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Dysmobility syndrome: a paradigm shift in fracture prevention

For cite: *Bol', Sustavy, Pozvonochnik*. 2017;7:1-6. doi: 10.22141/2224-1507.7.1.2017.102430

Abstract. Fragility fractures engender major healthcare cost, reduce independence/quality and life and increase mortality risk. Despite availability of multiple therapies to reduce risk for future fracture, few patients are treated even following hip fracture. Clearly, approaches of the past aimed at reducing fragility fracture risk, primarily by diagnosing osteoporosis and initiating bone-active medications, have failed. A different approach is required; such a change in focus is proposed here. Briefly, the dysmobility syndrome concept recognizes fragility fracture as the clinical outcome of consequence and appreciates that osteoporosis is only part of the syndrome leading to “osteoporosis-related” fracture. Other components of this syndrome include sarcopenia, obesity, diabetes, osteoarthritis, and potentially multiple other factors that increase risk for falls with attendant increased fracture risk. In summary, the dysmobility syndrome concept moves the field, and also, importantly, older adults at risk for fragility fracture, beyond a singular focus on bone to more appropriately focus on a holistic approach to fracture risk reduction.

Keywords: fracture; osteoporosis; sarcopenia; dysmobility syndrome; falls

Scope of the Osteoporosis-Related Fracture Problem: Why Propose a New Syndrome?

Despite a worldwide increase in the older adult population, with concomitant increase in number of fragility fractures and their attendant morbidity, mortality and healthcare costs, fewer people are receiving medication to reduce fracture risk even following fracture [1, 2]. This failure to treat has recently been described as a “crisis” in osteoporosis care [3]. To address this osteoporosis treatment gap, international efforts have been, and are currently, focusing on the Fracture Liaison Service (FLS) model [4, 5]. The FLS paradigm consists of a systematic approach to identify those who have sustained a fragility fracture and subsequently execute appropriate evaluation to investigate secondary causes of bone loss and initiate pharmacologic therapy to reduce fracture risk [6]. The FLS approach has been widely studied and validated to reduce fractures and healthcare expenditures [1, 7].

To summarize, despite the availability of multiple rigorously studied medications that reduce fracture risk, and in the presence of an effective paradigm (FLS) to implement medical therapies, few people are being treated even after sustaining an osteoporosis-related fracture. In essence, the approaches previously taken to reduce fragility fracture risk, primarily by diagnosing low bone mass and initiating bone-active medications, have failed. Continuing to take the tactics of the past to inform clinicians and patients

about the risks of “osteoporosis” seems similarly destined to fail; change is needed. This article suggests a different approach to the problem.

Dysmobility Syndrome: The Concept

It was recently advocated that the diagnosis of osteoporosis be expanded to include individuals at increased risk for fracture [8, 9]. At face value, this is a reasonable proposition as many older adults with osteopenia or even normal bone mineral density (BMD) sustain “osteoporosis-related” fractures [10]. Thus, diagnosing osteoporosis and treating only those with a BMD T-score ≤ -2.5 is not adequate to detect many people who will subsequently fracture. Conversely, some individuals with osteoporosis based upon BMD alone are at low fracture risk; clearly, moving beyond a BMD T-score based approach to guide fracture risk therapeutic initiation is appropriate. However, continued focus on a diagnosis of “osteoporosis”, or even on approaches for osteoporosis therapeutic intervention thresholds based upon estimated fracture risk, diverts attention from the other concomitant problems contributing to fragility fracture risk.

The pathophysiology underpinning fragility fracture is often multifactorial and includes low bone mass and micro-architectural deterioration of bone leading to bone fragility [11] (i.e., in our opinion the CORRECT diagnosis of osteoporosis). It is osteoporosis, in concert with age-related loss of muscle mass and quality (i.e., sarcopenia), often

combined with other age-related morbidities that negatively impact ambulation such as neuropathy, reduced balance, impaired vision, polypharmacy, osteoarthritis and others leading to increased falls risk that ultimately causes the vast majority of “osteoporosis-related” fractures. That these age-related fragility fractures result from much more than simply compromised bone mass is exemplified by the fact that approximately one in six fragility fractures occur in those with normal proximal femur BMD [10]. Moreover, the multitude of rigorous prospective studies of effective bone-directed pharmacologic agents reproducibly demonstrate only an approximate 50–80 % reduction in vertebral fractures and an approximate 35 % reduction in non-vertebral fractures [12–16]. In summary, despite the best available therapies directed solely at improving bone, large number of fragility fractures continue to occur as other contributing factors lead to falls generating a force on the skeleton which can exceed the load-bearing capacity of even bone with normal mass.

It is apparent that factors independent of bone loss contribute to the age-related increase in fracture risk as fragility fractures increase dramatically with advancing age, but bone mass does not have a comparable decline [17]. A major contributor to this increase in fracture risk is falls. Falls become common with advancing age and approximately 95 % of hip fractures result from a fall [18]. Indeed, fall risk factors such as prior falls and slow gait speed predict hip fracture independent of BMD [19, 20]. Thus, it is unsurprising that poor physical performance is associated with increased hip fracture risk [21]. Such observations point to the importance of including sarcopenia as an integral consideration in efforts to reduce fragility fracture risk.

Sarcopenia has been defined as: “*The age-associated loss of skeletal muscle mass and function... a complex syndrome associated with muscle mass loss alone or in conjunction with increased fat mass*” [22]. This decline in muscle mass/function becomes common with advancing age [23] and is associated with impaired walking, falls and fractures. The pathogenesis of sarcopenia is complex but includes hormonal declines, increased inflammation, inadequate nutrition, sedentariness and toxin exposure [24]; factors well known to also cause osteoporosis. Indeed, it has been proposed that sarcopenia and osteoporosis are manifestations of the same processes in muscle and bone respectively [25]. Currently, sarcopenia is rarely diagnosed clinically, in large part reflecting the absence of a universally accepted diagnostic definition. To fill this void, a number of recent consensus conferences have proposed definitions, all of which include measurement of muscle mass and muscle function [22, 26, 27]. The recent definition proposed by the Foundation of the NIH Sarcopenia Project importantly integrates consideration of sarcopenic obesity (in essence, too much fat for the amount of muscle present) [28] by suggesting a unique approach to define low muscle mass as appendicular (leg + arm) lean mass divided by BMI [27]. Essentially, this is muscle mass/height corrected weight.

Considering sarcopenic obesity as a risk factor for fragility fracture may seem counter-intuitive for some, as obesity has historically been thought of as being protective against fragility fractures by increasing mechanical load [29, 30].

However, that the relationship between fat and bone is much more complex than simple weight bearing is increasingly being recognized [31, 32]. To oversimplify, it is plausible that obesity leads to diversion of mesenchymal stem cells from osteoblasts to adipocytes thereby impairing bone formation. Moreover, infiltration of fat into muscle, or intramuscular adipose tissue (IMAT), leads to muscle dysfunction [33]. It is therefore not surprising that recent studies find obesity to increase fracture risk [34]. Clearly, consideration of obesity in fragility fracture risk estimation is appropriate.

We believe that direct support for the importance of non-bone related factors in fracture risk is apparent given the inclusion of demographic, lifestyle and medical history factors included in fracture risk calculators such as FRAX and Garvan [35, 36]. Additionally, evidence that these calculators are not currently comprehensive and continue to evolve was recently provided by the implementation of a trabecular bone score (TBS) adjustment to the FRAX calculator. TBS is a bone assessment tool that is a surrogate for bone microarchitecture, independent of BMD [37], its effect on fracture risk calculation demonstrated that non-bone factors must be part of the cause for increased fracture risk with age. Specifically, in a study conducted by McCloskey et al. [38] lower TBS values exert a less profound effect on fracture risk in older individuals (fig. 1) indicating that bone fragility contributes less to fracture risk in more elderly people. A likely explanation for this observation is that falls and other age-related morbidities play a greater role while bone fragility plays a lesser role with advancing age.

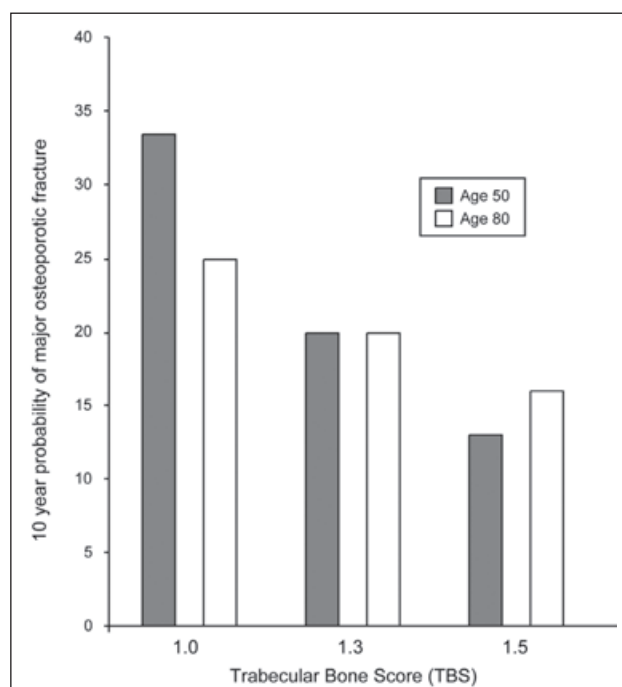


Figure 1. Effect of Age on the Trabecular Bone Score Adjustment of FRAX

Note: this figure depicts the effect of low or high TBS on FRAX-estimated 10 year risk of major osteoporosis-related fracture in two individuals (age 50 and 80 years) whose non-adjusted risk is 21 %. It is apparent that bone microarchitectural status, as estimated by TBS, has a much less pronounced effect on fracture risk at older age indicating that non-bone factors, likely falls, play a greater role in fractures in older adults.

Therefore, we believe that efforts to redefine osteoporosis as elevated fracture risk are off target. Instead, those interested in reducing fractures should focus on the multitude of diseases/conditions that lead to the ultimate adverse outcome of fragility fracture. Nonetheless, the “what’s in a name” publication [9] provide incentive and direction to bring forward our suggestion that fragility fractures be considered part of a larger syndrome, that we suggested be named “dysmobility syndrome” and encompasses osteoporosis, sarcopenia, obesity and other fracture risk factors as an approach to improve identification and ultimately treatment of older adults to reduce their risk for falls and fractures [39]. The term “dysmobility”, i.e., impairment of or difficulty with walking, was selected, but it is acknowledged that other terminology for this concept could well be equally, or even more, descriptive of this concept. This approach is analogous to the widely recognized metabolic syndrome in which various conditions (e.g., hypertension, hyperlipidemia, etc.) are recognized contributors to the adverse outcome of cardiovascular disease (fig. 2 a, b).

To summarize, the dysmobility syndrome concept moves the field, and also, importantly, older adults at risk for fragility fracture, beyond a singular focus on bone. It seems reasonable that patients would accept such an approach to reduce their fracture risk similar to the approaches currently routinely taken to reduce risk following myocardial infarction. However, a critical factor will be education to inform the lay public that fragility fractures are often indicative of multi-system treatable problems, not simply “I fell”. Moreover, in our opinion, educational efforts are sorely needed that emphasize the adverse consequences related to fracture, specifically mortality, and likely of equal, or greater, importance, loss of independence that occurs following fragility fracture. The latter not only being devastating to a community dwelling individual, but also has huge societal impact due to the cost of long-term care.

In addition to recognizing this concept, approaches to the clinical identification of individuals with dysmobility syndrome will be required. As an initial approach to this, our group proposed [39] a simple score based system in which slow gait speed (< 1 m/sec), a BMD T-score ≤ -2.5 , low appendicular lean mass as measured by DXA (4.45 and

7.26 kg/m² for women and men respectively), history of falls within the last year, low grip strength (< 20 kg; female and < 30 kg; male) and high total body fat mass were considered with each risk factor receiving one point with dysmobility arbitrarily being diagnosed if the composite score was \geq three.

It is certainly appropriate that fragility fracture risk factors other than these originally proposed be considered in the dysmobility syndrome concept. Two logical candidates include diabetes mellitus, and osteoarthritis. Diabetes is recognized to have adverse consequences upon bone and muscle [40, 41] and to increase fracture risk above that predicted by FRAX [42]. Similarly, some studies find osteoarthritis to be associated with increased risk for falls and fractures [43, 44]. Additionally, it is reasonable to consider use of narcotics for pain management or psychotropic medications as contributors to falls risk [45, 46]. Moreover, it is likely that factors considered for inclusion in dysmobility may not carry equal weight. Clearly, implementation of the dysmobility syndrome is a work in progress.

Nonetheless, we find the dysmobility syndrome concept to be a logical continuing evolution of the “osteoporosis” field. Notably, the field has moved beyond simple treatment based upon low BMD T-score to use of various calculators, e.g., FRAX, that were developed to improve detection of those at risk for fragility fracture. Such calculators clearly advance clinical decision-making, however, all are imperfect in that some individuals estimated to be at low risk sustain fractures [47]. Thus, improved approaches to identify at-risk individuals are needed; dysmobility syndrome seems a logical next step.

Is Dysmobility Syndrome Related to Adverse Health Outcomes?

The dysmobility syndrome concept is in its infancy. Nonetheless, an accumulating body of evidence finds dysmobility to be associated with adverse health outcomes. For example, in our initial editorial proposing the concept [39], we found dysmobility syndrome in 97 older adults, mean age 81 years, to be associated with a higher falls prevalence than proposed consensus sarcopenia definitions. Similarly, Edwards et al. in 398 older adults in the Herfordshire

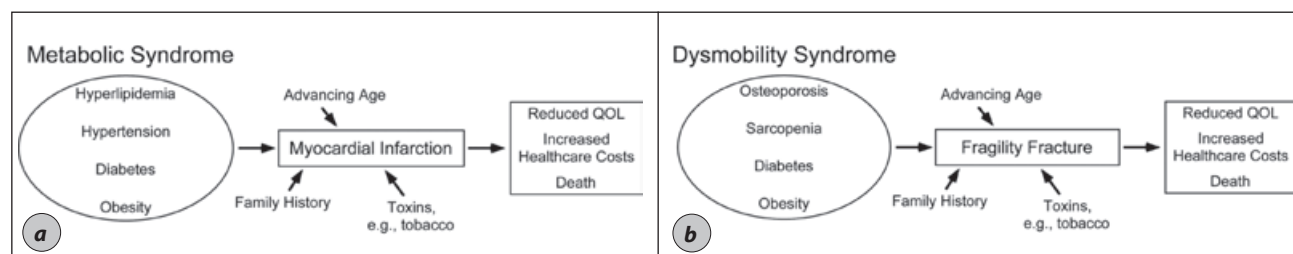


Figure 2. Analogous Situation of Metabolic Syndrome and Dysmobility Syndrome

Note: metabolic syndrome (2a) is familiar to clinicians being a group of conditions, predisposing such individuals to the development of cardiovascular disease. Each component of metabolic syndrome is appropriately viewed as a therapeutic target with optimization of each component contributing to reduced risk. Similarly, dysmobility syndrome (2b) consists of conditions predisposing to fragility fracture. Each component of dysmobility syndrome (others should also be considered e.g., osteoarthritis) would ideally be optimized to reduce fracture risk. This approach directly acknowledges that other conditions contribute to what is currently recognized as “osteoporosis-related” fracture. This paradigm directly acknowledges that the “failure” to prevent all fractures is not singularly linked to bone mass, but also the omission from consideration of these other conditions contributing to elevated fracture risk. A comprehensive approach that appropriately intervenes with each of these components is required to optimally reduce fracture risk.

cohort found dysmobility to be associated prospectively with falls, but interestingly not with fractures [48]. Data from the MrOS study (reported only in abstract form) followed 5,826 older men for a mean of 6.2 years and found those with dysmobility to be more likely than those without to sustain major osteoporosis related fractures and hip fractures with hazard ratios of ~ 3 and ~ 2 respectively [49]. In this report, the diagnosis of dysmobility was an independent risk factor for fracture even after adjustment for FRAX score. Finally, Looker evaluated 2,975 NHANES participants age 50+ and found dysmobility to be associated with increased mortality risk, with highest hazard ratios (~ 3) for those with dysmobility who were 50–69 years of age [50]. In summary, existing, albeit preliminary, data find dysmobility syndrome to be associated with falls, fractures and mortality. Further optimization of the dysmobility syndrome approach is needed to evaluate whether some of the factors should receive greater weight and if additional factors should be included to enhance the capability to predict adverse health outcomes.

Can Dysmobility Syndrome be Implemented Clinically?

It seems theoretically possible that parameters of the dysmobility syndrome could be included into risk calculators, perhaps even integrated into FRAX. A hypothetical example of this concept is depicted in fig. 3. Large datasets and extensive analyses will be required before such calculators would be ready for clinical application.

In the interim, we believe that clinicians can implement the concept into clinical care while further evaluation is performed to optimize the diagnostic approach to dysmobility. To this end, it is logical that the dysmobility

Figure 3. A Potential Approach to Clinical Implementation of Dysmobility Syndrome Components

Note: clinicians worldwide are familiar with the WHO FRAX calculator used to estimate 10-year fracture probability. It seems plausible that the FRAX tool could be directly altered to include components of the dysmobility syndrome as depicted here. Moreover, it further seems possible that FRAX, or a similar tool, could be developed to estimate short-term risk of falls and/or injurious falls as depicted here. It is apparent that development of such a tool would require multiple large datasets with prospective follow-up and as such any such tool will require a substantial amount of effort and time. Nonetheless, that the TBS-adjustment to FRAX has become a reality, the concept of adjusting FRAX via dysmobility syndrome, or its independent constituents, seems to be a viable option.

syndrome treatment paradigm follows, and expands upon, the approach used for “osteoporosis” today, i.e., recommendations for muscle strengthening exercise, optimization of nutrition (energy, calcium, vitamin D and protein), and bone active medications, i.e., our current “osteoporosis” medications. Moreover, it seems likely that a consensus definition for sarcopenia will be reached in the not too distant future, thus allowing clinicians to diagnose (and therefore treat) sarcopenia with non-pharmacologic measures. Additionally, it seems likely in the future that in addition to bone active medications, medications to increase muscle mass and function will be come available. Ideally, such new medications would improve both bone and muscle mass, and therefore physical function. Promising potential medications, including antibodies to myostatin [51] are in the research pipeline.

In conclusion, we find the dysmobility syndrome approach, (i.e., focusing on adverse health outcomes from falls and fractures, and not considering osteoporosis not as the single disease in need of diagnosis and treatment, but rather as simply a component of a risk profile) to be a logical extension of the “osteoporosis” treatment/fragility fracture prevention field. Moreover, it is the concept, not the name that is important; whether this is termed dysmobility syndrome or identified using other nomenclature is irrelevant. Such a paradigm change seems likely to further remove the focus on a BMD T-score diagnosis, explain why many people sustain “osteoporosis-related” fractures with normal BMD, emphasize the inter-related nature of osteoporosis with sarcopenia and highlight the importance on considering the entire person, not simply one organ system, i.e., bone. In essence, this approach reminds us of the wise advice of William Osler who stated “*The good physician treats the disease; the great physician treats the patient who has the disease*” [52].

Conflicts of interests. Authors declare the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

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Received 24.02.2017 ■

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Синдром дисмобильности: изменение парадигмы в области профилактики переломов

Резюме. Остеопоротические переломы обуславливают серьезные затраты на здравоохранение, снижают независимость/качество жизни пациента и повышают риск смерти. Несмотря на различные виды терапии по снижению риска будущих переломов, мало кто проходит лечение даже после перелома бедра. Очевидно, что подходы прошлого, направленные на снижение риска остеопоротических переломов, в первую очередь путем диагностики остеопороза и назначения препаратов, оказывающих влияние на костную ткань, не были успешными. Требуется другой подход; такое смещение фокуса и обсуждается в данной статье. Говоря коротко, в соответствии с концепцией синдрома дисмобильности остеопоротический перелом рассматривают как клинический исход послед-

ствия и полагают, что остеопороз является лишь частью синдрома, приводящего к перелому, «связанному с остеопорозом». Другими компонентами этого синдрома являются саркопения, ожирение, диабет, остеоартрит и теоретически множество других факторов, увеличивающих риск падений с сопутствующим повышенным риском перелома. Таким образом, концепция синдрома дисмобильности сдвигает область исследования, а также, что важно, изучение данных у пожилых людей, у которых возможны остеопоротические переломы, за пределы единственного фокуса на кость для более закономерного сосредоточения на целостном подходе к снижению риска переломов.

Ключевые слова: перелом; остеопороз; саркопения; синдром дисмобильности; падения

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Синдром дисмобильности: зміна парадигми в царині профілактики переломів

Резюме. Остеопоротичні переломи зумовлюють серйозні витрати на охорону здоров'я, знижують незалежність/якість життя пацієнта і підвищують ризик смерті. Незважаючи на різні види терапії щодо зниження ризику майбутніх переломів, мало хто проходить лікування навіть після перелому стегна. Очевидно, що підходи минулого, спрямовані на зниження ризику остеопоротичних переломів, насамперед шляхом діагностики остеопорозу і призначення препаратів, що впливають на кісткову тканину, не були успішними. Потрібен інший підхід; таке зміщення фокуса й обговорюється в даній статті. Кажучи коротко, відповідно до концепції синдрому дисмобильності остеопоротичний перелом розглядають як клінічний результат наслідку і вважають,

що остеопороз є лише частиною синдрому, який призводить до перелому, «пов'язаного з остеопорозом». Іншими компонентами цього синдрому є саркопенія, ожиріння, діабет, остеоартрит і теоретично безліч інших факторів, що збільшують ризик падіння із супутнім підвищеним ризиком перелому. Таким чином, концепція синдрому дисмобильності зрушує галузь дослідження, а також, що важливо, вивчення даних у літніх людей, у яких можливі остеопоротичні переломи, за межі єдиного фокуса на кістку для більш закономірного зосередження на цілісному підході до зниження ризику переломів.

Ключові слова: перелом; остеопороз; саркопенія; синдром дисмобильності; падіння