The Osteoporosis Manual

Reiner Bartl • Christoph Bartl

The Osteoporosis Manual

Biology, Prevention, Diagnosis and Treatment

Second Edition

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"Bone is every doctor's and everybody's business."

Preface

With the dawn of the twenty-first century has come the realisation that bone and joint diseases are the major cause of pain and physical disability worldwide. Moreover, according to the WHO Scientific Group, there are more than 150 diseases and syndromes of musculoskeletal conditions, usually associated with pain and loss of function. It is undoubtedly these insights that prompted the WHO to declare the first 10 years of the new century as "The Bone and Joint Decade 2000–2010". This declaration obviously made a highly significant impact on international, national and medical authorities, as well as on physicians, scientists and citizens worldwide as evidenced by an overwhelming flood (a regular tsunami) of articles, studies and books on the subject in the last few years alone! Not to mention the coverage in newspapers and journals, on the radio and television, and of course all the up-to-date information freely available on the Internet. The number of people suffering from these diseases—already many millions in the developed and underdeveloped countries in the world—is expected to double within the next 20 years. In many countries, this increase will be even greater due to the longer survival and consequently larger numbers of older people in the population. It is therefore inevitable that the already astronomical costs of health care will rise proportionally. According to the International Osteoporosis Foundation (NOF), the worldwide incidence of hip fracture is projected to increase by 240% in women and 310% in men by 2050, unless appropriate preventive measures will be taken on sufficiently large national and international scales, for which, hopefully, this book will provide a stimulus! (Fig. 1).

Fig. 1 Osteoporosis: a worldwide challenge!

Fig. 2 Osteoporosis: a silent thief!

On the positive side, the enormous amount of work, research and study of disorders of bone over the past 10–20 years or so has contributed greatly to our understanding of the causes, treatment and prevention of osteoporosis and other bone disorders. Most importantly, perhaps, the skeleton is now regarded in a new light, as a dynamic organ undergoing constant renewal throughout life from start to finish, from the cradle to the grave. And what is more: it is now abundantly clear that the skeleton participates, usually not to its advantage, in almost every condition that may affect the organs and tissues in the body! This applies especially to *osteoporosis*, which is now under control! (Fig. 2).

How did this come about?

- Because of the elucidation of many of the factors involved in osseous remodelling.
- Because of the development of simple, fast, reliable and non-invasive methods for measurement of bone density, and for testing other factors such as mineralisation, trabecular architecture, cortical thickness, and the bone cells themselves.
- Because of the identification of general and individual risk factors, so that appropriate measures can be taken to prevent development of osteoporosis and/or its progression, if and when fractures have already occurred.
- And finally, because effective medication for prevention and therapy is now readily available worldwide.

The efficacy of the classes of compounds known as “bisphosphonates” as well as of the “selective oestrogen receptor modulators” (SERMs) and more recently of the anabolic parathyroid hormone analogues, denosumab and romosozumab, has now been unequivocally established by numerous large multicentre trials involving literally millions of patients. In addition, simple methods such as a healthy life style, adequate nutrition, sufficient physical activity, and vitamin D and calcium supplements, as required, can be recommended and adopted on a large scale, beginning with the responsible authorities and reaching to the individual citizens (Figs. 3 and 4).

Fig. 3 Be active and be happy! The five main steps to preserve strong bones are: (1) Don't smoke, (2) Be active, (3) Eat well, (4) Think positive and (5) Take Vitamin D!

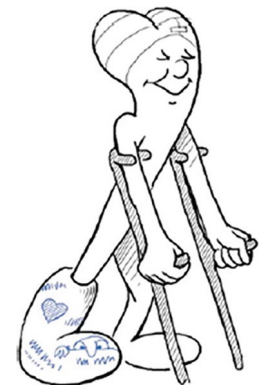

Fig. 4 "Osteoporosis-related" fractures: focussing not only on prevention and treatment but also on ways to deal with the personal and social consequences of the disease such as pain, depression, loss of self-esteem and social isolation!

Introduction and acceptance of these methods require public awareness and support and the realisation that every individual is the guardian and caretaker of his/her own bones and responsible for their structural and functional integrity. Fortunately, some progress has been made, as shown by the numerous articles recently published from the "four corners of the globe" which unequivocally establish the epidemic proportions of the problem. Well-founded diagnostic techniques and effective therapies—both antiresorptive and osteoanabolic—are now available for prevention, diagnosis and treatment of osteoporosis and many other bone disorders. It should be emphasised that the treatments recommended in this text are all founded on "evidence-based medicine" (unless otherwise stated) for which appropriate references are given in the book at the end of the text.

The aim of this book is to demonstrate that "*Bone is EveryBody's Business*" and especially every patient's and doctor's, and to provide guidelines for the diagnosis, therapy and prevention of bone disorders—from paediatrics to geriatrics. It is hoped and anticipated that this book will raise awareness and provide information to anyone seeking it, and especially to doctors across all

disciplines concerned with various "bone problems". Clinical osteology is now an independent specialty which nevertheless encompasses all branches of medicine and affects each and every one of us.

However, the most worrying finding in recent US and European studies is a stagnation/downward trend in the number of patients who receive osteoporosis medication following a first fragility fracture, which appears to have decreased by at least 30% over the last decade. It is assumed that less than 30% of patients with new fractures get adequate treatment according to the guidelines. Paradoxically the finding is most marked in the case of hip fractures, which account for the highest mortality rate and the major costs of all fractures. The underlying causes for this substantial *treatment gap* are unclear. Potential reasons are that many doctors, dentists and patients are in fear of very rare but serious complications and side effects of osteoporosis medications and ignore the clear advantage of these drugs in the benefit-to-risk analysis. When discussing the risk of osteonecrosis of the jaw (ONF) and atypical femoral fracture (AFF), it is important to make clear that the risk for fracture associated with not treating far exceeds the risk for these adverse effects of treatment! Also a decline in BMD testing due to unclear reimbursement policies may play a role.

Osteoporosis is a "*silent disease*" as low BMD is painless until a painful fragility fracture occurs—and many osteoporotic patients never receive a treatment. Patients often do not understand their risk for fractures and the negative impact a fracture could have on their quality of life. This is a challenge when treating osteoporosis in which symptoms do not get observably better or worse in response to treatment. A chance to close the treatment gap is the creation of worldwide *fracture liaison services* to better identify patients with fragility fractures and to improve prevention of further osteoporotic fractures. Improved public awareness and public health strategies to improve bone health from a young age will also contribute to prevention of osteoporosis in the future.

Osteoporosis is the most common metabolic disease in the world. By applying fracture risk assessment, pharmacologic treatment, risk reduction counselling and long-term monitoring, clinicians can contribute to extend the healthy and independent lives of their patients. However, until recently it remains an *underdiagnosed* and *undertreated* disorder, despite goal-directed treatment strategies, effective anti-fracture agents and the potentially lethal consequences of fractures. The majority of the highest risk women and men are not diagnosed and do not receive effective therapies. Taking into consideration the rapid ageing of the worldwide population and the importance of musculoskeletal health in old age, we have to ensure that in the present decade (2020–2030), the "*Decade of Healthy Ageing*" hailed by the WHO, bone health and fracture prevention become the priority they so urgently need to be. Osteoporosis detection, diagnosis and treatment must become routine components of medical practice. Because today, osteoporosis is preventable and treatable!

Osteoporosis is a disorder whose time has come! (Dennison E. Osteoporosis treatment, a clinical overview. Cham, Springer; 2021).

Consequently we have adhered stringently to simplicity, comprehensiveness and practicality of approach to examinations, methods and implementation of up-to-date testing, to strategies for prevention, to criteria for diagnosis and to presentation of therapeutic possibilities, as well as to our own particular goal which is to keep this text as "user-friendly" as possible, so that any doctor seeking information on a particular topic in osteoporosis has uncomplicated and time-saving access to it.

We would like to thank H. Konopatzki and R. Henkel who made significant contributions to this book with numerous high-quality illustrations.

We wish all our readers success in their endeavours to help patients and to reduce suffering in this strife-ridden, beautiful planet of ours!

Munich, Germany Reiner Bartl
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Abbreviations

25OHD	25-Hydroxyvitamin D
AACE	American Association of Clinical Endocrinologists
AFF	Atypical Femur Fractures
AI	Aromatase Inhibitor
ALP	Alkaline Phosphatase
ASBMR	American Society for Bone and Mineral Research
BASP	Bone-specific Alkaline Phosphatase
BJ	Bence-Jones Protein
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index
BMU	Basic Multicellular Unit
BMD	Bone Mineral Density
BMES	Bone Marrow Edema Syndrome
BMI	Body Mass Index
BMP	Bone Morphogenic Protein
BP	Bisphosphonate(s)
BRU	Bone Remodelling Unit
BSP	Bone Sialoprotein
BTM	Bone Turnover Marker
BUA	Broadband Ultrasound and Attenuation
CAM	Cell Adhesion Molecule
CaSR	Calcium-Sensing Receptor
CEA	Carcinoembryonal Antigen
CGRP	Calcitonin Gen-Related Peptide
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CRPS	Complex Regional Pain Syndrome
CT	Computed Tomography
CTX	Carboxy-Terminal Cross-Linked Telopeptide of Type I Collagen
DHEA	Dihydroepiandrosterone
DKK-1	Dickkopf WNT Signalling Pathway Inhibitor 1
DM	Diabetes Mellitus
DXA	Dual Energy X Ray Absorptiometry
EMA	European Medicines Agency
FDA	US Food and Drug Administration

FGF23	Fibroblast Growth Factor 23
FLS	Fracture Liaison Service
FN	Femoral Neck
FRAX®	Fracture Risk Assessment Tool
GC	Glucocorticoid
GFR	Glomerular Filtration Rate
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GnRH	Gonadotropin Releasing Hormone
Gy	Gray
HA	Hydroxyapatite
HAL	Hip Axis Length
HER2	Human Epidermal Growth Factor Receptor 2
HPP	Hypophosphatasia
HPT	Hyperparathyroidism
HRT	Hormone Replacement Therapy
IFNγ	Interferon γ
IGF	Insulin-like Growth Factor
IL	Interleukin
INF	Interferon
IU	International Unit
IV	Intravenous
IU	International Units
LSC	Least Significant Change
MDF	Myelopoiesis Depressing Factor
MGUS	Monoclonal Gammopathy of Undetermined Significance
MM	Multiple Myeloma
MMPs	Matrix Metalloproteinase
MRI	Magnetic Resonance Imaging
M-CSF	Macrophage Colony-Stimulating Factor
μSv	Micro Sievert
NIH	National Institutes of Health
NOF	National Osteoporosis Foundation
NTX	N-Terminal Telopeptide
OAF	Osteoclast Activation Factor
OC	Osteocalcin
ODF	Osteoclast Differentiation Factor
OI	Osteogenesis Imperfecta
OIF	Osteoblast Inhibitory Factor
ONJ	Osteonecrosis of the Jaw
OPG	Osteoprotegerin
PBM	Peak Bone Mass
PCLI	Plasma Cell Labelling Index
PDGF	Platelet-Derived Growth Factor
pDXA	Peripheral Dual X-Ray Absorptiometry
PG	Prostaglandin
pHPT	Primary Hyperparathyroidism
PPI	Proton Pump Inhibitors
PINP	Amino-terminal Propeptide of Type I Procollagen

PMMA	Polymethylmethacrylate
PO	Per Os
pQCT	Peripheral Quantitative Computed Tomography
PSA	Prostate Specific Antigen
PTH	Parathormone
PTHrP	Parathormone-Related Protein
QCT	Quantitative Computed Tomography
QUS	Quantitative Ultrasound
RANKL	Receptor Activator of Nuclear Factor-kB Ligand
RCT	Randomised Controlled Studies
ROD	Renal Osteodystrophy
ROI	Region Of Interest
RR	Relative Risk
SB2M	Serum Beta-2-Mikroglobulin
SC	Subcutaneous
SD	Standard Deviation
SERM	Selective Estrogen Receptor Modulator
SF	Subchondral Fracture
SHBG	Sex Hormone-Binding Globulin
SIF	Subchondral Insufficiency Fracture
SLE	Systemic Lupus Erythematosus
SMP	Sympathetically Maintained Pain
SOS	Speed Of Sound
SR	Strontium
SRE	Skeletal-Related Event
STIR	Short Tau Inversion Recovery
SXA	Single X-Ray Absorptiometry
T	Testosterone
TBS	Trabecular Bone Score
TENS	Trancutaneous Electrical Nerve Stimulation
TGF	Transforming Growth Factor
TNF	Tumour Necrosis Factor
TRANCE	TNF-Related Activation-Induced Cytokine (ODF, OPG-L, RANKL)
TRAP	Tartrate Resistant Acid Phosphatase
TSH	Thyroid-Stimulating Hormone
US	Ultrasound
VCF	Vertebral Compression Fracture
VDRA	Vitamin D Receptor Activator
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation