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Setting a Standard for a "Silent" Disease: Defining Osteoporosis in the 1980s and 1990s

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Abstract
Osteoporosis, a disease of bone loss associated with aging and estrogen loss, can be crippling but is "silent" or symptomless prior to bone fracture. Despite its disastrous health effects, high prevalence, and enormous associated healthcare costs, osteoporosis lacked a universally accepted definition until 1992. In the 1980s, the development of more accurate medical imaging technologies to measure bone density spurred the medical community's need and demand for a common definition. The medical community tried, and failed, to resolve these differing definitions several times at consensus conferences and through published articles. These experts finally accepted a standard definition at an international consensus conference convened by the World Health Organization in 1992. The construction of osteoporosis as a disease of quantifiable risk diagnosed by medical imaging machines reflects contemporary trends in medicine, including the quantification of disease, the risk factor model, medical disciplinary boundaries, and global standardization of medical knowledge.

Keywords: disease definition, standardization, risk factor, World Health Organization, medical imaging, osteoporosis

1. Introduction

Osteoporosis, a disease in which low bone density increases risk of fractures, affected at least 75 million people in the United States, Europe, and Japan in 2003, according to the World Health Organization (WHO).[1] In 2004 the American Surgeon General estimated that 'by 2020 one in two Americans over age 50 is expected to have or to be at risk of developing osteoporosis of the hip,' regardless of gender and race.[2] The high prevalence and major health impact of osteoporotic fractures resulted in annual healthcare costs of $12-18 billion in the United States in 2002, and £942 million in England and Wales in 1998.[3] Statistics like these appear in most scientific articles on osteoporosis because they powerfully portray a widespread, damaging, and expensive disease that requires clinical attention and medical research. But the measurable impact and very existence of osteoporosis depends crucially on how the medical community defines this 'silent' disease, which is symptomless before fracture.[4] As recently as the 1980s, there was no universal definition of osteoporosis. Instead, there were multiple conceptions of a disease of bone fractures, low bone density, or low bone density with fractures.[5]

This essay traces the construction of a universal definition of osteoporosis in the 1980s and 1990s, 'framed' in its historical context in accordance with Charles Rosenberg's view of the history of disease.[6] New diagnostic technology, raging debates about women's health and hormone replacement therapy, and a growing emphasis on the risk factor model of disease shaped the process of defining osteoporosis. This definition was thrust into the public awareness

[1] Anon. (1991); Anon. (1993); WHO (1994); WHO (2003)
[2] U.S. Department of Health and Human Services (2004), Chapter 4
[3] U.S. Department of Health and Human Services (2004), Chapter 4; WHO 2003, pp. 124
[4] Many sources, e.g. Azria (1989), pp. 7; WHO (1994), pp. 7
[5] Shapira and Shapira (1992)
[6] Rosenberg (1992)

under the influence of biomedical, pharmaceutical, political, and women's advocacy interest groups. However, we know little about how this research- and treatment-shaping definition developed. The only historical research specifically on osteoporosis exists in D. Shapira and C. Shapira's 1992 article on the history of the term 'osteoporosis', published in the medical journal *Osteoporosis International*, and two chapters in Elizabeth Siegel Watkins' 2007 book on the history of hormone replacement therapy.[7] Limited historical information is scattered through scientific articles and in research on related subjects such as treatments and individual scientists.[8] Despite its high prevalence and devastating health effects, the medical community did not agree on a universal definition of osteoporosis from its identification in the early 1940s until the mid-1990s. Disagreement and inconsistency reigned in research and practice until the WHO convened a conference of experts to settle the debates in 1992.[9] The medical community's quick acceptance and application of the osteoporosis definition determined by the WHO conference serves as a recent example of the perceived need for standardization in medicine and the process of debate and discussion by which it may be achieved. This conference thus offers a revealing case study of the WHO's role in defining standards for diseases and treatments, which has received little historical attention.

Osteoporosis has no or minimal initial symptoms, like other 'latent' diseases including anemia, hypertension, and end-stage renal disease.[10] These conditions are difficult to distinguish from the 'normal' until they advance enough to create measurable symptoms, by which point the disease may be irreversible. These diseases' modern definitions came to rely on quantitative laboratory tests, epidemiological statistics, and the emerging concept of risk factors for chronic

[7] Shapira and Shapira (1992); Watkins (2007)
[8] e.g., Forbes (1991); Milhaud (1992); Colman et al (2002)
[9] Kanis et al (1994), pp. 1139
[10] Wailoo (1997); Timmerman (2006a); Timmerman (2006b); Peitzman (1992)

diseases.[11] For osteoporosis, high prevalence and public awareness made diagnosis and prevention the research priorities, encouraging the development of quantitative bone density measurement technology in the 1970s and 1980s. These new measurements necessitated a numerical frame of reference for 'low' bone density, a widely variant physiological trait.[12] Interpretation of these measurements decides who has osteoporosis, thereby determining the scope of the disease and its required healthcare and funding. Thus the definition of a disease carries immeasurable power in the political, economic, social, and medical realms. Osteoporosis is a valuable case study of the standardization and quantification of latent diseases, illustrating the far-reaching implications of universal disease definitions and quantitative assessments of risk. The emerging risk factor model shaped late twentieth century disease concepts by introducing the idea of diagnosing a patient's risk for a certain disease prior to its clinical onset. Predicting a patient's likelihood of developing a disease in the future was advocated as the only way to prevent some diseases' irreversible effects. Therefore determining how to assess individuals' risks in a standardized, population-based method was crucial to the prevention of otherwise untreatable health problems such as heart attacks, stroke, and osteoporotic bones.

Bruno Latour, among others, has shown standardization of both definitions and measurements to be vital for making scientific information meaningful outside of its place of origin.[13] For example, physicists studying electricity in Victorian England created the ohm as a universal measurement to allow their work to spread internationally.[14] Communication of these scientists' work relied on 'the establishment of standard units for natural quantities', or

[11] Timmerman (2006a); Aronowitz (1998)
[12] Fogelman (1989), pp. 65
[13] Latour (1987); Schaffer (1998)
[14] Schaffer (1998), pp. 457

'metrology'.[15] A similar lack of standardization created confusion in diabetes research in the 1920s, when the exact quantity of insulin denoted by a 'unit' varied between countries.[16]

Despite the importance of metrology in medicine, little work has been done on quantitative disease standardization. Disease construction of 'sexual inversion' or homosexuality in the late nineteenth century exemplifies the definition of 'deviance' from the norm as pathological, though this norm refers to behavior, not to the average of measurements as in quantitative norms.[17] Hypertension resembles osteoporosis as a symptomless disease with a measurable indicator (blood pressure). Late twentieth century physicians selected a numerical value to demarcate normal and pathological measurements based on risk factor conceptions and blood pressure distributions in epidemiological studies.[18] In addition, Carsten Timmermann suggests that numerical definitions of hypertension were determined by available treatments.[19] Jeremy Greene similarly argues that the definitions of chronic diseases and their risk-lowering drugs co-construct each other, such as diabetes and Orinase, and cholesterol and Mevacor.[20] Treatments with these drugs required quantitative diagnostic thresholds, specifically blood sugar levels and cholesterol levels, to identify at-risk patients by comparing them to huge epidemiological datasets. Similarly, the need for prevention and the prediction of risk to determine treatment options drove numerical definitions of osteoporosis.

This essay examines debate among researchers in the late 1980s about how best to quantify osteoporosis, including selecting numerical boundaries that balanced individual and public health in terms of risk, treatment, and cost. The complexities and importance of consensus

[15] Schaffer (1998), pp. 457
[16] Sinding (2002), pp. 37
[17] Hansen (1992)
[18] Timmermann (2006a)
[19] Timmermann (2006b)
[20] Greene (2007)

in medicine are evident in the debates surrounding osteoporosis definitions. As Rosenberg notes, 'disease does not exist until we have agreed that it does'.[21] By considering the definition of osteoporosis in its 'frame' of medical imaging technology, professional debates, and internationally sanctioned standardization, this essay examines how the medical community developed and agreed upon a numerical disease definition.

2. Defining Latent Diseases and Risk Factors

Identifying processes that precede clinical symptoms as a 'disease' was a new and growing trend in late twentieth century medicine. People could be diagnosed with osteoporosis if they had never broken a bone, or diagnosed with hypertension without having had a stroke. Diagnosing a 'disease' in the absence of symptoms stems from interest in preventing irreversible symptoms, such as fractures and strokes, from occurring in the first place. Diagnostic technology has been adapted to fit these goals by the development of quantitative measures of disease distinct from qualitative clinical symptoms. An early example of a laboratory test for a symptomless disease is the 1917 identification of 'sicklemia', a disease in which blood cells become sickle-shaped under certain conditions but without clinical manifestations. The resulting qualitative 'haematological test for a latent disorder in a person who appeared to be healthy' was necessary to identify sicklemia because it was, according to Keith Wailoo, a 'latent', 'potential', or silent disease.[22] Quantitative tests for latent diseases were developed over the course of the twentieth century. For example, a patient cannot sense his or her blood pressure, but by 1920 a doctor could accurately measure it with a sphygmomanometer and stethoscope and then compare the measurement to other patients' to establish values for a 'norm' and for a 'disease',

[21] Rosenberg (1992), pp. xiii
[22] Wailoo (1997), pp. 142

hypertension. The perceived link between a measured physiological value and the future occurrence of symptoms forms the foundation of the risk factor model.

Robert Aronowitz dates the 'risk factor approach' to a 1961 report on a landmark epidemiological study of coronary heart disease aiming to define predictive lifestyle and physiological traits among residents of Framingham, Massachusetts.[23] From there, the risk factor approach expanded, especially in the context of quantifiable diagnostic signs like high cholesterol in the case of coronary heart disease. Calculations of risk began to enter all aspects of healthcare, from measuring disease prevalence to recommending treatment options: 'Risk factors are a central part of modern clinical, public health and financial strategies for predicting and managing individual variation in disease predisposition and experience'.[24] As a result, the risk factor model creates patients who 'are not quite healthy, but not quite ill either'.[25] The idea of normalizing or pathologizing individual variation echoes the problem in osteoporosis of whether low bone density implies high fracture risk or merely reflects one end of a spectrum of a physiological trait. Aronowitz explains the medical community's quick and broad acceptance of the risk factor model: 'Risk factors provided a reassuring explanatory framework because they gave some sense of who was at greatest risk and…risk factors embodied the cultural and medical ideals of precision, specificity, and quantification', making them an attractive option to rationalize chronic diseases with unclear causes.[26] Popularity and trust of the risk factor model became so widespread that it encouraged searches for more risk factors. The researchers leading the Framingham study remarked, 'anything that you could measure that became associated with

[23] Aronowitz (1998), pp. 118
[24] Aronowitz (1998), pp. 118
[25] Timmermann (1992), pp. 256
[26] Aronowitz (1998), pp. 125

a higher rate of heart attack or stroke later in life became known as a risk factor'.[27] However, statistics identify risk factors as correlated with disease onset, but cannot show risk factors to be causal.[28] This distinction is often overlooked because doctors and patients want a clear cause-and-effect explanation, but in reality diseases involve many physiological traits and behaviors as 'risk factors' that may encourage the development of a chronic disease.

Like many of the Framingham study's risk factors, the quantification of physiological traits also shaped the definition of osteoporosis. Twentieth century measurements of bone density were quantitative, a much preferred alternative to qualitative indications of bone strength, which were namely fractured or crushed bones. But these quantitative measurements required the naming of a frame of reference based on statistics from epidemiological studies. Similarly, in the 1950s two conflicting conceptions of hypertension defined it as a genetic disorder and as one extreme of a bell-curve distribution of blood pressure. Timmermann argues that the genetic conception reflected the old-fashioned focus on individualized medicine while the quantification of the disease was part of the new population-based biomedicine.[29] This new kind of medicine depended on the growing importance of statistics, technology, and the use of the risk factor model for chronic diseases.

A similar quantification of a physiological measurement occurred in Bright's disease, now known as end-stage renal disease (ESRD). In the 1940s, quantitative measurements of kidney physiological function replaced clinical assessment for ESRD diagnosis. Today ESRD diagnosis requires a blood level of creatinine (a waste product that healthy kidneys filter from the

[27] Quoted in Aronowitz (1998), pp. 144
[28] Aronowitz (1998), pp. 137
[29] Timmermann (1992), pp. 250

blood) that occurs when most patients feel only mild symptoms.[30] A slightly lower creatinine level indicates chronic renal failure, the high-risk but symptomless precursor to the disease, or the equivalent of osteopenia (low bone density, as compared to that of young healthy women) as a high-risk condition for osteoporosis.[31] Because they endure the side effects of dialysis treatment before symptoms of ESRD, Steven Peitzman argues that chronic 'renal patients become dialysis patients' as a result of creatinine measurement technology.[32] This idea of diagnosing a disease before its clinical onset and thus introducing treatment earlier in life is also the goal of predicting osteoporosis risk. Because non-hormonal methods to increase bone density (e.g. diet and exercise) work best in young women, early identification in the interest of early treatment means that young women would ideally experience treatment before clinical signs of disease. Charles Dent predicted this change in the 1970s by arguing that 'senile osteoporosis is a paediatric disease', meaning it has its origins in childhood bone formation.[33] This new conception of prevention as treatment would expand over the twentieth century, shaping the modern medical focus on preventative healthcare.

Defining medical disciplines and the boundaries between them was another trend of modern medicine that influenced not only the definition but also the research and treatment of osteoporosis. Interactions between different disciplines similarly defined anemia, another disease without clear clinical symptoms but with a definitive quantitative meaning that relies on diagnostic technology, specifically measurement of blood iron levels.[34] Keith Wailoo writes that late nineteenth and early twentieth century competition between medical specialists, such as

[30] Peitzman (1992), pp. 15
[31] Peitzman (1992), pp. 15
[32] Peitzman (1992), pp. 5
[33] Quoted in Mughal (2002), pp. 347
[34] Wailoo (1997), pp. 5

hematologists, general practitioners, and abdominal surgeons, made a universal conception of anemia impossible because each field wanted to control and 'own' the disease.[35] 'Anemia…was an amorphous disease category *given coherence* by the rising status of blood analysis technology in medicine, and *giving coherence* and legitimacy to medical roles'.[36] Diagnosis of osteoporosis similarly relied on improved measurement technology, and, like anemia, the wide diversity of specialists who studied and treated it hindered the defining process by promoting various definitions rather than a standard one. Thus researchers and physicians from different disciplines not only failed to establish a unified field of study focused on bone disorders, as anemia helped define the field of hematology, but they also failed to work together and share a common definition.

Another theme of late twentieth century medicine was patients' rising expectations of being active and healthy in old age. The development of total hip replacement surgery reflects patients' hopes for 'cures' for aging, as their expectations for the capabilities and lifespan of a prosthetic hip increased over time.[37] Likewise, hormone replacement therapy (HRT) for women was thought to reduce the risk of developing osteoporosis. These perceived 'magic bullets' for enabling a high quality of life for the elderly may reflect a changing perception of aging.

Thus set in the context of the emerging risk factor model, quantification of disease, conception of prevention as treatment, disciplinary incoherence, and new views of aging, the process of defining osteoporosis in the 1980s embodied the values and beliefs of its time as well as posed unique medical, technological, disciplinary, and social challenges. Timmermann points out that as a result of the 'normalisation' of hypertension by the creation of categories of risk,

[35] Wailoo (1997), pp. 7-8
[36] Wailoo (1997), pp. 10
[37] Anderson et al. (2007), pp. 134-136

similar to the categories of osteoporosis including osteopenia as an at-risk condition, 'the boundaries between healthy and ill, between normal and abnormal…became blurred'.[38] But how were these boundaries established in the case of bone density measurements and osteoporosis?

3. Diverse Definitions of Osteoporosis

Until the mid-1990s, osteoporosis had various meanings. 'Osteoporosis', from Greek for 'porous bone', was first used in France in the 1820s to describe post-mortem bones with abnormal hollow spaces.[39] It entered English terminology by 1885 but lacked a specific definition until endocrinologist Fuller Albright's groundbreaking work in Boston in the 1940s.[40] Prior to Albright's work, osteoporosis was difficult to distinguish from diseases with similar clinical manifestations of broken bones without a clear traumatic cause, such as osteomalacia, osteomyeletis, and osteogenesis imperfecta.[41] Albright and his colleagues first described the clinical aspects of 'postmenopausal osteoporosis' when they recognized a link between osteoporosis and natural or surgically induced estrogen loss. They further defined osteoporosis as an imbalance of bone formation and resorption (destruction), processes which normally occur continuously to repair microfractures from everyday stresses.[42]

Albright's definition guided the subsequent explosion of research on hormone treatment, risk factors, and diagnostic techniques in relation to osteoporosis. But researchers assigned

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[38] Timmermann (1992), pp. 255
[39] Shapira and Shapira (1992), pp. 165
[40] Albright et al (1940); Albright et al (1941); Albright and Reifenstein (1948); Nordin (1987), pp. 57; Forbes (1991)
[41] Osteomalacia is a softening of the bones caused by incomplete mineralization, known as rickets in children. Osteomyeletis is weakened bones caused by bacterial infection. Osteogenesis imperfecta is brittle and thus easily broken bones caused by a genetic inability to produce normal bone tissue.
[42] Albright et al (1941)

different meanings to 'osteoporosis', with varying emphases on clinical, physiological, and biochemical factors.[43] Medical dictionaries and reference books from 1972-1995 offer surprisingly inconsistent osteoporosis definitions. For example, *Medical Specialty Terminology* in 1971 defines osteoporosis as 'an example of atrophy of the bones in the aged'. Osteoporosis is thus just one of many conditions which may cause such atrophy, including 'hyperparathyroidism, hyperthyroidism, nutritional disturbances, and osteomalacia and rickets'.[44] The 1972 and 1979 editions of *Gould's Medical Dictionary* define osteoporosis as 'deossification with absolute decrease in bone tissue, resulting in…structural weakness'.[45] Both sources define osteoporosis as bone loss, but *Medical Specialty Terminology* restricts it to a certain population ('the aged') while *Gould's* links the bone loss specifically to a loss of bone strength. *Churchill's Illustrated Medical Dictionary* of 1989 defines osteoporosis as 'a reduction in the quantity and quality of bone by the loss of both bone mineral and protein content', giving a more specific definition of the associated bone loss.[46] A sub-entry in *Churchill's* for 'postmenopausal osteoporosis' defines it as 'seen in postmenopausal women. It…causes pain, the crushing of vertebral bodies, and pathologic fractures'. This definition focuses on the disease's affected population and clinical manifestations, not on physiological or causal factors. *Dorland's Illustrated Medical Dictionary* of 1994 and 2003 similarly links bone loss with bone fracture, by defining osteoporosis as 'reduction in the amount of bone mass, leading to fractures after minimal trauma'.[47] Only in 1995 does a medical text mention specific methods for diagnosing osteoporosis: 'Osteoporosis

[43] Shapira and Shapira (1992)
[44] Young and Berger (1971)
[45] Gould's Medical Dictionary (1972); Gould's Medical Dictionary (1979)
[46] Churchill's Illustrated Medical Dictionary (1989)
[47] Dorland's Illustrated Medical Dictionary (1994); Dorland's Illustrated Medical Dictionary (2003)

can be detected by quantitative digital radiography'.[48] These differences in definition could have varying and critical effects on delicate diagnostic decisions, especially because they gain a certain professional authority by being published specifically in medical texts.

These inconsistencies in definition may be an effect of researchers' diverse professional backgrounds and affiliations, including rheumatology, biochemistry, orthopedics, and even medical physics. Rheumatologist Anthony Woolf listed the many clinicians approached by patients about osteoporosis in 1992 as 'the family practitioner, the gynaecologist about hormone replacement therapy, the rheumatologist about back pain, the orthopaedic surgeon after a fracture, the geriatrician about loss of independence…would it be better if one specialist group took a major interest?'[49] But, unlike the interdisciplinary competition for disease 'ownership' concerning anemia, no group claimed osteoporosis and the diversity of involved disciplines continues today.[50] A feminist argument could be put forth to explain this lack of ownership claim. Osteoporosis primarily affects women, and women's healthcare has historically received less medical and research attention than men's. Osteoporosis may therefore not be considered a lucrative or desirable disease to specialize in or to claim for one's own field. However, this argument requires far more research and consideration than can be provided here.

Inconsistent definitions may also reflect the qualitative nature of osteoporosis diagnosis before the 1980s. Based on early physiological definitions, osteoporosis could be distinguished from other bone-weakening diseases by examination of a hipbone biopsy.[51] However, x-ray diagnosis of fractures had been an alternative to expensive and painful biopsies since the 1890s,

[48] Oxford Reference Concise Medical Dictionary (1995)
[49] Woolf (1992), pp. 130
[50] Wailoo (1997), pp. 47
[51] Freemont (1995), pp. 77; Riggs (1991), pp. 68; Wasserman and Barzel (1987), pp. 287

and x-ray assessment of bone density began in the 1930s.[52] Widely recognized x-ray indicators of osteoporotic vertebrae, as described by Albright in 1941, included 'fractured or crushed vertebrae…and herniation of the nucleus pulposus through the end plates of the vertebrae'.[53] Osteoporotic vertebrae become compressed, showing hairline fractures and crumbling edges on x-rays. Collapse of their centers or 'nucleus pulposus' makes vertebrae concave on both ends, leaving telltale oval-shaped spaces between them on x-rays.[54] Doctors also considered bones' radiolucency (how distinctly they appear on x-rays) as a measure of density.[55]

However, x-ray images were blurry and indistinct, making diagnosis of subtle crush fractures and shape irregularities difficult. Evidence of these clinical signs, particularly radiolucency, varied with machines, patient positioning, and clinicians' judgments.[56] Intervening soft tissue could alter radiolucency by 20% or more, and by the 1950s research showed that x-rays only revealed density changes after 30% or more bone tissue had been lost.[57] Despite these limitations, x-ray imaging was the primary tool for osteoporosis diagnosis until the 1980s, largely due to widespread professional agreement about clinical indicators. Medical practitioners and researchers accepted these signs as standard indicators of weakened bone structure, based on Albright's descriptions and on subsequent research linking these indicators with other signs of osteoporotic bone, such as bone biopsy results.

Diagnosis based on x-ray images meant osteoporosis was already too advanced for its effects to be reversed. Available treatments could prevent or stop bone loss but none could

[52] Goodwin (1987), pp. 293
[53] Albright et al (1941), pp. 2472
[54] Albright et al (1941), pp. 2472; Adams (1983)
[55] Adams (1983). This approach assumes that measurably more x-rays pass through less dense bone.
[56] Adams (1983), pp. 128; Jensen et al (1984); Ross et al (1993), pp. 167
[57] Forbes (1991), pp. 138; Kimmel and Recker (1994), pp. 51; Tovey (1995), pp. 91

restore bone. When the American Food and Drug Administration approved hormone replacement therapy for bone loss prevention in 1972, many doctors saw it as the ideal preventative method, which would wipe out postmenopausal osteoporosis as a health problem.[58] Pharmaceutical companies strongly promoted this view, despite HRT's high cost and ambiguous side effects such as decreased risk of heart disease and increased risk of endometrial cancer.[59] For effective use of HRT and other preventive therapies like calcium supplements, fluoride, calcitonin, and lifestyle changes, it was necessary to identify at-risk people *before* they broke bones.

4. Measuring Bone Density

In the search for indicators of future osteoporosis, bone density showed potential based on *in vitro* studies that linked it with bone strength.[60] Since it was generally agreed that osteoporosis involved a loss of bone, researchers considered the measurement of bone density a logical way to assess fracture risk, though it was difficult to test this idea because bone densities of people with and without fractures overlapped.[61] Like all new methods, bone densitometry had to prove its usefulness and accuracy relative to the previous methods of biopsies and x-rays. The assumed link between bone density and bone strength formed a major impetus for the development of bone densitometry technology, as a way to diagnose osteoporosis without clinical symptoms.

In 1963, John Cameron and James Sorenson, physicists at the University of Wisconsin, claimed that their single-photon absorptiometry (SPA) would 'eliminate errors resulting from the

[58] Watkins (2007), pp. 149
[59] Phillips and Rakusen (1978); Phillips and Rakusen (1989); Wasserman and Barzel (1987), pp. 289
[60] Albright et al (1941); Mazess (1987); Fogelman (1988); Johnston and Melton (1995)
[61] Mazess (1987); Fogelman (1989), pp. 66, Kanis (1990), pp. 210

variability of x-ray films…and reduce errors arising from the presence of [soft] tissue' by using a radioactive photon source.[62] SPA analyzed bone mineral content (mostly calcium) as a measure of bone strength. Dividing mineral content by area gives bone density (mass-to-area density, not typical mass-to-volume density), allowing comparison between different-sized patients, since larger bones have higher mineral content.[63] However, SPA's sensitivity to soft tissue interference (although less than that of x-rays) made it useful only for bones with little surrounding tissue and thus not the hips or spine, the most common sites of osteoporotic fractures. Studies showed that osteoporosis varied throughout the skeleton, so SPA's density measurement of a patient's hand or forearm could not predict the density of the patient's other bones.[64]

A very different technique, quantitative computed tomography (QCT), used CT scanning technology to measure bone mineral content and three-dimensional volume, allowing calculation of mass-to-volume bone density, which some researchers preferred to mass-to-area density.[65] QCT became available in 1976 but its expense, difficult operation, and high radiation doses made it less clinically useful than SPA.[66] Dual-photon absorptiometry (DPA), used for research in the late 1960s but clinically available only in the early 1980s, solved the problem of soft issue interference, thus enabling accurate measurement of the hips and spine.[67] But DPA was expensive and slightly less accurate than SPA.

When Richard Mazess and colleagues at University of Wisconsin's Department of Medical Physics developed DPA for commercial use in 1972, no manufacturer would produce it. In 1980 the scientists launched Lunar Corporation, which successfully built and sold their DPA

[62] Cameron and Sorenson (1963), pp. 230
[63] Adams (1995), pp. 111
[64] Kanis et al (1983), pp. 218; Anon. (1991), pp. 109
[65] Goodwin (1987), pp. 298; Adams (1995), pp. 117
[66] Kanis et al (1994), pp. 371; Adams (1995), pp. 117, 122
[67] Goodwin (1987), pp. 296; Adams (1995), pp. 113

machines.[68] Lunar's profitability in the 1980s coincided with a massive public awareness campaign about osteoporosis in the United States, largely funded by the HRT and dairy industries' promotion of their products as bone-building treatments.[69] The U.S. government also became involved, launching National Osteoporosis Awareness Week in 1985.[70] Awareness efforts were so widespread that by 1987 85% of Americans knew what osteoporosis was, as compared to 15% in 1982.[71] Growing public knowledge and worry about osteoporosis inspired more interest and demand for accurate diagnosis and risk prediction. This public demand encouraged Lunar's invention of dual-energy x-ray absorptiometry (DXA) in 1988. DXA yielded reliable measurements cheaply enough to become clinically available, and researchers and institutions including the WHO quickly celebrated it as the most accurate predictor of osteoporotic fracture risk.[72]

As quantitative bone density measurements replaced qualitative x-ray and biopsy examinations, definitions and diagnostic methods began to shape each other. Osteoporosis' definitions included porous bones, broken bones, and less dense bones, but the lack of a quantitative frame of reference for 'normal' or 'osteoporotic' bone density made the various qualitative definitions meaningless. According to the authors of the only article on the history of osteoporosis, Shapira and Shapira,

> most definitions of osteoporosis…refer to *low* or *unusually low* bone mineral density (BMD),…*increased* or *excessive* bone mass loss, etc. All of the terms emphasised above

[68] <http://www.fundinguniverse.com/company-histories/Lunar-Corporation-Company-History.html> Accessed 4/3/09.
[69] Watkins (2007), pp. 150
[70] Watkins (2007), pp. 169
[71] Watkins (2007), pp. 176
[72] Adams (1995), pp. 114; Riggs and Wahner (1988), pp. 294; Kanis et al (1994), pp. 371; <http://www.fundinguniverse.com/company-histories/Lunar-Corporation-Company-History.html> Accessed 4/3/09.

> have in common the semantic feature of implying a standard…[but] as long as the standard is not expressly specified, the definition remains invalid.[73]

Although researchers and clinicians had functioned for years without a specified standard, they would need one to give bone density measurements a universal meaning and thus be able to use this new method as a non-invasive predictor of fracture risk.

5. Definition Debate

Armed with relatively accurate bone density measurements by the late 1980s, researchers had high hopes for improved fracture risk prediction and thus for more effective prevention. Clinical uses of bone density already included individual assessments and measurement of bone density across populations. But these data showed a bell-curve distribution in both young and elderly populations, and overlapping bone densities for fracture and non-fracture populations.[74] How could clinicians best use bone density to identify people at risk of future fractures if there were no significant differences between people with and without fractures?

Debate on bone density standard setting and osteoporosis definitions erupted among experts from many disciplines and countries. The debate implicitly concerned use of the 'risk factor approach' that emerged in the 1960s, in which quantifiable traits are considered to correlate with future disease risk and thus these traits are treated to reduce risk of developing the disease.[75] Low bone density was considered a symptomless and quantitatively defined risk factor for a highly prevalent disease (osteoporosis) with major clinical implications (fractures). Setting a standard that normalizes or pathologizes a trait based on population statistics raises questions

[73] Shapira and Shapira (1992), pp. 166
[74] Kanis et al (1983), pp. 207; Fogelman (1989), pp. 66
[75] Aronowitz (1998), pp. 118; Timmermann (2006b), pp. 143

as to whether risk factors imply high disease risk or simply represent the extreme ends of statistical trait distribution. The debate regarding where to set osteoporosis standards reflects the complexity as well as the popularity of the use of the risk factor model in the late twentieth century.

The efforts to raise public awareness of osteoporosis in the 1980s created a demand for information about the disease. In response, endocrinologist Christopher Nordin called attention to the need for a universal definition by writing an editorial in *Calcified Tissue International*, a journal for bone disease researchers published by the European Calcified Tissue Society:

> It is surprising that osteoporosis research has made the progress it has when the central object of the work lacks a common definition. Such a definition is clearly overdue. Perhaps this Guest Editorial will help to fill this gap.[76]

Nordin's attempt 'to fill this gap' entailed setting the 'normal' average bone density to that of young adults, based on 'ample precedents in other fields of clinical physiology where normal range is usually derived from young healthy adults', such as blood pressure categories for hypertension.[77] Nordin defined osteoporosis as bone density two standard deviations below normal, an approach that labeled 50% of women over 65 and almost all women over 80 as osteoporotic. Nordin also differentiated normal ranges by gender and age, as factors that affect bone density.[78] Although his proposal did not immediately provide the 'overdue' universal definition, it did inspire several subsequent articles.

Mazess, inventor of DXA, responded immediately to Nordin's editorial in the next issue of *Calcified Tissue International.* He criticized Nordin's approach because two standard

[76] Nordin (1987), pp. 58
[77] Nordin (1987), pp. 57
[78] Nordin (1987), pp. 57-8

deviations below young average captured different risk populations depending on which bone is measured. According to Mazess, people with hip fractures (which technically occur at the femoral neck) have an average femoral density of 4.5 standard deviations below young average. Thus Nordin's definition of two standard deviations would include 'the upper 99th centile of hip-fracture cases for femoral density', meaning that all hip fracture patients have bone density more than two standard deviations below young average when measured at the femur.[79] However, if the same patients' bone density were measured at the wrist or spine, only 85-90% would qualify as osteoporotic. Mazess argued that this wide variation (14% of the fracture population, or the difference between 99% and 85%) revealed Nordin's standards as problematic: 'Such regional differences [in bone density according to bone site] prevent definition of osteoporosis as "a departure from normality"; different subsets of the fracture population would be included depending on the measurement site'.[80] Mazess suggested setting a standard derived from bone densities of people with fractures instead of young adults, a standard that he calls 'an arbitrary "breakpoint" of high fracture risk'.[81] His aim was to 'isolate a smaller subset of the population that has high risk of fracture', to direct expensive prevention therapies to fewer people.[82] Thus arbitrary quantitative disease definitions can be manipulated to reflect considerations of treatment and cost as well as patients' health. Mazess' participation in this debate may serve to promote bone density use, because he had monetary interest in creating demand for his DXA bone densitometers.

Quantitative researcher Clarita Odvina and colleagues at Loma Linda University's Department of Medicine in California supported Mazess' idea of an arbitrary breakpoint but they

[79] Mazess (1987), pp. 117
[80] Mazess (1987), pp. 117
[81] Mazess (1987), pp. 118
[82] Mazess (1987), pp. 118

rejected Mazess and Nordin's attention to age. They used statistical analysis to identify a fracture threshold at two standard deviations below the average bone density of women with fractures. This value did not vary with patients' age, suggesting that normal bone density range exists independently of age. The authors argued that the best way to predict fractures was to 'individualize fracture threshold values by adjusting for differences in variables other than TVBD [trabecular vertebral body density]', such as lifestyle, weight, and vertebrae size.[83]

Joseph Melton and Heinz Wahner, epidemiologist and orthopedic surgeon at Minnesota's Mayo Clinic, questioned the fracture threshold approach based on the 'continuous gradient of increasing fracture risk with decreasing bone mass'.[84] They opposed both a threshold based on fracture populations and one based on an average from young people because neither distinguishes '*present* and *future* fracture risk'.[85] They argued, 'The definition of clinical osteoporosis for treatment (nonviolent fracture and bone mass below a fracture threshold) must be different from the definition of osteopenia for prophylaxis (bone mass associated with a doubling or tripling of lifetime fracture risk, for example)'.[86]

However, Ignac Fogelman, radiologist at King's College London, supported Nordin's young average because bone density fails to reliably indicate risk as people age. Bone density falls in all elderly people and thus the difference between osteoporotic and non-osteoporotic bone densities shrinks. But Fogelman also considered fracture thresholds too simplified, and argued like Melton and Wahner that 'a spectrum of risk' is more accurate.[87] Fogelman suggested measuring each person's peak bone density and rate of bone loss to determine individualized

[83] Odvina et al (1988), pp. 221, 227
[84] Melton and Wahner (1989), pp. 263
[85] Melton and Wahner (1989), pp. 263
[86] Melton and Wahner (1989), pp. 264
[87] Fogelman (1989), pp. 66

risk.[88] However, Fogelman recognized this technique's impractical requirements of peak bone density measurement, which is impossible to measure for older patients, and very precise measurements of bone loss rate.

John Kanis, clinician and researcher in metabolism at the University of Sheffield, expanded the idea of risk spectrum by arguing that definitions of osteoporosis and osteopenia must consider risk factors besides bone density. Kanis agreed with Melton and Wahner that the risk factor, osteopenia (meaning low bone density), is distinct from the disease, osteoporosis (meaning fractures). He pointed out that any threshold or 'normal' average could be functional despite its arbitrariness, but all numerical standards assume that bone density is paramount in determining fracture risk, despite evidence of other contributing factors.[89]

6. Consensus: The WHO Definition

This complex and multifaceted debate reveals experts' perceived need for definition consensus. In response, major organizations including the European Foundation for Osteoporosis and Bone Disease and the American National Osteoporosis Foundation organized international consensus conferences, but these efforts failed to produce a common quantitative or qualitative osteoporosis definition.[90] Also, a rift was developing between the American National Osteoporosis Foundation, which strongly supported widespread use of bone densitometry as a screening method, and many European researchers and clinicians. Kanis cites this controversy as one reason for convening another conference, and one sponsored by the WHO to boost the likelihood of consensus: 'The aim was to clarify the reality of BMD testing, and to base its

[88] Fogelman (1988a), pp. 541-2
[89] Kanis (1990), pp. 209-10
[90] Anon. (1987); Anon. (1991); Anon. (1993)

strengths and weaknesses on science rather than politics. In this context, the WHO was a very useful agency, since it can be seen to be apart from nationalistic partisan issues'.[91] As a researcher at a WHO Collaborating Centre, Kanis could 'secure the imprimatur of the WHO' for an international conference, according to Glen Blake, bone imaging researcher at King's College London who worked with Kanis and Fogelman.[92] The resulting WHO Study Group, chaired by Kanis, met in Rome on 22-25 June 1992.[93]

The Study Group's main challenge was to choose boundary values for osteoporosis. In practice researchers and clinicians used Nordin's proposed T-score of two (i.e., two standard deviations below young average), and even the result printouts of DPA and DXA machines in the 1980s identified osteoporosis at T-scores of two.[94] However, Blake explained, 'The difficulty of using a threshold of -2 SD is simply that it identifies too high a percentage of the population in the high-risk group'.[95] Kanis agreed, as 'a T-score of -2 would have meant that there was a high prevalence of osteoporosis in young healthy adults, and indeed in 16% of women at the time of the menopause', percentages which he, Blake, and other researchers considered inaccurately high.[96] Alternatively, T-scores of -3 or even -4 were proposed, 'to increase the specificity of bone mineral measurements to predict fractures', but 'this would exclude many of the women who ultimately will fracture'.[97]

[91] Kanis, pers. comm. 11/3/09
[92] Blake, pers. comm. 12/3/09
[93] WHO (1994), pp. 1
[94] Nordin (1987); Blake, pers. comm. 12/3/09
[95] Blake, pers. comm. 12/3/09
[96] Kanis, pers. comm. 11/3/09
[97] Mazess (1987); Melton et al. (1992), pp. 1007; Melton, pers. comm. 30/3/09

In the end, the Study Group designated a T-score of 2.5, a choice Kanis describes as 'somewhat pragmatic'.[98] The Study Group justified its choice epidemiologically:

> A measured value of bone mineral more than 2.5 standard deviations below the mean for young healthy adult women at any site (spine, hip or mid-radius) identifies 30% of all postmenopausal women as having osteoporosis, more than half of whom will have sustained a prior fracture.[99]

Melton noted that in addition to these epidemiological justifications, 'by coincidence, -2.5SD was also close to the imagined fracture "threshold"', thus satisfying those groups who favored the idea of a fracture threshold.[100] This value includes most of the fracture population but only 30% of postmenopausal women, thus defining a relatively high-risk group small enough for cost-effective treatment.

Based on these statistics, the Study Group created four diagnostic categories of bone density: 'normal' as bone densities less than one standard deviation from the young average or T-score of +/-1, osteopenia as T-score -1 to -2.5, osteoporosis as -2.5, and severe osteoporosis as -2.5 with fracture (Figure 1).[101] The Study Group's report, published in 1994, presents osteopenia as a treatment threshold, such that women with osteopenic bone densities should consider taking HRT or other therapies to prevent further bone loss.[102] As implied by 'postmenopausal' in the report's title, the Study Group primarily addressed osteoporosis in women and thus defined categories only for women.

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[98] Kanis, pers. comm. 11/3/09
[99] WHO (1994), pp. 5
[100] Melton, pers. comm. 30/3/09
[101] WHO (1994), pp. 5
[102] WHO (1994), pp. 184

The Study Group published a 13-page report synopsis in *Osteoporosis International*, the International Osteoporosis Foundation's journal for 'practical information to apply to the daily management of osteoporosis patients'.[103] A few group members also wrote a four-page article of quantitative information in *Journal of Bone and Mineral Research*, the American Society for Bone and Mineral Research's journal for bone biology researchers.[104] These articles broadened the audience of the WHO's 129-page report by condensing it (many later articles cite these summaries and not the report) and dividing its information into general information for clinicians and quantitative details for researchers.

The standards inspired initial debates but won approval, shown by their almost immediate clinical and research use, and their inclusion in medical reference books by 1995.[105] According to Kanis, 'despite the navel inspection [referring to initial debates about the standards] the dust has settled and most authorities now use the WHO definition'.[106] Blake believed that 'the 1994 WHO report swept the board because at the time it met an unfulfilled need for a way of reporting clinical BMD studies'.[107] A 2003 WHO report restates the 1994 standards, a powerful indication of their usefulness and acceptance: 'The cornerstone of diagnosis is the measurement of bone mineral density. Diagnostic thresholds offered by the WHO have been widely accepted'.[108]

Acceptance of the Study Group's standards can be attributed to the WHO's unifying and apolitical influence, but Blake claimed to be 'always careful to say that the threshold was set by the WHO Study Group [not the WHO]', stressing the role of 'the group of experts' and not the

[103] Kanis and WHO Study Group (1994)
[104] Kanis et al (1994)
[105] e.g., Kanis (1996); Riggs and Melton (1995)
[106] Kanis, pers. comm. 11/3/09
[107] Blake, pers. comm. 12/3/09
[108] WHO (2003), pp. 7

global organization.[109] However, the WHO has participated in international standard setting since its creation in 1947. Today, the WHO collaborates with the broader-scope International Organization for Standardization, and the WHO Expert Committee on Biological Standardization defines concentrations of biological substances like vaccines to serve as universal standards.[110] WHO-defined 'Norms and Standards' most often apply to medications, but the Committee's responsibilities extend to biotechnology standardization. A 1994 Committee report claims that as a result of the Committee's work, 'biological standards are now universally used and are fundamental to the control of almost all biological medicines and, to a lesser extent, of diagnostic products, whether prepared by conventional means or by newer biotechnological methods'.[111] Further, the WHO's constitution describes its 'functions' as including 'to standardize diagnostic procedures as necessary'.[112] Thus it was well within the WHO's power and responsibility to convene an international group to address questions surrounding osteoporosis diagnosis and bone densitometry standards.

7. Conclusion

Disease definitions are shaped by their historical context and acquire meaning based on the social purposes they serve. They hold major implications for patients, doctors, researchers, and health policymakers. In the late twentieth century, preventative medicine and the risk factor model introduced the challenge of 'silent' diseases and diagnosis without symptoms. Osteoporosis was once known as a crippling disease of broken bones, but its definition now

[109] Blake, pers. comm. 12/3/09
[110] Rothery (1996), pp. 24-5; <http://www.who.int/biologicals/expert_committee/en/> Accessed 10/3/09.
[111] WHO Expert Committee (1994), pp. 1
[112] WHO Constitution 10/2006

entails hormonal and genetic factors, pre-fracture diagnosis, preventive therapies, and patient-controlled lifestyle choices to decrease risk, as well as diagnostic numerical standards of bone density.

The process of defining osteoporosis based on bone density measurements illuminates the importance of standardization and quantification in modern Western medicine. Standardization was considered necessary for knowledge communication, research collaboration, and consistent diagnosis in an increasingly globalized healthcare system. The definition of 'normal' and osteoporotic bone density values made bone density an easily measured quantitative risk factor for osteoporotic fractures, just as standardization turned other traits into measures of disease risk, such as hypertension as a risk factor for stroke. By examining the histories and meanings of disease definitions, medical imaging technology, debate, and consensus building, the quantitative standardization of osteoporosis by the WHO Study Group reveals itself as a long-anticipated event with far-reaching implications.

Questions remain about these themes and events. The social context of the 1980s leading to the standardization debate requires further study, including the public awareness campaign about osteoporosis and feminist movements' calls for research on women's health. Closer inspection of individual experts may reveal why they promoted certain viewpoints concerning bone density standards. Analysis of the failure of previous consensus conferences may suggest why successful standardization followed the work of the WHO Study Group. But this initial account of the definition of osteoporosis highlights key trends and issues in modern Western medicine, including the risk factor model, quantification of disease, disciplinary boundaries, and global standardization. The under-researched topic of defining modern diseases also illustrates

how standardization, quantification, and consensus among medical experts were vitally interconnected in twentieth-century medicine.

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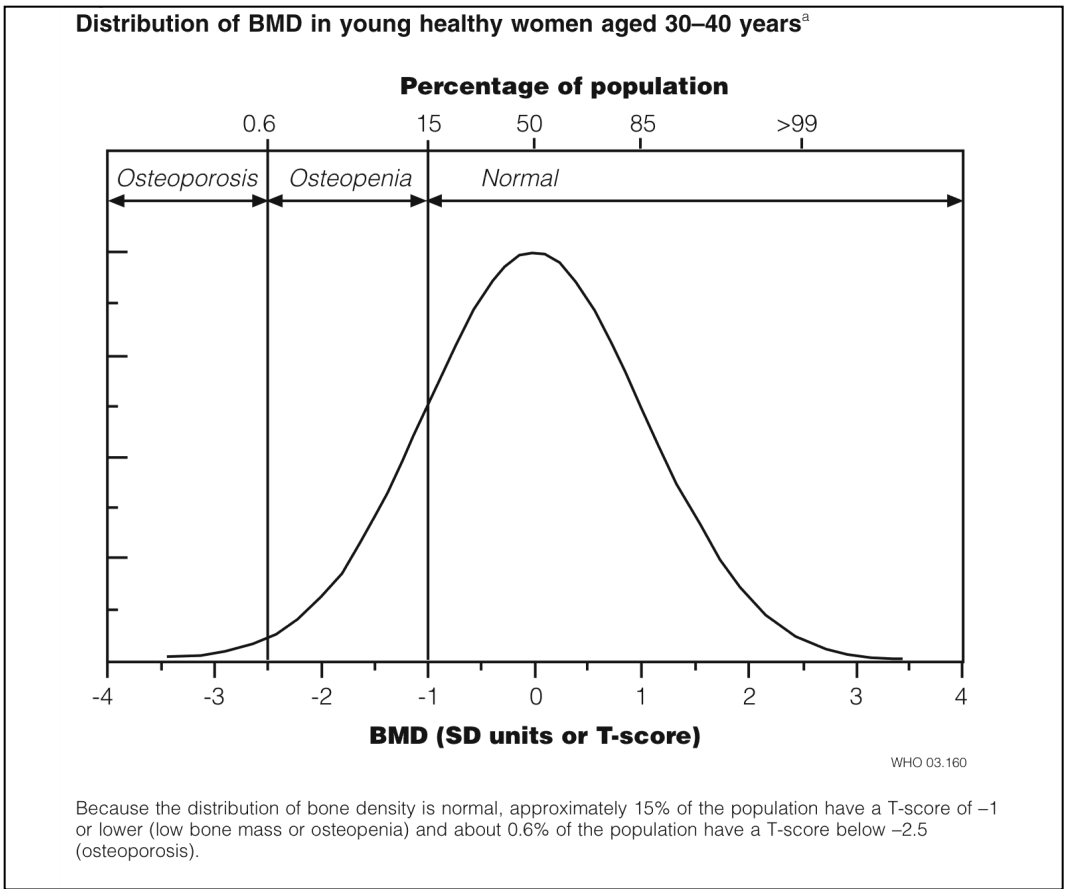

Figure 1: Diagnostic categories for osteoporosis based on bone mineral density (BMD). This image was produced for a 2003 World Health Organization report to illustrate the categories proposed by the 1992 WHO Study Group (WHO, 2003:60). Reprinted with permission of the WHO.