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Review article

Absorptiometry and "osteoporosis": problems

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Abstract "connecting the dots" between diverse clinical and other matters and an updated bone physiology reveals relationships that could modify some ideas about the roles and uses of absorptiometry in "osteoporosis" work. Herein, absorptiometry means that part of "clinical densitometry" that depends on X-ray absorption by bone and other tissues, thus excluding ultrasound methods and magnetic resonance imaging. The modifications concern, in part, some limitations of bone mineral "density" data, the kinds of physiological information that absorptiometry can and cannot provide, the relative importance of bone "mass" and whole-bone strength, how to define and study bone health and "osteoporosis," and two kinds of "osteoporotic fractures." As those modifications concern important national health care issues, they deserve answers based on hard evidence. Identifying those modifications might help others to evaluate them.

Key words physiology · bone health · biomechanics · fractures · bone strength · densitometry

Introduction

In this world's aging populations, the prevalence of "osteoporosis" exceeds that of osteoarthritis or of hard and soft tissue healing problems. Absorptiomtry has become an important tool in the diagnosis, management, and research of "osteoporosis." This article will share with readers the idea that combining an updated understanding of bone physiology with other evidence and ideas could suggest some different ideas about the roles of absorptiometry in "osteoporosis," as well as different ideas about the nature of "osteoporosis" itself. The second part of this article summarizes pertinent features of that updated bone physiology. The third part "connects some dots" between that physiology and other factors to reveal some formerly obscure relationships. If someone might view such connecting the dots as an unworthy kind of serious scientific work, please note that more than 80 years ago connecting the dots between varied kinds of physics data provided by other people let an inquisitive Swiss postal clerk realize that $E = mc^2$.

The meaning of the terms disorders and diseases in this article requires a comment. Herein, "disorders" signifies all departures from normal averages, and "diseases" signifies the subgroups of all disorders in which an organ's health has become impaired. Thus, one brown and one blue eye in the same person represents a disorder that constitutes a healthy departure from normal averages, but for bony vertebrates the inability to form bone constitutes a disorder and a lethal disease. One could encode that idea thus:

All disorders
↙ ↘
Healthy departures from norms *Diseases*

Pertinent features of an updated bone physiology

Accumulating evidence from many lines of inquiry, plus increasing inadequacies of early ideas and terminology, necessitated updating some early views about bone physiology. That led to the Utah paradigm [1–4], which injects belatedly recognized tissue-level realities about bone and its disorders into the former gap between organ-level realities and cell-level and molecular biologic realities. Eleven general features of that updated bone physiology seem pertinent to this article's subject, as follows.

1. Skeletons have load-bearing bones (femurs, vertebrae, mandibles, etc.) that carry substantial physical loads, and other bones (cranial vault, nasal bones,

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ethmoids, turbinates, etc.) that presumably serve other purposes [3]. Only load-bearing bones develop problems in "osteoporosis."

2. Stress and pathological fractures excepted, voluntary mechanical loads on healthy mammalian postnatal load-bearing bones do not break them, whether the loads are very small, as on a mouse rib, or huge, as on an elephant femur. One could view such bones as healthy in that special sense (voluntary means intentional instead of caused by trauma, so it would imply muscle forces). Herein let Proposition 1 signify that bone health criterion [2]: (A) It would define a load-bearing bone's health as a function of the bone's presumed chief purpose in the body and (B) as a three-way relationship between the bone's strength, the size of the voluntary loads on it, and any nontraumatic (spontaneous) fractures caused by those loads, whether suddenly or in fatigue.
3. Whole-bone strength should rank above bone "mass" (the amount of bone tissue in a bone) in physiological importance. "Whole bone" distinguishes bones as organs from bone as a material or tissue.
4. An elegant stratagem would make the loads on a mammal's postnatal load-bearing bone determine its strength, and bone's tissue-level "mechanostat" apparently does just that [1]. Parfitt called this mechanostat "... the most important unsolved problem in bone biology. ..." [5].
5. That mechanostat combines the following aspects, among others [6–9]. Multicellular tissue-level mechanisms called modeling by drifts [6] (not osteoblasts alone) have the function of increasing but not decreasing a bone's strength. The "disuse mode" of different multicellular tissue-level mechanisms called remodeling BMUs (basic multicellular units [6], not osteoclasts alone) has the function of decreasing a bone's strength [3].
6. Mechanical loads on bones generate strain-dependent signals [7].
7. Special ranges of those signals (the modeling and remodeling threshold ranges, the MESm and MESr, respectively) comprise further parts of bone's mechanostat [1].
8. Aided by dedicated signaling mechanisms [7], those thresholds help to turn the foregoing modeling and remodeling functions on and off, somewhat like the thermostats that control the heating and cooling systems in a house.
9. Repeated loads on load-bearing bones can cause microscopic fatigue damage or microdamage (MDx) in the bones [10]. Remodeling BMUs can repair limited amounts of this damage (which defines another function of such BMUs), but larger amounts can escape repair, accumulate, and lead to nontraumatic fractures, stress fractures in athletes, and pseudofractures in osteomalacia. This MDx has its own operational strain threshold (the MESp) [9].
10. Feedback and dedicated signaling systems let the mechanostat's parts "communicate" with each other, and some humoral agents can modulate its workings, partly by affecting that feedback [8]. Presumably, bone's mechanostat has the chief purpose of making load-bearing bones strong enough to satisfy Proposition 1.
11. The modeling and remodeling thresholds apparently make a load-bearing bone adapt to the largest daily loads on it and be minimally affected by smaller loads. Injuries excepted, after birth lever arm and gravitational effects make voluntary muscle forces instead of body weight put the largest such loads on bones [11]. As a result, the total load on a soccer player's femur during a game on earth can briefly but often exceed five times body weight. Thus, muscle strength and daily physical activities can strongly if indirectly influence the strength of mammalian load-bearing bones after birth, so strong muscles would usually associate with strong bones and weak muscles would usually associate with weak bones.

Lanyon and Smith initiated the studies of in vivo bone strains that helped to reveal the foregoing points [12].

"Connecting some dots"

Connecting some dots between that updated bone physiology and other factors can lead to questions about some present uses of absorptiometry in "osteoporosis" work. (Please note that this article does not discuss "risk-of-fracture" analyses.)

Evaluating whole-bone strength by absorptiometry

If whole-bone strength ranks above bone "mass" in physiologic importance, that strength would need noninvasive evaluation in patients. That strength depends strongly on the amount and kind of bone tissue in a bone (the bone "mass" factor) and on the bone's longitudinal and cross-sectional size and shape and the distribution of bone tissue in it (the geometry or architectural factor) [13,14].

X-ray absorptiometry can help to evaluate bone noninvasively by measuring how much of one or more X-ray beams is absorbed by a bone's mineral deposits [14,15]. Dual-energy X-ray absorptiometry (DEXA) can evaluate the bone "mass" factor in terms of bone mineral content (BMC) and bone mineral "density"

(BMD) values. Unfortunately, currently popular BMD values provide very unreliable indicators of whole-bone strength [14,16,17]. For example, healthy mouse and horse femurs by the Proposition 1 criterion would have similar volumetric BMD values (speed of sound values, too), yet their strengths differ more than 1000 times. The same is true for human ribs and femurs.

However, groups headed by Ferretti in Buenos Aires, Schiessl in Pforzheim, and Felsenberg in Berlin found that peripheral quantitative computed tomography (pQCT, a kind of CAT scan of extremities) can evaluate both the "mass" and architectural factors in whole-bone strength, from which suitable software can calculate bone strength indices (BSIs) that indicate whole-bone strength quite well [14,16,18–21]. As an indication of the architectural factor's importance in whole-bone strength, doubling a hollow bone's diameter while keeping the same amount and kind of bone in its cross section (so its cortex becomes thinner) would increase its bending strength about eight times. The BSIs of the bone would indicate that increase, but the BMD values would decrease and the BMC values would not change [14].

Absorptiometry and two kinds of "osteoporotic fractures"

Stress fractures in athletes and special forces trainees and pathological fractures due to bone tumors and cysts excepted, traumatic and nontraumatic osteoporotic fractures have very different causes. However, absorptiometry cannot distinguish them from each other.

Injuries, typically falls, cause the traumatic fractures, which usually affect the ends of extremity bones instead of their diaphyses [13,22]; hence, hip and wrist fractures, and less common traumatic fractures of the humeral surgical neck, ankle, femoral supracondylar legion, pelvic rami, and vertebral bodies.

Although any osteopenia (less bone and/or less whole-bone strength than normal, or less than previously in the same person) certainly facilitates traumatic fractures, it does not cause them. Age-related impairments of vision, balance, muscle strength (and power?), and neuromuscular coordination help to increase falls and the related traumatic fractures in aging humans [23–25].

In some people, however, ordinary daily voluntary activities instead of injuries cause nontraumatic fractures [2,22] that can affect both extremity and spinal bones in uncommon diseases such as osteogenesis imperfecta and idiopathic juvenile osteoporosis [26,27]. In other and more common diseases, such "fractures" (see following paragraph) mainly affect the thoracic and lumbar vertebral bodies but not the cervical spine, and they rarely affect extremity bones [22].

Many authorities currently classify as "fractures" some slow and usually asymptomatic changes in vertebral body morphology that occur in some osteoporoses (see following) [22]. In my experience, unlike traumatic fractures most such changes seem to occur slowly and without pain while (or when?) they occur, and without any known trauma. Of course, the postural changes they can cause, such as the "dowager's hump" and increased lumbar lordosis, can cause postural back pain later on. When nontraumatic fractures affect extremity bones such as a femur or tibia, clinical features make them apparent promptly. Lateral spine X-ray can reveal these, usually, asymptomatic nontraumatic vertebral body fractures.

Absorptiometry and diagnosing "osteoporosis" and "osteopenia"

The World Health Organization (WHO) advised diagnostic criteria for "osteoporosis" and "osteopenia" that depend on bone "mass" deficits [28]. Deficits 2.5 or more SD below applicable norms would diagnose "osteoporosis" whereas lesser deficits would diagnose an "osteopenia" (in this article, those terms when in quotation marks have the WHO meaning, but without quotes they have the meanings given below). The WHO criteria could foster the notions that bone health equates with bone "mass," and that "osteoporosis" and "osteopenia" represent different severities of the same thing, similar to mild and severe pernicious anemias. The updated bone physiology plus clinical evidence suggested different diagnostic criteria that propose three groups of osteopenias [2]. Clinical evidence shows that those groups do exist [22]. In the following, Proposition 1 constitutes the criterion of a healthy postnatal load-bearing bone. The proposed groups follow.

Group 1. In *physiological osteopenias*, healthy mechanostats cause osteopenias in which voluntary activities do not cause nontraumatic fractures, so by Proposition 1 such osteopenias would constitute healthy departures from normal averages instead of diseases. Chronic muscle weakness can cause these osteopenias [11], and Table 1 lists putative examples. Other such osteopenias follow loss of estrogen or its effects in postpubertal women and in Turner's syndrome, and androgen loss in postpubertal men [22]. If aging itself has similar effects seems unclear, at least to me, because past studies thought to support that idea did not account for the accompanying muscle strength and sex hormone changes. A temporary and regional such osteopenia usually accompanies a severe injury such as a fracture, crush injury, or burn. These naturally reversible osteopenias have been called transient osteopenias [2]. Only injuries, typically falls, cause fractures in these

Table 1. Debilitating conditions that can accompany chronic muscle weakness in humans (and accompany related osteopenias)[a]

Asthma
Renal failure
Malnutrition
Metastatic cancer
Muscular dystrophy
organic brain syndrome
Lou Gehrig disease
Cystic fibrosis
Drug addiction
Stroke
Emphysema
Hepatic failure
Anemia
Depression
Multiple sclerosis
Huntington's chorea
Paralyses
Still's disease
Nursing home residence
Aging
Pulmonary fibrosis
Cardiac failure
Polyarthritis
Stroke
Alzheimer's disease
Myelomeningocele
Leukemia
Alcoholism
Turner's syndrome
Wheelchair bound

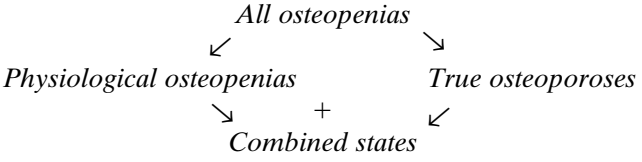
[a] Modified from [2]. In causing an osteopenia the relative importance of the mechanical disuse and muscle weakness, and of the biochemical-endocrinological abnormalities accompanying some of these entries, remains uncertain. Few past studies have tried to account for the muscle and mechanical usage effects

osteopenias, usually of extremity bones such as the hip and wrist. Without injuries, these people do not develop fractures. To repeat, impairments of coordination, balance, vision, and muscle strength (and power?) help to increase falls and traumatic fractures in aging adults [23–25].

Group 2. In *true osteoporoses*, still enigmatic malfunctions, presumably of the mechanostat, cause osteopenias in which voluntary activities do cause nontraumatic fractures, so affected bones do not satisfy Proposition 1. By the definitions in this article's second paragraph, these disorders would also be diseases. In uncommon examples of these diseases (osteogenesis imperfecta, idiopathic juvenile osteoporosis [26]), the nontraumatic fractures can affect both the spine and extremity bones. In a much commoner example that affects some pre- and postmenopausal women and some aging men [22], nontraumatic "fractures" affect thoracic and lumbar vertebral bodies but, curiously, not the cervical spine or wrist, and rarely the pelvis, hip, or other bones (see earlier). Presumably, accumulated MDx in affected bones helps to cause nontraumatic fractures in most or all of these osteoporoses [10].

Group 3. Features of the foregoing osteopenias and osteoporoses could and apparently do combine variably in some patients to form *combined states* (personal observations).

Nota bene: (A) Deficits in whole-bone strength and bone "mass" in each of these osteopenias and osteoporoses can range from quite mild to very severe, so absorptiometry alone cannot distinguish them from each other. (B) The proposed criteria would classify osteopenias and osteoporoses as follows:



Absorptiometry and evaluating whole-bone health

The updated bone physiology proposes that bones that satisfy Proposition 1 would be healthy regardless of their deficits in whole-bone strength or bone "mass." Although some authorities could question viewing a bone with a severe bone "mass" deficit as healthy, that would depend on how one defines bone health. To repeat, Proposition 1 would define a mammal's postnatal load-bearing bone's health in terms of its ability to carry voluntary loads without letting those loads break it, whether suddenly or in fatigue.

If one can accept that concept, nontraumatic fractures should reveal unhealthy mechanostats and bones (again, stress and pathological fractures excepted). Yet when typical voluntary physical activities no matter how feeble or strenuous do not cause nontraumatic fractures, one could consider whole-bone strength adequate for those mechanical demands, so in that special sense such bones could be healthy.

Clinical features could evaluate bone health in that sense, but no present absorptiometric method can do that.

Absorptiometry and the muscle-strength/whole-bone-strength relationship

Human muscle strength usually increases during growth, plateaus in young adults, and then slowly declines, so less than half the young adult muscle strength (and power?) can remain in octogenarians [11]. In principle, healthy mechanostats should make strong muscles associate with correspondingly strong bones,

and should make persistently weak muscles usually associate with corresponding osteopenias and weak bones. If so, some strong associations should occur, and five examples follow.

(1) When compared to their young adult bones, loss of muscle strength (and power?) in most aged people should usually lead to an osteopenia. (2) Aging adults who keep their young adult muscle strength better than other aging adults should usually keep their young adult bone strength better also. (3) In edentulous states, loss of tooth and mastication forces should usually cause osteopenias of the alveolar ridge, mandible, and pterygoid, zygomatic, and maxillary bones. (4) Increased muscle strength should usually make healthy mechanostats increase whole-bone strength, especially during growth. (5) Marathon running puts smaller loads on bones than weight lifting, so healthy mechanostats should make weight lifters have the stronger bones.

In fact, all those five associations just described do occur. In that regard, long ago D'Arcy Thompson wrote, ". . . between muscle and bone there can be no change in the one but it is correlated with changes in the other . . ." [29]. Later studies revealed the responsible biological mechanisms, which were unknown in 1917 and to Wolff (of Wolff's law) in 1892 [30].

Although one can measure muscle strength directly in cooperative humans, one can estimate it by DEXA as lean body mass [19] and by pQCT as the maximum cross-sectional area of one or more muscles [20,21], in both humans and laboratory animals. One can measure a bone's strength ex vivo in laboratory animals [16] and in cadaver material [21], and one can estimate it noninvasively in terms of BSIs obtained by pQCT [14,16].

Conclusion

Seventeen implications of the foregoing material have clear relevance to clinical work and research that involve absorptiometry (and "osteoporosis").

1. The poor evaluation of whole-bone strength by BMD data could weaken many arguments that depend on such data.
2. BSIs should see more use in future work and BMC and BMD values less use.
3. A good BSI should satisfy this BSI criterion: multiplying the BSIs of mouse and elephant femurs by the same constant (k) would correctly predict their hugely different fracture strengths (Fx). or, $BSI \times k = Fx$. The BSIs used by the cited authors approach that criterion [14,16,20,21], noting that a bone's metaphyseal and diaphyseal regions might require different BSIs.
4. Bone "mass" alone cannot reliably evaluate whole-bone strength, and the converse is also correct.
5. Absorptiometry cannot diagnose or distinguish nontraumatic and traumatic fractures from each other, but clinical features and X-ray findings can do so.
6. Many future osteoporosis studies, including risk-of-fracture analyses and searches for genetic factors in "osteoporosis," should account for the distinctions between traumatic and nontraumatic fractures as some past studies did, and also between physiological osteopenias and true osteoporoses.
7. The WHO criteria, BMC and BMD values, and BSIs cannot distinguish physiological osteopenias from true osteoporoses, but other kinds of information can do this, as noted earlier.
8. By facilitating falls, impairments of balance, neuromuscular coordination, muscle strength (and power?), and vision provide important extraosseous and direct causes of extremity bone "osteoporotic fractures." Although many physicians tend to attribute such fractures to an associated osteopenia, without falls or other injuries such fractures do not occur, regardless of the size of the whole-bone strength deficit. No current absorptiometric method can evaluate the tendency to fall.
9. Trauma can fracture any osteopenic or osteoporotic bone, so traumatic fractures per se cannot rule out or rule in diseased bones (or mechanostats).
10. The WHO absorptiometric criteria for diagnosing "osteopenias" and "osteoporoses" would need revision or supplementation.
11. Calling a woman's normal postmenopausal bone loss an "osteoporosis," and likewise the bone loss that follows ovariectomy or orchidectomy in otherwise healthy postpubertal mice, rats, and primates, may have outlived its usefulness.
12. Absorptiometrists and osteoporosis authorities need to agree on how to define bone health. The definition in this article acknowledges that many departures from normal averages can constitute healthy ones instead of diseases, something that experienced clinicians know very well.
13. No current absorptiometric or other densitometric method can evaluate bone health as Proposition 1 defines it.
14. Classifying as "fractures" the nontraumatic changes in vertebral body morphology (wedging, "codfishing," etc.) should be revised.
15. More studies of and norms for the human muscle-strength/whole-bone-strength relationship are needed. Both DEXA and pQCT have proven useful in such work and should remain useful [19–21,31].

16. Although one can measure muscle strength in cooperative humans, in both humans and laboratory animals pQCT can help to evaluate it in terms of muscle cross-sectional area [20], and DEXA can help to evaluate it as lean body mass [19].
17. No currently known biochemical "markers" of bone physiology can evaluate bone health as Proposition 1 would define it, nor can they distinguish between modeling and remodeling activities, or distinguish changes in compacta from those in spongiosa; however, pQCT can distinguish these.

Reasonable people can usually find more than one explanation for a given set of facts, so although the foregoing features stand on facts, reasonable people could question some of those features. Because such questions concern important national health care issues, in my view at least they deserve a hearing and resolution. Given informed choices of methods and informed interpretation of data, absorptiometry could help to answer many such questions, and I expect it will.

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