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Review Article

Hylonome

Multifactorial pathogenesis of falls as a basis for multifactorial interventions

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Clinical experience and epidemiological data demonstrate that mobility is a key determinant of successful aging and quality of life in old age. Loss of mobility is one of the most prominent threats in old age[1,2]. Gait disorders and falling are manifestations of mobility impairment and increase with advancing age[3,4]. Gait and balance disorders, falling, and fall-related fractures are interrelated in a pathogenetic cascade[5]. Multiple falling is a sign of locomotor failure and physical frailty[6].

Falling in old age has disastrous consequences. About five per cent of falls lead to fractures, a fifth of them are hip fractures. Another 5% to 10% of falls result in serious injuries which require medical care[5,7]. Falls break bones, self-esteem and activity. Fear of falling leads to self-restriction of physical activity and social contacts and initiates a vicious cycle of deconditioning.

Fractures are also the relevant outcome of osteoporosis. Sixteen per cent of all postmenopausal women will sustain a hip fracture, and up to 40% some type of osteoporotic fracture during their lifetime[3,8,9]. In the year 2000 in Germany 114,000 hip fractures, 63,000 humeral, 23,000 pelvic and 110,000 forearm fractures, which led to in patient treatment, have been registered (Statistisches Bundesamt 2000). In relation to falling vertebral and extravertebral fractures have a different pathogenesis. The common term "osteoporotic fracture" is focused on bone strength and does not reflect the fact that 90% of all extravertebral fractures, i.e., hip, humerus, wrist and pelvic fractures, are the result of a fall[10-18].

In the Rotterdam study[19] only 20.7% of men and 44.1% of women with non-vertebral fractures had osteoporosis defined by the WHO criteria (T-score<2.5).

It is the combination of reduced bone strength and increased fall risk which causes these types of age-, fall- and osteoporosis-related fractures. Therefore, preventing falls means preventing fractures. However, most vertebral fractures occur without trauma because of material failure.

The strong correlation between falls and extravertebral fractures requires inclusion of a fall risk assessment and a fall prevention program in the management of osteoporosis – in contrast to the traditional approach, which is mainly concentrating on bone strength alone. The steep increase in the incidence of hip fractures with advancing age arises from the interaction between bone strength, propensity to fall and fall mechanisms[20]. Bone strength is one but not the only determinant of hip fractures.

Falls in the aged are frequent occurrences. About one third of all elderly (65+) experience one or more fall a year[21,22]. Eighty per cent of these falls happen without loss or change of consciousness, and without overwhelming external force, during normal daily activities. We speak of non-syncopal or locomotor falls[5].

Falling from a standing height generates enough energy to break even a non-osteoporotic elderly femur. The use of simple physics illustrates this point. We calculate the force resulting from a fall of 50 kg from a height of 80 cm, decelerated by a soft tissue of 4 cm thickness. The potential energy (which equals the kinetic energy in the moment of impact) is 400 J (500 N, height 0,8 m). Because energy respectively work is the product of force times distance, we have to divide the energy by the decelerating distance to get the resulting force. 400 J divided by 0,04 m tissue thickness results in a force of 10 000 N, which the femur is loaded with. That can hardly be called a "minimal" trauma.

Most falls in the elderly are not caused by external hazards in contrast to younger age groups. External hazards are not found strongly correlated to falling. In the environment of elderly fallers, we find the same amount of hazards as in non-fallers, and fallers have lived for decades in the same environment with the same hazards without having fallen. What has changed, when some elderly start to sustain frequent falls? The answer is deceptively obvious. Their ability

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to control body posture during locomotion has declined.

Falls are not randomly distributed among the elderly population. People who fall show a certain pattern of characteristics. It is a consistent finding of prospective studies, that the faller accumulates an individual profile of fall risk factors. It is not a single disease or a single factor which causes a fall. For 100 falls we can find 300-400 causes. Each fall is caused by a combination of multiple risk factors[3,23-25].

We need an understanding of the risk factors for identifying persons at high risk in order to aim our preventive measures, and we need the knowledge of the individual risk profile to guide an individualized therapy in case of fall propensity.

Hundreds of parameters have been found to be significantly correlated with falling in bi-variate analysis, but most of them are highly interrelated. Their bi-variate correlation has not proved them to be independent risk factors in multivariate analyses. Only a small number of factors have been found to be independently correlated with falling. Unfortunately each research team has investigated its own selection of factors. Many studies have not investigated the variables that have been already proved to be risk factors in other studies. Therefore, the precise relationships between different risk factors remain unresolved.

Not surprisingly, all methodologically convincing studies have found some parameters of neuromuscular function to be highly fall-related. Unfortunately neuromuscular function has been operationalized in very different ways. The following list comprises these factors that have been found most consistently to be independent risk factors in multivariate analysis[3,10,11,25-33]:

1. Muscle power or muscle strength of lower extremities, 2. postural competence/lateral balance, 3. impairments of vision, 4. taking multiple (>4) medications or taking certain groups of fall-related drugs, 5. cognitive impairment.

Two test procedures of lower extremity function have been found to be good independent predictors of falling: chair rising – representing muscle power, and tandem maneuvers – representing lateral postural capacity. Quantifying these performances by timed tests enables us to evaluate therapy effects[1,18,19,26,30,34,35].

Test procedure - chair rising:

To stand up from a chair of usual height 5 times as quickly as possible without using the arms.

Test procedure - tandem standing/ tandem walking:

To stand in a position with both feet directly in line: the heel of the leading foot is directly in front of the toes of the other.

In combination with freely chosen gait velocity these two motor performances are predictive for increased mortality, impending impairment of mobility, increasing probability of functional dependence, additional nursing home placement, and additional hospitalization[1].

As a preliminary conclusion: we have some clinical tests which give us valuable information about risks of falling, but operationalization of neuromuscular function related to falling remains variable and unsatisfying. There are too many motor performance tests, which are highly interrelated, and apparently depend on the same anatomical and neurological subsystems. We do not know whether we measure the same factor with different tests, or to which degree the subsystems which are measured are overlapping or mutually exclusive.

Human movement like any other phenomenon of nature has to be described in terms of physics. In a mechanical analysis, gait and falling can be seen as a complex combination of different oscillations. The body itself can be seen as an inverted and therefore unstable pendulum. Its center of gravity (COG) is oscillating in a vertical and horizontal plane and describes a sinusoidal curve. Oscillations are the universal means nature uses to transform and store energy. By the oscillations we are constantly transforming potential energy to kinetic energy and vice versa. There are spring-like and pendulum-like oscillations in the body. The elastic elements of muscles and tendons act as springs storing energy, arms and legs and trunk oscillate like pendula. In this approach neuromuscular control of locomotion is the phase-adapted variation of stiffness of different body parts, which determines the resonance and oscillations of the body parts and the whole body.

Balance can be defined as the ability to control the movements of the COG with respect to the base of support. In a static description, falling happens if the projection of the COG lies outside the base of support. During walking the COG is mostly not over the base of support, but is oscillating between the right and left foot as successive base of support (dynamic balance). Walking means to bring cyclically the base of support under the COG. Falling as loss of balance is an uncontrolled involuntary downward movement in the direction of gravity with coming to rest on a deeper level. It has to be counteracted by eccentric decelerating muscle action.

Movement has to be described in terms of velocity and acceleration. Force [N] causes acceleration, i.e., we have to know the forces involved in movement. Each movement is the action of force along a distance in a certain time, has therefore measured as power (Force times distance = work. Work/ time respectively force times velocity = power).

These equations define the variables, which we have to investigate in respect to locomotion and falling: force, velocity, power and the spatial projection of the movement of the COG in relation to the base of support.

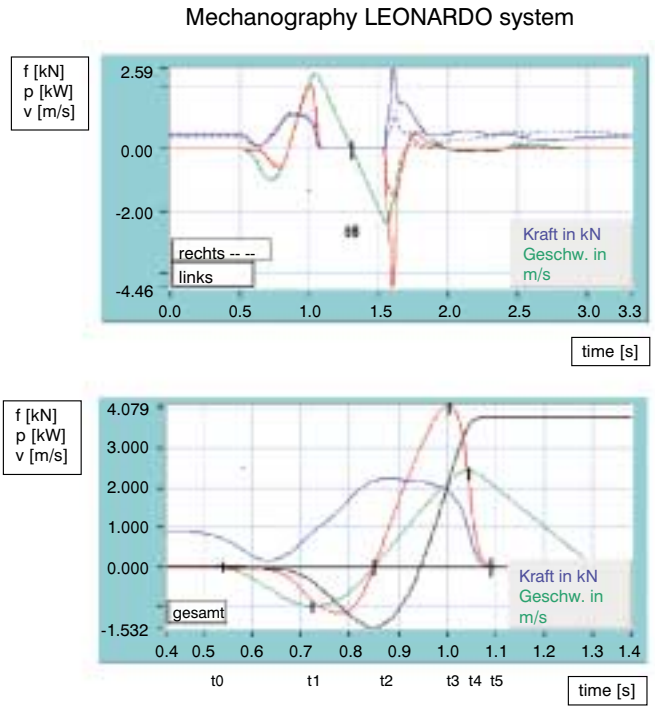
The mechanical approach enables us to measure and calculate human movement in accordance with scientific concepts, and does not lead to an endless number of different motor performance tests. Description of movement in terms of physics is necessary for precise scientific communication.

For measuring the objective parameters of movement H. Schiessl (Novotec Pforzheim, Germany) has constructed a force plate, which measures force and calculates by integration of acceleration the vertical velocity of the COG (F/m= a; a x t= v), and calculates using force and velocity the power of vertical movements (Leonardo mechanography system). We have coined the term mechanography for this method which records the time course of ground reaction forces, velocity of

the vertical movements of the COG and power during physiological unrestricted movements. In the mechanogram eccentric and concentric phases of movements can be differentiated and the storage of energy in the elastic elements of the body can be examined. Without release of previously stored energy the motor system cannot produce quickly enough the necessary energy to jump. The force we need for a movement against gravity is a summation of quickly released energy which has been previously stored in elastic elements during eccentric countermovements, and currently generated muscle force by the actin-myosin-system. During the eccentric phases the elastic elements are stretched by which energy is stored. The Leonardo system enables us to analyse these eccentric phases, which cannot be adequately clinically tested. They have been proven to be most sensitive to motor disorder and are early and pathognomonic signs of motor disorder. In contrast to this kind of measurement the commonly used muscle testing methods have certain shortcomings. Isometric motor tests are by definition without movement and can therefore not reveal these developments. Physiological movements are not isokinetic, isokinetic ones have another speed compared with physiological movements.

A standard motor task of mechanography is a vertical jump of maximal exertion with both feet, measured after instruction and practice. The first phase of jumping is squatting as a countermovement to store energy in the elastic elements. The velocity curve shows during the squatting a negative velocity, because we are moving downwards. The deepest point of the velocity curve represents the slowing of downward movement, braking the downward movement and simultaneously storing the kinetic energy of downward movement in elastic elements of the muscle-tendon unit. This is a classic eccentric muscle task. The curve reaches the zero point again, when the deepest point of squatting is reached. Kinetic energy is now zero and has been transformed to potential energy, stored spring-like in the elastic elements. The mechanogram demonstrates that the maximal force has already been generated before the upward movement of jumping. The momentary production of force by the actin-myosin-system would not be quick enough to accelerate the body to jump, but the elastically stored energy can be released quickly enough. The subsequent development of the force after peak point demonstrates declining force during increasing velocity. This corresponds to Hill's equation! The energy for jumping (like any other movement) is the summation of released elastically stored energy and continual production of force by the actin-myosin-system. So the mechanography gives deep insight into the kinetics and timing, respectively, coordination of movements, representing an ideal tool for studying influence of any treatment on muscle function. The comparison of mechanography with usual locomotor tests demonstrates a high reliability[71]. The muscle power, measured by mechanography, shows a strong correlation to the aging process[72].

Because the fall-related (extravertebral "osteoporotic") fractures are both associated with reduced bone strength and



upper diagram: right (dotted) and left foot (solid) separately registered
lower diagram: right and left foot combined

f= force	blue curve	ground reaction force
v= velocity	green curve	vertical velocity of the center of gravity
p= power	red curve	power= force times velocity

t_0 start of downward movement (negative velocity)
t_1 maximal negative velocity, start of deceleration
t_2 v=0, deepest point of squatting
t_3 maximal power
t_4 maximal positive velocity
t_5 f=0, feet have left the force plate, subject is airborne
t_6 v=0, highest point of jumping, start of downward movement

Data of the test subject: male, body weight = 89.3kg
Results: maximal power per kg BW = 46 W/kg
jump height = 0.42 m, velocity = 2.43 m/s,
max. power = 4.08 kW, right = 2.07 kW, left = 2.01 kW
max. force = 2.22 kN, right = 1.13 kN, left = 1.09 kN

Figure 1. Normal mechanography of a vertical jump.

propensity to fall, a comprehensive treatment should have two targets: enhancing bone strength and reducing fall risk. The traditional approach of treating osteoporosis focuses on bone without regarding either the whole muscle-bone system with its feedback loop or the role of falls, but nature has interconnected muscle and bone with each other (Wolff's law, Utah paradigm[36,37,38]). Form follows function, growth of bone is ruled by the stress, which is generated by muscle forces. These interrelationships could be used to supplement and optimize osteoporosis treatment. We have to understand the vital role

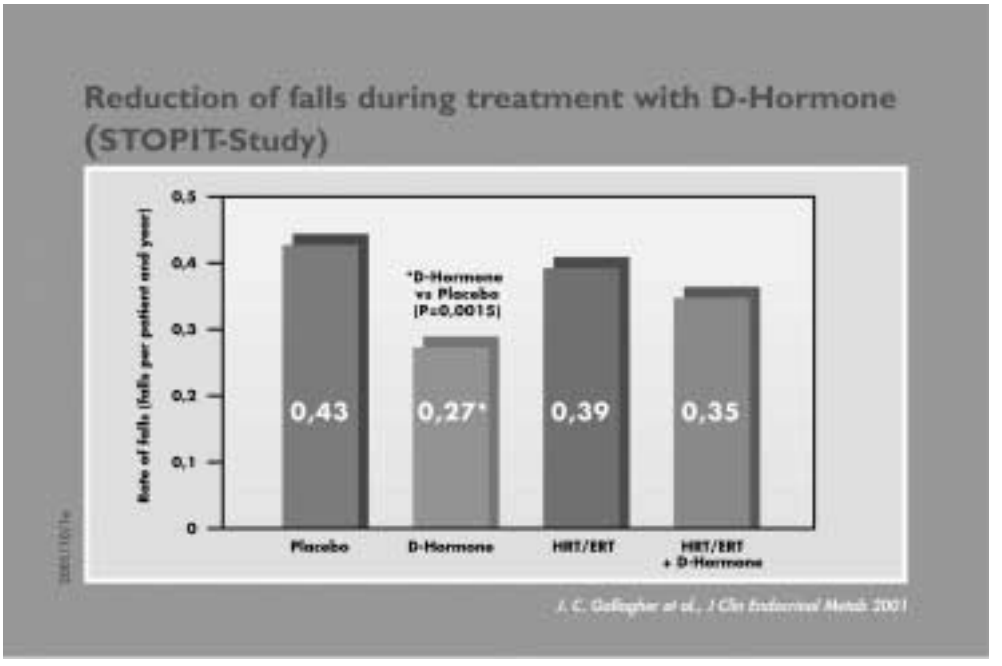


Figure 2. Significant reduction of falls after treatment with D-hormone (Gallagher et al. 2001).

of muscle function on bone and falls.

Aiming at the muscle means therefore improving bone[39,40] and reducing falls simultaneously[28,41]. A systematic review and meta-analysis of 40 randomized clinical trials has been performed[70]. A multifactorial fall risk assessment and management programme to prevent falls in older adults was the most effective component on risk of falling (adjusted RR= 0.82; 95% Cl, 0.72 - 0.94). Exercise interventions also had a beneficial effect (adjusted RR = 0.86; 95% Cl, 0.75 - 0.99).

There is a continuous positive relationship between physical activity and bone mass in normal white men[42], and a site-specific influence of muscle force on bone mass[43] (further references[39]). Strengthening exercises can maintain or enhance bone mass[44,45]. Unfortunately, the evidence for the negative impact of reduced muscle force or immobilisation on bone strength is far more overwhelming than the positive effect of muscle training on bone development. There are not yet convincing data proving the reduction of fracture rate by physical exercise. A number of animal studies have proven that bone strength can be effectively improved by muscle activities which lead to an increase of bone loading. In rats five jumps of 40cm height a day are sufficient to improve the maximal breaking force of femur and tibia from a bending moment of 354 (+-30) to 409 (+- 30) Nmm and 216 (+- 15) to 266 (+-21) Nmm, respectively[40].

Corresponding to the multifactorial pathogenesis of falling, a multifactorial treatment is the most promising approach to counteract gait disorders and the risk of falling[28,46].

Firstly we have to avoid bad advice. We find patient advice leaflets which advise patients to always use their arms for support when standing up from a chair. This habit would deprive the patient of one of the best conditioning stimulus of lower extremity force in daily life.

For a person at high risk of falling, hip protectors should be advocated. The safehip hip protector, developed by Lauritzen and colleagues, has been found to be effective in preventing hip fractures[49].

The deterioration of locomotor and balance functions associated with advancing age can be counteracted by gait and balance training[47,48]. Tai Chi and balance programs have been proven effective in reducing fall frequency[41]. A multifactorial program, including strength training and revision of medication has also reduced fall frequency[28].

We should minimize using fall-related drugs like neuroleptics, benzodiazepines, tricyclic antidepressants, SSRI-antidepressants and cortisone[23,29,50,51,52].

Besides adequate exercising we have to look for drugs with positive effects on muscle function and postural capacity. The D-hormones (alfacalcidol, calcitriol) are promising candidates for enhancing muscle function[53]. D-hormone receptors (VDRs) have been found in skeletal muscles and nerves[54] through which muscle contraction and relaxation will be controlled by influx and efflux of calcium and in addition the muscle protein synthesis[53]. It has been recently confirmed in VDR gene-deleted mice that the absence of VDRs cause a reduction of skeletal muscle fiber size based on an increased expression of myogenic regulation factors (Myf5, Myogenin, E2A) through which the strict regulated differentiation and maturation of muscle cells will be disturbed[67]. The muscular abnormalities are independent from secondary, metabolic changes,

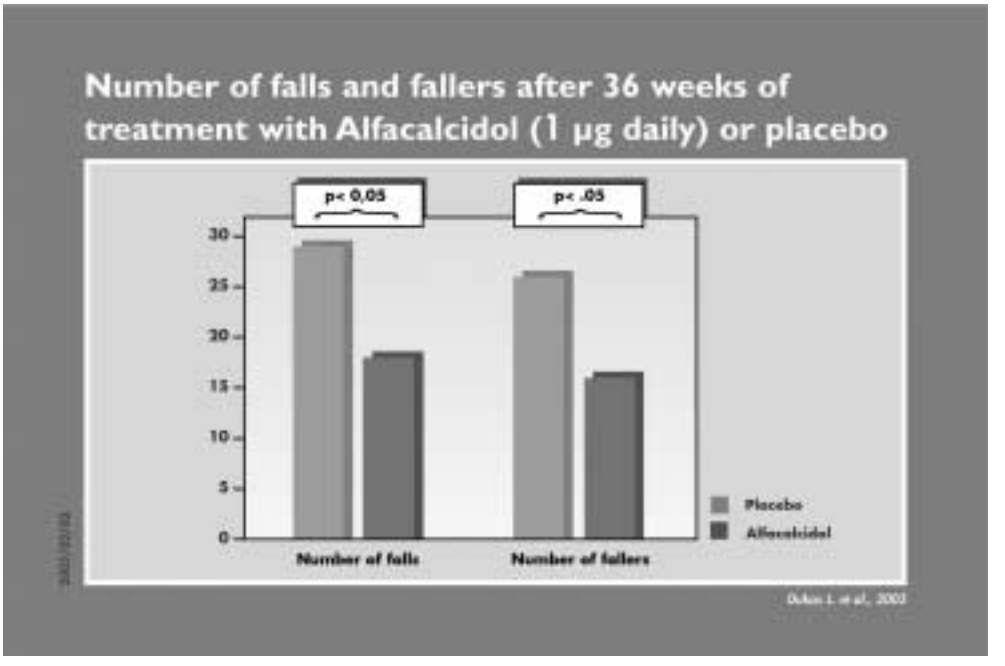


Figure 3. Significant reduction of falls and fallers in community-dwelling elderly persons after 36 weeks of treatment with alfacalcidol (Dukas et al. 2004).

e.g., hypocalcemia or hyperparathyroidism. This confirms the direct efficacy of VDRs. The fact that a treatment with D-hormone of VDR-positive myoblasts *in vitro* downregulates the mentioned myoregulating transcription factors, point out in addition the important role of D-hormone and VDRs in muscle development[67]. Older age is significantly associated with decreased VDR expression in human skeletal muscle tissue[68]. A positive correlation was found between femoral muscle strength and function and D-hormone serum levels in the elderly[55,69]. These results suggest that the age-related decline in muscle strength and function and the increase of falls could be in part explained by a decrease of VDRs and a decrease of D-hormone in serum and/or at receptor level.

There is emerging clinical evidence that alfacalcidol, a prodrug of D-hormone, improves muscle function[56-58]. Histochemical classification based on muscle biopsies of the fibre composition revealed that a treatment of osteoporotic patients with 1µg alfacalcidol for 3-6 months induced an increase in the relative number of fast-twitch fibers[56]. The time taken to dress was significantly less after treatment[56]. The serum concentrations of 25(OH)D were constant during the study[56].

Alfacalcidol, 0.5µg daily, improved muscle strength (isometric knee extension strength) and functional ability (walking distance over 2 minutes) significantly after 6 months of treatment in elderly D-hormone deficient women[57].

In patients with rheumatoid arthritis and osteopenia, muscle strength increased significantly by 60% receiving 1 µg alfacalcidol daily compared to 18% in patients receiving 1000 IU vitamin D daily[58].

Gallagher et al. described a significant decrease in the number of falls and the incidence rate of falls and fall-related fractures after 3-years treatment with 0.5µg D-hormone daily in osteopenic elderly women without vitamin D deficiency[59,60] (Figure 2).

In a randomized, double-blind, placebo controlled study Dukas et al. have shown that 1 µg alfacalcidol daily reduce significantly the number of falls (-54%) and fallers (-55%) in community dwelling elderly women and men with a total calcium intake of more than 500 mg daily and normal vitamin D serum levels[61] (Figure 3).

A reduced creatinine clearance (CrCl) of <65 ml/min is significantly associated with low D-hormone serum levels and with a significant four-fold increased risk of falls[62]. Thirty six weeks of treatment with alfacalcidol (1 µg daily) significantly and safely reduces in community dwelling elderly women and men with a CrCl of <65 ml/min the low CrCl associated increased number of fallers (-74%) and the high risk of falls (-71%)[63].

Alfacalcidol was able to reduce the hip fracture rate significantly and very quickly after 6-months treatment with 1 µg daily in stroke patients[64] and after 18 months in elderly patients with Parkinson's disease[65].

The positive effects of alfacalcidol and calcitriol on the muscle fibers, daily living activities, muscle strength in patients with rheumatoid arthritis and especially on the reduction of falls was not due to correction of age-related vitamin D deficiency like in some other studies since most of the patients had normal vitamin D serum levels at baseline.

The D-hormone preparations acted as pharmacological treatments by increased levels or action of D-hormone in the target organs muscle and/or nerves.

Based on further confirmation of these findings alfacalcidol opens a new therapeutic strategy for treating osteoporosis by simultaneously increasing bone strength and decreasing falls by improving muscle function. D-hormones could have a double impact on fracture risk by both enhancing bone strength and muscle function.

Regarding the interrelationships between muscle, falls and bones, the traditional bone-oriented approach on extravertebral, osteoporosis-related fractures should be supplemented by fall risk assessment, fall management and treatment of muscle function[66].

References

1. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995; 332:556-561.
2. Alexander NB. Gait disorders in older adults. J Am Geriatr Soc 1996; 44:434-451.
3. Campbell AJ, Reinken J, Allan BC, Martinez GS. Falls in old age: a study of frequency and related clinical factors. Age Ageing 1981; 10:264-270.
4. Ferrucci L, Penninx BW, Leveille SG, Corti MC, Pahor M, Wallace R, Harris TB, Havlik RJ, Guralnik JM. Characteristics of non-disabled older persons who perform poorly in objective tests of lower extremity function. J Am Geriatr Soc 2000; 48:1102-1110.
5. Runge M. Die multifaktorielle Genese von Gehstörungen, Stürzen und Hüftfrakturen im Alter. Z Gerontol Geriat 1997; 30:267-275.
6. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Cardiovascular Health Study. Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56:M146-156.
7. Tinetti ME. Falls. In: Cassel CK, Cohen HJ, Larson EB, Meier DE, Resnick NM, Rubenstein LZ Sorenson LB (Hrsg.) Geriatric Medicine. 3. Aufl. Springer, New York; 1996:S787-799.
8. Melton LJ III. Hip fractures: a worldwide problem today and tomorrow. Bone - 1993; 14:S1-S8.
9. Melton LJ III. Epidemiology of hip fractures: implications of the exponential increase with age. Bone 1996; 18(Suppl.3):121S-125S.
10. Nevitt MC, Cummings SR and the Study of Osteoporotic Fractures Research Group: Falls and fractures in older women. In: Vellas B, Toupet M, Rubenstein L, Albarede JL, Christen Y (eds). Falls, balance and gait disorders in the elderly, Elsevier, Paris; 1992:21-38.
11. Rubenstein LZ, Josephson KR. Causes and prevention of falls in elderly people. In: Vellas B, Toupet M, Rubenstein L, Albarede JL, Christen Y, eds. Falls, balance and gait disorders in the elderly. Elsevier Paris 1992; p21-38.
12. Grisso JA, Kelsey JL, Strom BL, Chiu GY, Maislin G, O'Brien LA, Hoffman S, Kaplan F, Northeast Hip Fracture Study Group: Risk factors for falls as a cause of hip fracture in women. N Engl J Med 1991; 324:1326.
13. Norton R, Campbell AJ, Lee-Joe T, Robinson E, Butler M. Circumstances of falls resulting in hip fractures among older people. J Am Geriatr Soc 1997; 45:1108-12.
14. Ytterstad B. The Harstad injury prevention study: the characteristics and distribution of fractures amongst elders - an eight year study. Int J Circumpolar Health 1999; 58:84-95.
15. Kelsey JL, Browner WS, Seeley DG, Nevitt MC, Cummings SR. Risk factors for fractures of the distal forearm and proximal humerus. The Study of Osteoporotic Fractures Research Group. Am J Epidemiol 1992; 135:477-489.
16. Luukinen H, Koski K, Laippala P, Kivela SL. Factors predicting fractures during falling impacts among home-dwelling older adults. J Am Geriatr Soc 1997; 45:1302-1309.
17. Morris RO, Sonibare A, Green DJ, Tahir Masud T. Closed pelvic fractures: characteristics and outcomes in older patients admitted to medical and geriatric wards. Postgrad Med J 2000; 76:646-650.
18. Lee SH, Dargent-Molina P, Breart G. EPIDOS Group: Risk factors for fractures of the proximal humerus: results from the EPIDOS prospective study. J Bone Miner Res 2002; 17:817-825.
19. Schuit SCE, van der Klift M, Weel AEAM, de Laet CEDH, Burger H, Seeman E, Hofman A, Uitterlinden AG, van Leeuwen JPTM, Pols HAP. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone 2004; 34:195-202.
20. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med 1995; 332:767-773.
21. Tromp AM, Smit JH, Deeg DJ, Bouter LM, Lips P. Predictors for falls and fractures in the Longitudinal Aging Study Amsterdam. J Bone Miner Res 1998; 13:1932-1939.
22. Blake AJ, Morgan K, Bendall MJ, Dallosso H, Ebrahim SB, Arie TH, Fentem PH, Bassey EJ. Falls by elderly people at home: prevalence and associated factors. Age Ageing 17:365-372.
23. Campbell AJ, Borrie MJ, Spears GF. Risk factors for falls in a community-based prospective study of people 70 years and older. J Gerontol 1989; 44:M112-117.
24. Tinetti ME, Williams TF, Mayewski R. Fall risk index for elderly patients based on number of chronic disabil-

ities. Am J Med 1986; 80:429-434.
25. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988; 319:1701-1707.
26. Nevitt MC, Cummings SR, Kidd S, Black D. Risk factors for recurrent nonsyncopal falls: a prospective study. JAMA 1989; 261:2663-2668.
27. Robbins AS, Rubenstein LZ, Josephson KR, Schulman BL, Osterweil D, Fine G. Predictors of falls among elderly people. Results of two population-based studies. Arch Intern Med 1989; 149:1628-1633.
28. Tinetti ME, Baker DI, McAvay G, Claus EB, Garett P, Gottschalk M, Koch ML, Trainor K, Horwitz RI. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med 1994; 331:821-827.
29. Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ III. Psychotropic drug use and the risk of hip fracture. N Engl J Med 1987; 316:363-369.
30. Lipsitz LA, Nakajima I, Gagnon M, Hirayama T, Connelly CM, Izumo H, Hirayama T. Muscle strength and fall rates among residents of Japanese and American nursing homes: an International cross-cultural study. J Am Geriatr Soc 1994; 42:953-959.
31. Rubenstein LZ, Josephson KR, Robbins AS. Falls in the nursing home. Ann Intern Med 1994; 121:442-451
32. Nevitt MC, Cummings SR, Hudes ES. Risk factors for injurious falls: a prospective study. J Gerontol 1991; 46:M164–M170.
33. Oliver D, Britton M, Seed P, Martin FC, Hopper AH. Development and evaluation of evidence based risk assessment tool (STRATIFY) to predict which elderly inpatients will fall: case-control and cohort studies. BMJ 1997; 315:1049-1053.
34. Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E, Meunier PJ, Breart G. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. Lancet 1996; 348:145-149.
35. 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; 43:603-609.
36. Frost HM. Defining osteopenias and osteoporoses: another view (with insights from a new paradigm). Bone 1997; 20:385-391.
37. Schiessl H, Frost HM, Jee WSS. Estrogen and bone-muscle strength and mass relationships. Bone 1998; 22:1-6.
38. Rittweger J, Beller G, Ehrig J, Jung C, Koch U, Ramolla J, Schmidt F, Newitt D, Majumdar S, Schiessl H, Felsenberg D. Bone-muscle strength indices for the human lower leg. Bone 2000; 27:319-326.
39. Runge M, Schießl H, Rittweger J. Klinische Diagnostik des Regelkreises Muskel-Knochen am Unterschenkel. Osteologie 2002; 11:25-37.
40. Umemura Y, Ishiko T, Yamauchi T, Kurono M, Mashiko S. Five jumps a day increase bone mass and breaking force in rats. J Bone Miner Res 1997; 12:1480-1485.
41. Wolf SL, Barnhart HX, Kutner NG, McNeely E, Coogler C, Xu T. Reducing frailty and falls in older persons: an investigation of Tai Chi and computerized balance training. Atlanta FICSIT Group. Frailty and Injuries: Cooperative Studies of Intervention Techniques. J Am Geriatr Soc 1996; 44:489-497.
42. Need AG, Wishart JM, Scopacasa F, Horowitz M, Morris HA, Nordin BEC. Effect of physical activity on femoral bone density in men. BMJ 1995; 310:1501-1502.
43. Blain H, Vuellemin A, Teissier A, Hanesse B, Guillemin F, Jeandel C. Influence of muscle strength and body weight and composition on regional bone mineral density in health women aged 60 years and over. Gerontology 2001; 47:207-212.
44. Layne JE, Nelson ME. The effects of progressive resistance training on bone density: a review. Med Sci Sports Exerc 1999; 31:25-30.
45. Ernst E. Exercise for female osteoporosis: a systematic review of randomised clinical trials. Sports Medicine 1998; 25:359-368.
46. Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. Lancet 1999; 353: 93-97.
47. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Tilyard MW, Buchner DM. Randomised controlled trial of a general practice programme of home based exercise to prevent falls in elderly women. BMJ 1997; 315:1065-1069.
48. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Falls prevention over 2 years: a randomized controlled trial in women 80 years and older. Age Ageing 28:513-518.
49. Lauritzen JB, Petersen MM, Lund B. Effect of external hip protectors on hip fractures. Lancet 341:11-13.
50. Schwartz AV, Kelsey JL, Sidney S, Grisso JA. Characteristics of falls and risk of hip fracture in elderly men. Osteoporos Int 1998; 8:240-246.
51. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc 1999; 47:30-39.
52. Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA. Antidepressants and the risk of falls among nursing home residents. N Engl J Med 1998; 339:875-882.
53. Boland R. Role of vitamin D in skeletal muscle function. Endocr Rev 1986; 4:434-448.
54. Bischoff HA, Borchers M, Gudat F, Duermueller U, Theiler R, Stähelin HB, Dick W. *In situ* detection of 1,25-dihydroxyvitamin D receptor in human skeletal muscle tissue. Histochem 2001; 33:19-24.
55. Bischoff HA, Stähelin HB, Urscheler N, Ehrsam R, Vontheim R, Perrig-Chiello P, Tyndall A, Theiler R. (1999). Muscle strength in the elderly: its relation to vitamin D metabolites. Arch Phys Med Rehabil 80:54-58.

56. Sörensen OH, Lund BI, Saltin B, Lund BJ, Andersen RB, Hjorth L, Melson F, Mosekilde F. Myopathy in bone loss of ageing: improvement by treatment with 1-alpha- hydroxycholecalciferol and calcium. Clin Sci (Lond) 1979; 56:157-161.
57. Verhaar HJJ, Samson MM, Jansen PAF, de Vreede PL, Manten JW, Duursma SA. Muscle strength, functional mobility and vitamin D in older women. Aging (Milano) 2000; 12:455-460.
58. Scharla SH, Schacht E, Bawey S, Kamilli I, Holle D, Lempert UG. Pleiotropic effects of alfacalcidol in elderly patients with rheumatoid arthritis. Arthritis Rheum 2003; 23:268-274.
59. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab 2001; 86:3618-28.
60. Gallagher JC, Haynafzki G, Fowler S. Effect of estrogen, calcitriol or the combination of both on falls and non-vertebral fractures in elderly women. J Bone Miner Res 2002; 17:S210.
61. Dukas L, Bischoff HA, Lindpaintner LS, Schacht E, Birkner-Binder D, Damm TN, Thalmann B, Stähelin HB. Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. J Am Geriatr Soc 2004; 52:230-236.
62. Dukas L, Schacht E, Stähelin HB. Ein signifikanter unabhängiger neuer Risikofaktor für Stürze im Alter: Eine erniedrigte Creatinin-Clearance unter 65 ml/min. Osteologie 2004; 13:179.
63. Dukas L, Schacht E, Stähelin HB. Die mit erniedrigter Creatinin-Clearance assoziierte erhöhte Sturzrate ist mit Alfacalcidol behandelbar. Osteologie 2004; 13:180.
64. Sato Y, Maruoka H, Oizumi K. Amelioration of hemiplegia-associated osteopenia more than 4 years after stroke by 1α-hydroxyvitamin D_3 and calcium supplementation. Stroke 1997; 28:736-739.
65. Sato Y, Manabe S, Kuno H, Oizumi K. Amelioration of osteopenia and hypovitaminosis D by 1a-hydroxyvitamin D3 in elderly patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1999; 66:64-68.
66. Runge M. Gehstörungen, Stürze, Hüftfrakturen. Steinkopff Verlag Darmstadt 1998.
67. Endo I, Inoue D, Mitsui T, Umaki, Y, Akaike M, Yoshizawa T, Kato S, Matsumoto T. Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. Endocrinology 2003; 144:5138-5144.
68. Bischoff-Ferrari HA, Borchers M, Gudat F, Dürmüller U, Stähelin HB, Dick W. Vitamin D receptor expression in human muscle tissue decreases with age. J Bone Miner Res 2004; 19:265-269.
69. Dukas L, Schacht E, Bischoff HA. Better functional mobility in community dwelling elderly is related to D-hormone and a minimal calcium intake of more than 512 mg/day. Osteoporos Int 2003; 14:S34.
70. Chang JT, Morton SC, Rubenstein LZ, Mojica WA, Maglione M, Suttorp MJ, Roth EA, Shekelle PG. Interventions for the prevention of falls in older adults: systematic review and meta-analysis of randomised clinical trials. BMJ 2004; 328:1-7.
71. Rittweger J, Schiessl H, Felsenberg D, Runge M. Reproducibility of the jumping mechanography as a test of mechanical power output in physically competent adult and elderly subjects. J Am Geriatr Soc 2004; 52:128-131.
72. Runge M, Rittweger J, Russo CR, Schiessl H, Felsenberg D. Is muscle power output a key factor in the age-related decline in physical performance? A comparison of muscle cross-section, chair-rising test and jumping power. Clin Physiol Funct Imaging 2004; 24:335-340.