Review article Acta Med Hist Adriat 2023; 21(1);157-170
Pregledni članak https://doi.org/10.31952/amha.21.1.7

OSTEOPOROSIS FROM YESTERDAY TO TODAY – A NARRATIVE REVIEW

OSTEOPOROZA OD JUČER DO DANAS – NARATIVNI IZVJEŠTAJ

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SUMMARY

Despite different lifestyles, humankind has suffered from osteoporosis for thousands of years. A literature review concerning the history of osteoporosis in the following databases: Index Medicus, Medline, PubMed, and PMC Citations was done. In the final analysis, 18 review articles and 31 original papers were included. The works were published during the period 1705-2020. Although there is evidence of the existence of osteoporosis for many centuries, it was first described as a disease at the beginning of the 18th century. It was first perceived as an unavoidable course of aging with no possibility to cure. This approach changed only in the 20th century thanks to sudden diagnostic and therapeutic progress. This paper presents the milestones and most important researchers in osteoporosis history. Rapid progress in diagnostic and therapeutic possibilities sheds new light on osteoporosis' nature. A comprehensive outlook on its history may help find answers for the still unsolved problems of this disease.

Keywords: *osteoporosis, age-related bone loss, senile osteoporosis, history*

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Introduction

Osteoporosis is a chronic metabolic disease characterized by progressive bone loss leading to higher susceptibility to low-energy fractures (Consensus Development Conference, 1991). Postmenopausal women are at a high risk of osteoporosis due to the sudden loss of the protective function of estrogens. In addition, the majority of the elderly presents an increased risk of developing osteoporosis mainly due to low calcium intake and low level of active vitamin D leading to secondary senile hyperparathyroidism. The other risk factors are dietary mistakes, smoking, alcohol abuse, co-morbidities, i.e., hyperthyroidism, low physical activity, and medication usage. Despite the nowadays knowledge about osteoporosis, bone fracture frequency is rising, and the individual, social, and economic costs are enormous (Becker, Kilgore & Morrisey, 2010; Hernlund et al., 2013): in the European Union, the annual treatment of osteoporosis amounts to about €37 billion, and only 6% of those accounts for pharmacological proceedings.

Humankind has been accompanied with osteoporosis for thousands of years. Porotic bones have already been revealed by scientists in skeletons of ancient mummies, nevertheless, susceptibility and risk factors were different from those known today (Stride, Patel & Kingston, 2013). Dewey, Armelagos & Bartley (1969) were probably the first to show osteoporosis existence in archeological populations. The human skeletons from 350 BC to 1350 were analyzed, and a significant thinning of the cortical layer of the femoral neck dependent on women's age was found. Nevertheless, Umbelino et al. (2019) tested metacarpal cortical bone fragility in Portuguese Mesolithic remains, Spinek et al. (2016) and Lorkiewicz et al. (2019) assessed bone mineral density in skeletons from present-day Poland, dating from Neolithic to early modern times. These studies described a significant loss of bone mass, associated mainly with sex and age. Interestingly, compared to the modern-day population, bone loss was lower than it is nowadays. It is also worth mentioning archeological research on skeletons from Giza Necropolis from the Old Kingdom (2687–2191 BC) and from the New Kingdom period (1550–1070 BC) to the Roman period (30BC–395AD) (Zaki, Hussien & El Banna, 2009; Giuffra et al., 2009).

Aim

The aim of this review was to track the changes in knowledge about osteoporosis, its diagnosis, and personal attitude throughout the centuries.

Material and method

A literature review on osteoporosis was conducted in the following databases: Index Medicus, Medline, PubMed, and PMC Citations. The Mesh terms searched for were: "*osteoporosis*" OR "*age-related bone loss*" OR „*bone fracture*" OR "*postmenopausal bone loss*" OR "*pathologic bone demineralization*" OR *"senile osteoporosis*". Only historical publications on humankind with available abstracts were chosen. The review was conducted on the databases in 2020.

Next, a list of 380 abstracts in the English language was prepared and completed with hand-searched papers. Those concerning anthropology were excluded from the reviewed abstracts. In the final analysis, 18 reviews and 31 original papers were included.

Systematized information concerning osteoporosis history is presented in the Results. The oldest available paper concerning osteoporosis history was published in 1705, and the newest – was in 2017.

Results

Beginnings of osteoporosis

Although there has been evidence of the existence of osteoporosis in various cultures for many centuries (Mays, 2000 & 2006; Cho & Stout, 2011), the real progress in osteoporosis knowledge came in the 70s of the last century. The first one who described osteoporosis as a phenomenon of excessive bone fragility was a professor of anatomy and surgery from Jardin du Roi (a medical school established by Louis XIV), Joseph Guichard Duverney (Duverney 1751; Curate, 2014). In his research at the beginning of the 18th century, Jean-Louis Petit had already considered pathological bone fragility (1705). John Hunter's contribution should not be omitted – his research on bone structure and formation was set in 1754 (Meikle, 1997). He was the first to describe the process of bone growth and distinguished bone resorption as an inherent element of bone remodeling. His discoveries were 60 years ahead of the first microscope invention and the establishment of cell theory, so he was not able to explain the physiology of those processes. It was only in 1820 that the term "*osteoporosis*" was coined (from Greek words "*ostéon-oûn*" and "*póros*") and was first used in French pathologist Johann Lobstein's (1820) paper "*De l'osteoporose*" (Bijlysma & Meskers, 2012). In this work, Lobstein described cavities in the bones appearing in part of autopsies. The matter of the disease was suspected as a

bone formation with parallel thinning of its internal structure. Nowadays, we know that the process described by Lobstein was probably characteristic of another bone disease – *osteogenesis imperfecta* (O'Neill, 2005; Grob, 2011; Wylie, 2010). At the same time, the altered bone structure was investigated by surgeon Astley Cooper – he described the bones of some of his patients as "*thin in their shell and spongy in their texture*" (1832). Although convergent, Lobstein and Cooper's observations had no impact on the medical proceedings of that time (O'Neill, 2005; Grob, 2011). Nevertheless, more attention was paid to older patients with frequent bone fractures. The level of knowledge about osteoporosis was stable until the second decade of the 20th century, when numerous endocrinologists and physiologists became interested in bone metabolism. Their research changed the traditional conception of the human skeleton – from stiffness to elasticity conception. Further research started to shed light on the process of bone demineralization in which other organs, such as parathyroids, thyroid gland, liver, and microelements (calcium, phosphorus) participate.

Diagnostic methods

Before 1890, bone biopsy was the only available diagnostic instrument, although painful, imprecise, invasive, and expensive (Freemont, 1995). Until 1963, osteoporosis was diagnosed only on the basis of X-ray pictures – when vertebral fracture, fracture of any bone after low-energy injury, or serious bone atrophy was found (Bijlysma & Meskers, 2012; Wylie, 2010). Radiological assessment was found to be a cheaper and noninvasive alternative but was still fraught with many limitations. First, it depended on the radiograph's quality, the patient's anatomical conditions, the radiologist's experience, and X-ray equipment accuracy. It is assumed that bone atrophy is seen in radiological assessment only after 30% of bone loss, which is equal to advanced osteoporosis (Tovey & Stamp, 1995). Without the possibility of early diagnosis, there was no chance for effective treatment of osteoporosis – all attempts were started after a first bone fracture, when all medical procedures were aimed only at stopping the further progression of osteoporosis but did not improve bone density. An alternate way of radiogram use was the measurement of cortical thickness of the femoral or second metacarpal shaft. This method is still used as it is easy, cheap, and available, nevertheless, it is fraught with the risk of lower accuracy of the metacarpal index or omission of cortical wall thinning in the femoral index (Barnett & Nordin, 1960).

In 1963 two physicians, John Cameron and James Sorenson, from the University of Wisconsin, announced that their new invention, single-photon

absorptiometry, eliminates misdiagnosis of osteoporosis compared to X-ray (Wylie, 2010; Cameron & Sorenson, 1963). When using absorptiometry, bone toughness was assessed regarding its mineral content (especially calcium). Nevertheless, the still circumfluent soft tissue disturbances made this method applicative only for the bones lying underneath the skin, which means not for the spine and hip. When quantitative computed tomography was invented, it was also used for osteoporosis diagnosis. This method turned out to be more precise –three-dimensional bone assessment and calculation of mass-to-volume ratio (not only mass to surface like in single-photon absorptiometry) became possible. Quantitative computed tomography was first used in 1976, but its costs and high radiation dose discouraged its wide use (Wylie, 2010). An alternative to those two measurements was already available in the late 1960s (but available for commercial use only in the 1980s) as a dual-photon absorptiometry first used only in clinical research. It was less precise and more expensive than single-photon absorptiometry, but its main advantage was an ability to assess fundamental bones in the aspect of the natural course of osteoporosis – spine and hip. Dual-photon absorptiometry in commercial form was designed by Richard Mazess from the University of Wisconsin in 1972. However, it took the next several years of ineffectual looking for a company that would produce it for widespread use (Wylie, 2010; International Directory of Company Histories, 1999; Miller P., 2017). It was not until 1980 that the researchers created a company called Lunar Corporation and started the mass production and sales of densitometers. It coincided with growth in United States osteoporosis awareness fueled by pharmacological companies promoting hormonal therapy. The escalating interest of Americans fastened looking for its diagnosis and treatment innovations (Blake & Fogelman, 2010). In 1988, Lunar introduced dual-energy X-ray absorptiometry to the market, which was cheap enough, available for outpatient use, and precise to set new criteria and standards in osteoporosis (International Directory of Company Histories, 1999).

Meanwhile, due to limited access to big and bulky DXA devices that use radiation, searching for new methods of osteoporosis diagnosis started. One of them was quantitative ultrasound – first used for bone examination in 1984 by Christian Langton. The QUS device is small, portable, and measures ultrasound attenuation in bone (Geusens, 1997). It is usually used for phalanges and calcaneal bone examination. There is still a lack of clear guidelines for the diagnosis with the use of this equipment – maybe soon, the history of

osteoporosis will come full circle, and, as with DXA, criteria for osteoporosis based on ultrasound will be worked out.

Since the DXA invention was a general tool to diagnose osteoporosis, the definition of the disease has changed. Bone status has been assessed in the quantitative aspect, not only qualitative (bones fractured or crushed). Osteoporosis was diagnosed based on quantitative measurements before the first fracture, and therefore became an asymptomatic disease. Non-pharmacological methods, such as a balanced diet and regular physical activity, had the best impact on bone health in young women. Therefore, this age group benefited the most from new diagnostic methods. This phenomenon was described by Charles Dent in the 70s: "*senile osteoporosis is a pediatric disease*" (van der Sluis et al., 2002).

Osteoporosis definition

At the beginning of the 20th century, still, the only known causes of osteoporosis were age and atrophic processes, and the only role of a woman was coming down to draw a man's attraction and give birth. Last menstruation initiated a period of life that was considered as declining independence and, finally, senility. A vision of a stoop-shouldered woman walking uneasily was a synonym of senility and an index of natural biological processes; nowadays, it is called in medical terminology "widow's hump" and is one of the symptoms of advanced osteoporosis.

Osteoporosis definition was changed many times along with the current state of knowledge (Grob, 2011; Wylie, 2010). Based on x-rays, it was defined as noticeable bone atrophy or status in which resorption overbalanced bone synthesis (Nordin, 1987). Interestingly, osteoporosis definition was present in dictionaries and medical terminology since J. Lobstein named it (Grob, 2011; Faulkner, 2005). However, at that time, it was considered an unavoidable process resulting from natural aging. Changes came no sooner than in the 20th century, when American endocrinologist, Fuller Albright, linked osteoporosis with vertebral fractures in postmenopausal women and initiated estrogen therapy (Reifenstein & Albright, 1947; Forbes, 1991; Manring & Calhoun, 2011; de Villiers, 2014). According to Albright's definition, osteoporosis results from too little formation of calcified bone with proper bone calcification and bone resorption rate (Albright, Smith & Richardson, 1941a; Albright, 1989; Nordin, 2009). A bit later, Albright & Riefenstein proposed osteoporosis differentiation between two types: postmenopausal and senile (1948). Since then, according to Harrison's medical book titled "*Internal diseases*" – in

edition from 1950, osteoporosis was presented as a consequence of bone loss secondary to organism aging (Harrison et al., 1950). Postmenopausal osteoporosis was defined as bone loss in women over 65, whereas in older people, osteoporosis was diagnosed as a senile type. Those rules were used until 1970, when osteoporosis was excluded from natural aging processes. Since then, it has been understood as pathology (Harrison & Wintrobe, 1970). Age was considered as a cause of primary osteoporosis, but other risk factors such as long immobilization, abuse, sex hormones deficiency, and steroid therapy – secondary osteoporosis. In 1986, Riggs & Melton modified this selection to two types: I and II.

Meanwhile, precise diagnostic measurements detecting osteoporosis at its early stage became available for public use. Nordin first initiated the discussion concerning the need to work on a new definition of the disease in the late 80s in the scientific magazine "*Calcified Tissue International*". He proposed setting norm ranges of bone mineral density based on the values of a healthy, young population (Wylie, 2010). He wanted to diagnose osteoporosis when bone mineral density differed by two or more standard deviations from healthy individuals. Nordin differentiated the norm ranges depending on gender and age as well (Nordin, 1987). Although his conception found no acceptance in the medical community, it initiated further research in diagnostic criteria based on DXA. The following paper, "*Calcified Tissue*", appeared to answer Nordin's proposition written by Mazess, the densitometry inventor. He faulted his conception with no relevance to risk fracture (Mazess, 1987).

"Despite the current prominence of AIDS, osteoporosis may well be the disease of the 1990s," wrote Robert P. Heaney (1991). Three important milestones in 1990-1993 confirmed this theory. In October 1990, a conference took place that summarized the actual state of knowledge about osteoporosis, and in the same month, Osteoporosis International was launched. It is a journal that publicizes researchers focused on only one disease. Finally, the discussion concerning osteoporosis diagnosis was closed with consensus acclaimed on 22-25th of June 1992 in Rome at a conference dedicated to the Workgroup WHO Report led by John Kanis. Since then, osteopenia has been diagnosed based on densitometry when a T-score ranges between (-1) and (-2.5), and osteoporosis when it is below (-2.5) (Faulkner, 2005). Two researchers, Neer and Kelly, created the T-score index and its name– the "*T*" letter in the index name was derived from the second one's name (Watts, 2002). T-score means a ratio between the difference in mineral density in examined patients and healthy control and standard deviation for the general population.

Pathogenesis

Three parallel processes characterize osteoporosis: failure to achieve optimal strength during an organism's growth, excessive bone loss, and failure to replace lost bone. Actually, Galileo already suspected that mechanical loading had an impact on bones' shape but could not explain its mechanism. No earlier than the 19th century, Hermann von Meyer started his research in bone structure (Skedros & Brand, 2011). This great anatomist, in a companion of mathematician Karl Culman, described the similarity between femoral trabecular structure and layout of lines depicting permanent loading trajectory. This led another great researcher, Julius Wolff, to another observation – trabecular layout in spongy bone is in accordance with major loading directions. It was published in 1892 in a book titled "The law of bone remodelling" as Wolff's rule: "Every change in the form and the function of a bone or in the function of the bone alone, leads to changes in its internal architecture and in its external form." It was supplemented by Roux as a theory of functional adaptation.

Pathogenesis humankind had to wait until the latter half of the 20th century for the next step in the knowledge of osteoporosis.

Until Albright's hormonal theory, osteoporosis was assumed as natural bone atrophy. His discovery started a new scientific interest in this field. The second initiator of the scientific revolution in this area was Harold Frost, who first described Bone Mineral Units (BMU) localized whether on the surface of trabecular bone (in Howship lacunae) or in cortical bone (in haversian systems) (Frost, 1969). The precise role of particular bone cells, especially osteoclasts responsible for bone resorption, was investigated in further research (Jaworski, Duck & Sekaly, 1981, Miller S., 1981). Frost was not only responsible for the cellular explanation of bone remodeling. He is perceived as a father of contemporary functional bone adaptation understanding, thanks to his mathematical model publicized in 1964 (Farrow, 1964). He was also the author of the "mechanostat" theory, according to which bone remodeling processes can be predicted (Frost, 1987). His assumptions were verified and completed many times, which gave new hypotheses – Pauwels& Kummer law (Firoozbakhsh & Cowin, 1981) and Cowin's adaptive bone-remodeling theory (Cowin et al., 1978a, 1993b).

A continuation of the cellular basis of osteoporosis is its molecular pathway. This level of disease understanding became possible in accordance with huge technical progress in science. The first point of interest was the Tumor

Necrosis Factor family, which included interaction between osteoblasts, osteoclasts, RANKL (ligand for the receptor activator of NF-kB-RANK), and osteoprotegerin which blocks RANKL-RANK complex (Suda et al., 1999). Next – Wnt signaling pathway, sclerostin, bone morphogenetic protein 2, prostaglandins, IL-1 (Klein & Raisz, 1970; Katagiri et al., 1990; Kusu et al., 2003).

Along with mathematical models and the cellular theory of bone modeling, many laboratories, especially British ones, due to big problems with rickets, searched for the cause and cure for this disease. This led the nutritional biochemist Mc Collum, who conducted experiments on rats fed with a plain cereal diet, to the vitamin D discovery in 1922. The precise role of vitamin D at the beginning was unknown. There were even discussions about whether it should be classified as a vitamin. Interaction between calciferol, calcium, and bone metabolism was shown in further research and opened new doors in osteoporosis prevention, treatment, and understanding (Shipley, Kramer & Howland, 1925; Nicolaysen, 1937; Carlsson, 1952; Schachter & Rosen, 1959).

Thanks to those researchers, we now know that osteoporosis is a continuous bone loss and microarchitecture deterioration caused by multiple pathogenic mechanisms. Understanding its pathogenesis leads us to the precise treatment of osteoporosis, i.e., vitamin D supplementation and anti-sclerostin antibodies treatment.

Conclusion

Despite the fact that osteoporosis has accompanied humans for centuries, we have only gotten to know it better for several dozen years. Rapid progress in diagnostic and therapeutic possibilities did not start sooner than in the 20th century with the invention of absorptiometry. What is most important, understanding osteoporosis changed the human approach to this disease – from a natural process to pathological status. This has opened new and closed old doors. How many of those doors are still hidden, and will those that are open lead us to correct solutions – for the answers to these questions, we still have to wait.

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SAŽETAK

Unatoč različitim stilovima života, čovječanstvo već tisućama godina pati od osteoporoze. Pregled literature o povijesti osteoporoze proveden je u sljedećim bazama podataka: Index Medicus, Medline, PubMed i PMC Citations. Konačna analiza obuhvatila je 18 preglednih članaka i 31 izvorni rad. Radovi su objavljeni u razdoblju 1705. – 2020. Iako već stoljećima postoje dokazi o njezinu postojanju, osteoporoza je početkom 18. stoljeća prvi put opisana kao bolest. Isprva se na nju gledalo kao na neizbježan tijek starenja bez mogućnosti izlječenja. Taj se pristup promijenio tek u 20. stoljeću zahvaljujući naglom napretku u dijagnostičkim metodama i terapiji. U ovom su radu prikazane velike prekretnice i predstavljeni najutjecajniji istraživači u povijesti osteoporoze. Brz napredak u dijagnostičkim i terapijskim mogućnostima baca novo svjetlo na prirodu osteoporoze. Sveobuhvatan pogled na njezinu povijest mogao bi pomoći u pronalaženju odgovora na još uvijek neriješena pitanja vezana uz ovu bolest.

Ključne riječi: *osteoporoza, gubitak koštane mase povezan sa starenjem, senilna osteoporoza, povijest*