT (1997) Role of IgF1 in muscular atrophy of aging. Endocrinol 7:61–63
33. Renganathan M, Messi ML, Delbond O (1998) Overexpresion of IgF-I exclusively in skeletal muscle prevents age related decline in the number of dihydropyridine receptors. J Biol Chem 237:28845–28851
34. Poehlmann ET, Toth MJ, Fishman PS, et al (1995) Sarcopenia in aging humans: the impact of menopause and disease. J Gerontol 50 A (suppl):73–77
35. Bonnefoy M, Kostka T, Patricot MC, et al (1998) Physical activity and DHEA-I, IgF-I, and testosterone in healthy active elderly people. Age and Ageing 27:745–751
36. Raina N, Jeeseebhoy KN (1998) Changes in body composition and dietary intake induced by TNF alpha and cortisone individually and in combination. Am J Clin Nutr 68:1284–1290
37. Larsson L (1995) Motor units: remodeling in aged animals. J Gerontol 50 A (suppl):91–95
38. Evans WJ, Cyr-Campbell D (1997) Nutrition, exercise and healthy aging. J Am Diet Assoc 97:632–638
39. Evans WJ, Campbell WE (1993) Sarcopenia and age related changes in body composition and functional capacity. J Nutr 123 (suppl):465–468
40. Evans WJ (1997) Functional and metabolic consequences of sarcopenia. J Nutr 127 (suppl):998 S–1003 S
41. Daynes RA, Araneo BA, Erschler WB, et al (1993) Altered regulation of IL6 production with normal aging. J Immunol 150:5219–5230
42. Moulias R, Salvatore R, Weill-Engerer S, Lesourd B, Meaume S (1994) Influence des facteurs nutritionnels et inflammatoires sur le métabolisme et la fonction musculaire. Revue de Gériatrie19, n° 9:613–618
43. Roubenoff R (1997) Inflammatory and hormonal mediators of cachexia. J Nutr 127/S suppl:1014 S–1016 S
44. Baumgartner RN, Koehler KM, Romero L, Garry PJ (1996) Serum albumine is associated with skeletal muscle in elderly men and women. Am J Clin Nutr 64: 552–558
45. Evans WJ (1996) Reversing sarcopenia: how weight training can build strength and vitality. Geriatrics 51:46.7–51.3
46. Bamman MM, Clarke MS, Feeback DL, et al (1998) Impact of resistance exercise during bed rest on skeletal muscle sarcopenia and myosin isoform distribution. J Appl Physiol 84:157–163
47. Evans WJ (1997) Functional and metabolic consequences of sarcopenia. J Nutr 127 (suppl):998 S–1003 S
48. Harris T (1997) Muscle mass and strength: selection to function in population studies. J Nutr 127 (suppl):1004 S–1006 S
49. Ferrucci L, Guralnik JD, Buchner D, et al (1997) Departures from linearity in the relationship between measures of muscular strength and physical performances of the low extremities. J Gerontol Biol Sci Med 52:M 275–285
50. Guralnik JM, Ferrucci L, Simonsick EG, et al (1995) Low extremity functions in persons over the age of 70 years as a prediction of subsequent disability. N Engl J Med 332:556–561
51. Wolfson L, Judge J, Whipple R, King M (1995) Strength is a major factor in balance, gait, and the occurrence of falls. J Gerontol 50 A (suppl):64–67
52. Schultz AB (1995) Muscle function and mobility biomechanics in the elderly. J Gerontol 50 A (suppl):60–63
53. Hughes VA, Fronter WR, Dallal GK, Lutz KJ, et al (1995) Muscle strength and body composition: association with bone density in older subjects. Med and Sci in Sport and Exercise 2707:967–973
54. Laukkanen P, Heikkinen E, Kauppinex M (1995) Muscle strength and mobility as predictors of survival in 75–84 y.o. people. Age and Ageing 24:468–473
55. Bean N, Bennett KM, Lehmann AB (1995) Habitus and hip fracture revisited: skeletal size, strength and cognitive rather that thinness? Age and Ageing 24:481–484
56. Kenney WL, Buskrik ER (1995) Functional consequences of sarcopenia : effects on thermoregulation. J Gerontol 501: 78–85
57. Kohrt WM, Holloszy JO (1995) Loss of skeletal muscle mass with aging: effect on glucose tolerance. J Gerontol 50 A:68–72
58. Freyssenet D, Berthon P, Denis C, et al (1996) Effect of a 6 weeks endurance training progress and branch chain amino acids supplementation on histomorphometric characteristics of aged human muscle. Arch Physical Biochem 104:157–162
59. Fielding RF (1995) Effects of exercise training in the elderly. Proc Nut Soc 54:665–675
60. Evans WJ (1995) Exercise nutrition and aging. Clin Geriatr Med 11:725–734
61. Fielding MA (1995) The role of progressive resistant training and nutrition in the preservation of lean body mass in the elderly. J Am Coll Nutr 14:587–594
62. Fiatarone MA, Marki EC, Ryan ND, et al (1990) High intensity strength training in nonagenarians. JAMA 263:3029–3034
63. Clark DO (1996) The effect of walking on lower body disability among older Blacks and Whites. Am J Public Health 86:57–61
64. Glick Z (1995) Energy balance. In: Morley JE, Glick Z, Rubenstein LZ (eds) Geriatric Nutrition. Raven Press, pp 15–24
65. Bidlack WR, Wei Wang (1995) Nutrition requirement of the elderly. In: Morley JE, Glick Z, Rubenstein LZ (eds) Geriatric Nutrition. Raven Press, pp 25–49
66. Rudman D, Feller AG, Nagras HS (1990) Effects of human growth hormone in men over 60 y.o. N Engl J Med 323:1–6
67. Moulias R, Belmin J, Lesourd B, Laurent M, Meaume S (1990) Effects of human growth hormone in men over 60 years old. New Engl J Med 323:1561–1562
68. Tsujinaka T, Fujita J, Ebisui C, et al (1996) Interleukine 6 receptor antibody inhibits muscle atrophy in interleukine 6 transgenic mice. J Clin Invest 97:244–249
69. Wendruch R (1995) Intervention based on the possibility that oxydative stress contributes to sarcopenia. J Gerontol 507:157–161