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Imaging of Prosthetic Joints

A Combined Radiological and Clinical Perspective

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This book is dedicated to Professor Roberto Passariello, eminent radiologist and great teacher, who taught us with humility and tenacity to face the hardest challenges in research and in commitment to science

Preface

The concept of this book on Imaging of Prosthetic Joints—A Combined Radiological and Clinical Perspective arose from the work experience of the editors as musculoskeletal radiologists working closely with orthopedic colleagues. The continuous exchange of technical know-how and research as well as extensive professional collaboration aimed at solving the different clinical and diagnostic problems in the specific field of joint replacements have stimulated this project.

Considerable improvements in surgical techniques, in prosthetic biomaterials, and design make joint replacement a safe procedure. Nevertheless, a life-long implant does not exist, and early failures are registered in a small but significant number of cases. Moreover, a consistent number of the remaining implants can last for more than 15 years, allowing the manifestation of bone aging processes such as bone loss and medullary enlargement which could threaten a longer survival. Considering the large number of patients involved, the impact of the procedure on the quality of life, and the severe consequences of implant failure, the monitoring of prostheses became mandatory in order to improve their longevity. The longevity of the implants depends on the achieved mechanical stability and on osseointegration with the hosting bone, i.e., the interaction between the hosting bone and the implant and the adapted surgical procedures.

Over the years we have witnessed extraordinary progress in this fascinating field of medicine. Major advances have occurred at the level of basic science, clinical practice, and diagnosis, technological development material properties, design, and fixation of articular prostheses—and we have incorporated all of them in this volume.

Part I provides an introduction to the mechanism of osseointegration, from recent progress in the elucidation of the unique molecular regulatory mechanisms of bone cells and extracellular matrix, to biomechanics and prosthetic osseointegration and material implants. The treatment of orthopedic diseases has changed considerably over the past decades, allowing patients to live longer and to have better quality lives. The introduction of new biomaterials has contributed much to this success. The material properties and fixation methods of joint implants is paramount to prosthesis performance and service time. New developments in bearing surfaces and coating materials represent the attempt

to bring joint prostheses to the next level and get a further increase as in performance as well as in longevity by decreasing the wear degradation and osseointegration problems.

Part II provides a dynamic view of the diagnostic techniques indicated in preoperative surgery planning and postsurgery surveillance of prosthetic survival. Imaging is required for the initial assessment, routine follow-up, and in patients with suspected complications.

As joint replacement has become prevalent, a myriad of prostheses became available. The radiological criteria for diagnosis of failure of prostheses may depend on the type and technique used. However, the imaging of complications of prostheses may be challenging. Fractures, dislocations, and most cases of aseptic loosening can be diagnosed with a combination of clinical and diagnostic techniques. In the immediate postoperative period, a plain film is routinely performed. In the prosthesis follow-up the main purpose of the plain film is to diagnose loosening of the prosthesis. MRI will often provide better anatomical detail for preoperative planning. MRI and CT are useful for assessing the patients in case of complications, but are limited by the presence of artefacts caused by the metallic prostheses, which may degrade the imaging of the adjacent portions. The role of nuclear medicine in the evaluation of painful joint replacement and in differentiating the aseptic loosening from infection of the prosthesis is also described.

This is the first book that includes both the most well-known diagnostic techniques used for periprosthetic surveillance including the dual-energy X-ray absorptiometry (DXA) method. In the last 25 years, due to an improvement in hardware and software of DXA there has been increasing interest within the orthopedic community in the noninvasive measurement of bone mineral mass and bone remodelling around metal joint prostheses in clinical practice and research. This interest has been stimulated, in part, by the recognition and understanding that the various diagnostic tools available for clinical diagnosis of a failed arthroplasty are neither sensitive nor accurate for the diagnosis of early bone loss. Using the DXA technique, the amount of bone mass after joint stem implantation can be determined with high precision, minimal radiation exposure, and negligible affection by metallic implants. The according chapter summarizes the technical aspects and clinical applications of periprosthetic DXA in the two common and most currently well-accepted orthopedic applications such as after implantation of total hip and total knee joints.

Part III summarizes the most common implants and surgical techniques used in hip and knee replacement procedures as well as widely used pre- and postoperative imaging techniques. In orthopedic surgery practice the use of foot, ankle, shoulder, elbow, wrist, and hand prostheses has become very common over the past decades, even if relatively few total arthroplasties are still performed each year considering the total number of hip and knee implants. The various types of implants and materials, the potential complications, and the clinical indications of these joint implants are also dealt with.

Part IV is devoted to progress made in the clinical practice. The potential use of different pharmacological compounds to enhance periprosthetic bone quality and bone mass, thus to prevent early implant failure, is described, as well as the different therapeutic approaches that have been proposed over the years in experimental and clinical studies to improve osseointegration of prosthetic implants. As physical rehabilitation is extremely important in the overall outcome of any joint replacement surgery, particular importance has been given to the chapter about postsurgery rehabilitation. The goals of physical therapy are to prevent contractures, improve patient education, and strengthen muscles around the joint through controlled exercises. Therefore, the use of physical therapies is a fundamental support to the rehabilitative programs for patients that underwent surgical intervention of joint prostheses.

We hope that this volume will be a reference tool not only for specialists in the field, such as radiologists and orthopedists, but also for medical students allowing them to expand their educational and scientific interests as well as their interest in practical medicine. The full credit for any educational benefit that this book may offer goes to the many scientists who have captured their knowledge and experience in this volume. They deserve our deepest gratitude for the high quality of their contributions and their enthusiastic cooperation. We would also like to express our sincere appreciation to the editorial staff at Springer for their guidance and assistance in preparing and publishing this book.

Carlina V. Albanese
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Contents

Part I
Cellular Elements, Bone Matrix, Bone Remodeling, Osseointegration, Implant Material

Bone Cells

1

Angela Oranger, Graziana Colaianni and Maria Grano

1.1 Osteoblasts

Osteoblasts, the bone-making cells, are mononuclear, polygonal and able to secrete bone matrix. They are polarized cells, and the part of the cell membrane which is in direct contact with the bone surface possesses many cytoplasmic processes that extend into the newly deposited matrix called osteoid before mineralization. Osteoblasts form tight junctions with adjacent cells and have regions of the plasma membrane specialized in vesicular trafficking and secretion [1].

An important role for osteoblast has been recognized in osteoclast regulation through the secretion of receptor activator of nuclear factor–κB ligand (RANKL) and osteoprotegerin (OPG) [2]. The idea that osteoblast lineage cells control osteoclast differentiation and function originated more than 30 years ago with the observation that receptors for osteoclastogenic hormones, such as parathyroid hormone, are present on cells with osteoblastic characteristics but not on osteoclast progenitors [3]. Subsequent works showed that cell lines with osteoblastic characteristics or cell preparations rich in osteoblast progenitors support osteoclast formation and activity in cocultures with osteoclast progenitors [4, 5]. These works in the light of recent knowledge preluded to the presence of RANKL in the culture system utilized.

1.1.1 Osteoblast Differentiation

During embryonic development, osteoblasts originate from local mesenchyme and, postnataly, from connective tissue mesenchymal stem cells (MSCs) or bone marrow stromal cells. In response to specific stimuli, these precursor cells commit to osteogenic lineage and differentiate into mature osteoblasts. Numerous studies have defined the sequence of events that results in the maturation of osteoblasts [6]. Osteoblastogenesis is defined by several phases: lineage commitment, proliferative expansion, synthesis and mineralization of extracellular matrix (ECM), and establishment of osteocyte. All these stages are characterized by sequentially expressed genes that lead to the expression of specific markers such as alkaline phosphates (ALP), collagen 1 (coll 1), bone sialoprotein (BSP), osteonectin (ON) osteopontin (OPN), and osteocalcin (OSTC) (Fig. 1.1).

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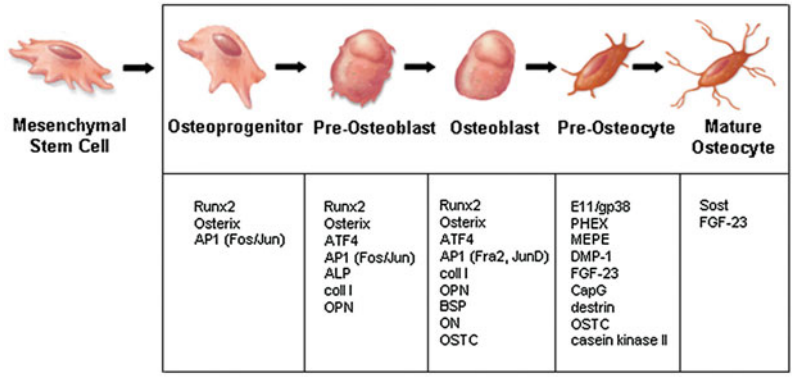

Fig. 1.1 Specific gene expression during osteoblast-to-osteocyte ontogeny. Different stages of osteoblast differentiation, from mesenchymal stem cells to mature mineral matrix-embedded osteocytes, are illustrated. Specific genes involved in both osteoblastogenesis and osteocytogenesis are schematically summarized

1.1.2 Transcriptional Regulation of Osteoblast Differentiation

The differentiation of osteoblasts from mesenchymal progenitors, which also originate chondrocytes, myoblasts, from adipocytes, and tendon cells, requires the activity of specific transcription factors that are expressed at distinct time points during the differentiation process, thereby defining various developmental stages of the osteoblast lineage.

Runt domain-containing transcription factor (*Runx2*) is a master switch for osteoblast differentiation. Levels of Runx2 gradually increase in subsequent stages of osteoblast differentiation, with maximum expression observed in the mature osteoblasts. Homozygous deletion of Runx2 in mice resulted in a complete lack of osteoblasts [7]. Runx2 is both necessary and sufficient for mesenchymal cell differentiation toward the osteoblast lineage [8]. It was demonstrated that Runx2 controls bone lineage cells by binding to the Runx regulatory element in promoters of osteoblastogenic genes. Runx2 target genes include genes expressed by both immature and differentiated osteoblasts. Such as TGF-β receptor, ALP, collagen type I alpha 1 and alpha 2 chain, OPN, OSTC, Vitamin D receptor, BSP, ON, and collagenase [9]. Thus, Runx2 is necessary for both osteoblast differentiation and function.

Osterix is another DNA-binding transcription factor that is absolutely required for osteoblast differentiation. Osterix/SP7 is a member of the zinc-finger-containing SP family and is abundantly expressed throughout osteoblast differentiation. Genetic inactivation of Osterix in mice results in the absence of mineralized bone matrix, defective osteoblasts, and perinatal lethality [10]. Similar to Runx2, forced expression of Osterix in non-bone cells, promotes expression of both early and late marker genes of osteoblasts. However, molecular and genetic studies revealed that Runx2 is expressed in mesenchymal tissues of Osterix null mice [10]. Thus, Osterix acts downstream of Runx2 in the transcriptional cascade of osteoblast differentiation. Consistently, Osterix expression is positively regulated by direct binding of Runx2 to a responsive element in the promoter of the Osterix gene.

Activating Transcription Factor 4 (*ATF4*), a member of the basic Leu zipper family of transcription factors, has important roles in the more mature osteoblast lineage cells. Misregulation of ATF4 activity has been linked with the skeletal abnormalities seen in human patients with Coffin–Lowry syndrome and neurofibromatosis type I [11]. ATF4 may function in osteoblast lineage cells through two distinct mechanisms. First, it directly regulates the expression of OSTC and RANKL [11]. Second, ATF4 promotes efficient

amino acid import to ensure proper protein synthesis by osteoblasts [11].

Activator Protein 1 transcription factor family (*AP1*) is composed of heterodimers of Fos-related factors (cFos, Fra1, Fra2, and FosB) and Jun proteins (cJun, JunB and JunD). Multiple Fos and Jun proteins are highly expressed in proliferating osteoprogenitors. Their expression decreases during differentiation, except for Fra2 and JunD that are the primary AP1 components present in mature osteoblasts [12]. Some observations indicated that c-Fos [12], Fra1, ΔFosB (an alternative splice variant of FosB) [12], and JunB [13] proteins promote bone formation. In contrast, JunD promotes a decrease in bone mass repressing other AP1 protein expressions in osteoblasts [14]. A number of direct targets of AP1 in osteoblasts have been identified, and include the OSTC, collagenase-3, BSP, and ALP promoters [12].

1.1.3 Regulation of Osteoblast Differentiation by Secreted Molecules

Skeletal cells produce numerous growth factors and cytokines that signal in both autocrine and paracrine way to control cell proliferation, differentiation, and survival. These secreted factors and signaling pathways either promote or suppress the expression of transcription factors essential for osteoblast differentiation.

Transforming Growth Factor-β (*TGF-β*) is one of the most abundant cytokines in bone matrix and plays a major role in development and maintenance of the skeleton, affecting both cartilage and bone metabolism [15]. By binding to its specific receptors, TGF-β induces activation of Smad-2 and Smad-3 intracellular proteins that transduce extracellular signals from TGF-β to the nucleus, regulating osteoblast gene expression [16]. TGF-β is important in the maintenance and expansion of the mesenchymal stem/progenitor cells. TGF-β signaling also promotes osteoprogenitor proliferation, early differentiation and commitment to the osteoblastic lineage through the Smad2/3 pathways, and the cooperation between TGF-β and PTH, Wnt, BMP, as well as FGF signaling.

Bone morphogenetic proteins (*BMPs*) belonging to the TGF-β superfamily were originally identified as the active components in bone extracts capable of inducing ectopic bone formation. BMPs are expressed in skeletal tissue and are required for skeletal development and maintenance of adult bone homeostasis and play an important role in fracture healing [17]. Genetic studies have demonstrated an important role for BMP2 and BMP4 in promoting osteoblast differentiation and function [18]. Recent studies have also shown that BMP3 inhibits the signal transduced by BMP2 or BMP4 [19], working as a negative regulator of osteoblast differentiation.

The Wingless (Wnt) family of glycoproteins has recently emerged as central regulators of bone mass. Upon engaging various membrane receptors, Wnt ligands activate numerous intracellular pathways that are either dependent or independent on β-catenin. In the β-catenin-dependent signaling, Wnt binds to Frizzled receptors and their co-receptors low-density lipoprotein receptor-related protein 5 or 6 (LRP5/6) to stabilize cytosolic β-catenin that enters the nucleus and stimulates the transcription of Wnt target genes such as Runx2 and Osterix [20]. Thus, activation of the canonical pathway promotes the differentiation of osteoblast progenitor cells into mature osteoblasts. Wnt signaling is tightly regulated by a delicate balance of extracellular agonists and antagonists. There are different antagonists, such as soluble frizzled-related proteins (sFRPs), which inhibit Wnt signaling by binding to and sequestering Wnt ligands and others belonging to the Dickkopf (DKK), family members or the SOST gene product (sclerostin) that bind to and sequester the Wnt co-receptors LRP5/6 [21]. In human, receptor mutations that render Wnt signal constitutively active result in a generalized increase in bone mass [22]. Loss-of-function mutations in the gene encoding the Wnt co-receptor LRP5 cause osteoporosis-pseudoglioma syndrome [23], a form of juvenile-onset osteoporosis. Conversely, mutations in LRP5 that inhibit the interaction between the co-receptor

and DKK1 or sclerostin cause high-bone mass syndrome [24, 25]. In addition, loss-of-function or loss-of-expression mutations in SOST result in the bone-thickening diseases, sclerosteosis or Van Buchem disease, respectively [26, 27]. β-catenin-independent Wnt signaling has also been implicated in promoting osteoblast differentiation [28]. In particular, Wnt5A is thought to promote osteoblast differentiation by inhibiting the activation of adipogenic genes [29]. Thus, both β-catenin-dependent and β-catenin-independent Wnt signaling are able to control differentiation of osteoblast progenitors into mature osteoblasts.

Fibroblast Growth Factors (FGFs) are a large family of proteins (23 different ligands) that transduce their signal through one of the four FGF receptors (FGFR). FGFs initiate condensation of the mesenchyme and proliferation of progenitor cells. In particular, FGF2 is important for preosteoblast proliferation and maturation [30], while FGF18 is essential in mature osteoblast formation [31].

1.2 Osteocytes

Osteocytes account for about 95 % of cells in the mature bone tissue. They are entombed individually in lacunae of the mineralized matrix and have cytoplasmic processes that radiate from the cell body and give osteocytes the aspect of neuronal cells. The processes run along canaliculi and are linked by gap junctions with the processes of neighboring osteocytes, as well as with cellular elements of the bone marrow, endothelial cells of the bone marrow, and bone surface cells including the lining cells. In contrast to osteoclasts and osteoblasts, which are relatively short-lived and transiently present only on a small fraction of the bone surface, osteocytes are long-lived cells and are deployed throughout the skeleton.

Nowadays, osteocytes are considered the choreographers of the remodeling process. They are able to direct the homing of osteoclasts to the site that is in need of remodeling [32] and to control and modify mineralization of the matrix produced by osteoblasts [33]. Moreover, they produce factors that influence mineral homeostasis and also mediate the homeostatic adaptation of bone to mechanical loading. Osteocytes are considered mechanosensory cells because of their peculiar location in bone and complex dendritic network. It was demonstrated that osteocyte may sense load through the cell body, the dendritic processes and the cilia [34]. Moreover, it was demonstrated that 20 % of the osteocytes are active in bone formation [35] and that could surprisingly directly remove minerals from their lacunae and canaliculi, playing a role in mineral homeostasis during a calcium-demanding condition such as lactation [36]. Literature data also demonstrate the ability of osteocytes to negatively regulate osteoblast formation and activity through the secretion of sclerostin, a well known Wnt inhibitor [37]. Recently, the ability of osteocytes to influence osteoclast formation through the secretion of the osteoclastogenic cytokine RANKL was also showed [38].

1.2.1 Osteocyte Differentiation

It has been known that osteocytes are derived from osteoblasts. However, the precise mechanisms by which an osteoblast becomes an osteocyte remain elusive. At the end of the bone formation phase, osteoblasts can either become embedded in bone as osteocytes, become inactive osteoblasts or bone lining cells, or undergo programmed cell death (apoptosis) [39]. It remains unclear whether osteocyte formation is a process induced by a specific pattern of gene expression in a subset of osteoblasts and also whether this is a cell autonomous response rather than a response modulated via the surface cells receiving signals from already embedded osteocytes. It is also not known whether every osteoblast has equal possibilities of becoming an osteocyte or whether there are specific subpopulations with predefined fates.

Osteocytogenesis is now considered an active rather than a passive process that includes different changes in cellular features. The formation of dendritic processes and the reduction in

cytoplasmic volume take place in the embedding cell (Fig. 1.1). Generation of cell processes such as lamellipodia, pseudopodia, and dendrite formation is a dynamic event that required the cleavage of collagen and other matrix molecules [40]. Thus, the cell undergoes a dramatic transformation from a polygonal cell to a cell extending polarized dendrites toward the mineralizing front, which is followed by dendrites extending toward the vascular space or bone surface. Once embedded in bone, the osteocyte appears to maintain its polarity with regard to the directionality of its dendrites.

1.2.2 Osteocyte-Specific Genes

Within the past two decades, a lot of osteocyte markers have been identified. In particular, early embedding young osteocytes are high producers of E11/gp38 (also known as podoplanin), a protein that play an important role in dendrite formation (Fig. 1.1). In fact, it was demonstrated that conditional deletion in bone cells in vivo resulted in decreased canaliculi and increased trabecular bone [41]. Controversially, more mature, deeply embedded osteocytes express high levels of sclerostin, the protein product of the SOST gene [37] known to be a negative regulator of bone formation (Fig. 1.1). Mutation of SOST causes high bone mass in humans and deletion results in high bone mass in mice [42].

It was also demonstrated that as the osteoblast transitions to an osteocyte, ALP is reduced, and OSTC and casein kinase II, a serine/threonine protein kinase that controls the mineralization process, are elevated [41].

Several osteocyte-specific markers play critical roles in phosphate homeostasis. These include phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX), matrix extracellular phosphoglycoprotein (MEPE), dentin matrix protein 1 (DMP-1), and fibroblast growth factor 23 (FGF-23) [41] (Fig. 1.1). Autosomal recessive mutations in DMP-1 in humans provoke hypophosphatemic rickets. DMP-1-null mice have a similar phenotype to Hyp mice carrying a PHEX mutation that of osteomalacia and rickets owing to osteocyte elevated FGF-23 levels. Both DMP-1 and PHEX appear to down-regulate FGF-23 expression, which allows resorption of phosphate by the kidney, thereby maintaining sufficient circulating phosphate levels [43]. Thus, osteocyte network can function as an endocrine system, targeting distant organs such as kidney.

Moreover, osteocytes, under certain conditions such as lactation, can also express osteoclast markers such as tartrate-resistant acid phosphatase and cathepsin K, in order to remodel their perilacunar matrix [36].

1.2.3 Osteocyte Cytoskeletal Components

Cytoskeleton components and/or molecules involved with cell motility are expressed in a different way in osteocytes compared to osteoblasts. The previously cited E11/gp38 is thought to regulate actin cytoskeleton dynamics, and, in particular, it was suggested that it may play an important role in dendrite osteocyte formation. Moreover, osteocytes are also enriched with CapG and destrin molecules, all necessary for cytoskeletal rearrangement (Fig. 1.1). Differences in distribution of the actin-binding proteins, villin, fimbrin, filamin, and spectrin, have been demonstrated during osteocyte differentiation. An organized expression of tubulin, vimentin, and actin in cell bodies and dendrites of osteocytes, crucial to maintain osteocyte dendritic morphology, was also described [41].

Interestingly, an increase in dendritic processes number in the bone of adult rats compared with juvenile ones was also demonstrated, suggesting that the internal structure of compact bone changes with age [44].

1.3 Osteoclasts

Osteoclasts are terminally differentiated multinucleated cells that are the principal resorptive cells of bone, playing a central role in the

formation of the skeleton and regulation of its mass [45, 46]. The osteoclasts are usually found in contact with a calcified bone surface and within a lacuna (Howship's lacunae) that is the result of its own resorptive activity. The zone of contact with the bone is characterized by the presence of a ruffled border, which consists of complex folds of plasma membrane juxtaposed to bone and surrounded by the actin ring or sealing zone. The ruffled border and the sealing zone appear only in osteoclasts adherent to the mineralized matrix and in a resorptive state. The sealing zone is formed by a ring of focal points of adhesion (podosomes) with a core of actin and several cytoskeletal and regulatory proteins around it that attach the cell to the bone surface, thus sealing off the subosteoclastic bone-resorbing compartment. The attachment of the cell to the matrix is performed via integrin receptors, which bind to specific RGD (Arginine-Glycine-Aspartate) sequences found in matrix proteins, and the $\alpha v\beta 3$ is the integrin predominantly expressed by osteoclasts. The plasma membrane in the ruffled border area contains proteins that are also found at the limiting membrane of lysosomes and a specific type of electrogenic vacuolar proton ATPase involved in acidification. The basolateral plasma membrane of the osteoclast is specifically enriched with Na+, K+-ATPase, HCO_3^-/Cl^-, and Na+/H+ exchangers [47]. Lysosomal enzymes such as tartrate-resistant acid phosphatase and cathepsin K are secreted, via the ruffled border, into the extracellular bone-resorbing compartment and are involved in bone matrix digestion.

1.3.1 Osteoclast Differentiation

The osteoclast derives from cells in the mononuclear phagocyte lineage. Their differentiation requires the transcription factors PU-1 and MiTf at early stages, committing the precursors into the myeloid lineage. Macrophage colony-stimulating factor (MCSF) is then required to engage the cells in the monocyte lineage and ensure their proliferation and the expression of the RANK receptor. At that stage, the cells require

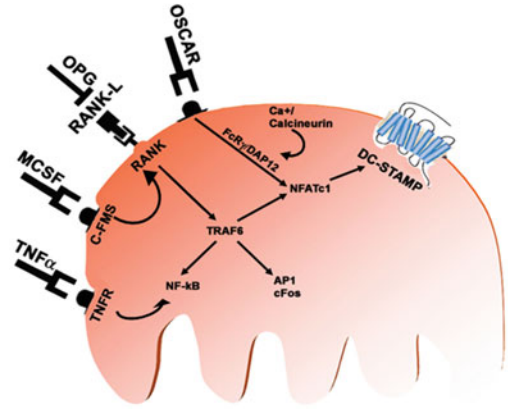

Fig. 1.2 Extracellular ligands, receptors, and intracellular signals activated during osteoclast differentiation

the presence of RANKL, a member of the TNF family of cytokines produced by stromal cells, to truly commit to the osteoclast lineage and progress in their differentiation program. This step also requires expression of TRAF6, NFκB, c-Fos, and NFATc1, all downstream effectors of RANK signaling (Fig. 1.2).

1.3.2 Essential Factors Regulating the Development of Osteoclasts

MCSF is a homodimeric glycoprotein, produced by osteoblasts and bone marrow stromal cells, that binds to high-affinity receptors (c-Fms) expressed on cells of the monocyte/macrophage lineage. Homozygous disruption of MCSF coding sequences in osteopetrotic (op/op) mice severely impairs production of macrophage populations underlying the importance of MCSF for their development [48].

OPG. In 1997, Simonet et al. [49] reported the discovery of OPG, a member of the TNF receptor family that inhibited bone resorption. Tsuda et al. in 1997 [50] independently isolated the same protein [called "osteoclastogenesis inhibitory factor (OCIF)"] as a heparin-binding protein from the conditioned media of human fibroblast cultures and showed that its cDNA sequence was identical to that of OPG [51]. The physiological roles of OPG have been studied in

OPG-deficient mice produced by targeted disruption of the gene: OPG knock-out mice were viable and fertile, but they exhibited severe osteoporosis caused by enhanced osteoclast formation and function. Moreover, destruction of growth plates and lack of trabecular bone with an increase in the number of osteoclasts were detected in long bones of these adult mice, and the strength and mineral density of their bones were dramatically decreased [52]. These results have indicated that OPG is a physiological regulator of osteoclast-mediated bone resorption during postnatal bone growth. The discovery of OPG led to understand which was the counterpart molecule acting to induce osteoclastogenesis. At the beginning, it was called osteoclast differentiation factor (ODF) or OPG-Ligand, since it was supposed to bind and block the activity of OPG; later, the molecular cloning of an isolated ODF/OPGL revealed that this molecule was identical to TRANCE (TNF-related activation induced cytokine) and RANKL, which were independently identified by other groups as a novel member of the TNF ligand family.

RANKL is a TNF superfamily cytokine and was originally identified as an activator of dendritic cells expressed by activated T cells [53]. Subsequent studies revealed RANKL to be a key cytokine for osteoclastogenesis [2, 54]. Targeted disruption of RANKL results in the defective formation of lymph nodes as well as severe osteopetrosis due to impaired formation of osteoclasts [55], indicating that this molecule is critical for both the immune and bone systems. The receptor for RANKL (RANK) is expressed in osteoclast precursor cells as well as in mature osteoclasts and dendritic cells. Targeted disruption of RANK also results in severe osteopetrosis [53], suggesting the RANK–RANKL interaction plays an essential role in osteoclast formation in vivo. OPG acts as a physiological inhibitor of RANKL [56], and the dynamic balance between RANKL and OPG regulates the levels of bone resorption.

The signals immediately activated by RANKL have been extensively studied. RANK contains three TRAF6-binding sites [57], and TRAF6-deficient mice exhibit severe osteopetrosis, indicating that TRAF6 is an essential mediator of RANK signaling during osteoclastogenesis. RANKL induces rapid activation of NF-kB, while such activation is severely abrogated in TRAF6-deficient cells [58]. NF-kB is a dimeric transcription factor complex composed of p65 (RelA), c-Rel, RelB, NF-kB1 (p50/p105), and NF-kB2 (p52/p100). Although *p50*- or *p52*-deficient mice have no obvious bone phenotype, mice doubly deficient in p50 and p52 develop osteopetrosis due to a defect in osteoclast differentiation, suggesting a critical role for NF-kB in osteoclastogenesis [59].

NFAT NF-kB and AP-1 are activated by RANKL. In the early phase and thus play an essential role in osteoclastogenesis, but these transcription factors are also activated by other cytokines, such as IL-1, which are not capable of inducing osteoclast differentiation *per se*. These observations suggested that RANKL had an as yet unknown target gene that is specifically linked to osteoclast differentiation.

In a genome-wide search for such genes was found that NFATc1 is the transcription factor most strongly induced by RANKL. The activation of NFAT is mediated by a specific phosphatase, Calcineurin, which is activated by calcium/calmodulin signaling. Accumulating evidence suggests that a number of osteoclast-specific genes are directly regulated by the transcription factor NFATc1 [60].

Ca^{2+}/CALMODULIN/CALCINEURIN. Involvement of NFATs directly implicates Ca^{2+} signaling in osteoclastogenesis since NFAT activation and subsequent nuclear translocation are directed by the Ca^{2+}/calmodulin-dependent serine/threonine phosphatase calcineurin [61]. RANKL activation of RANK induces a rise in cytosolic and nuclear Ca^{2+} [62]. Presumably, RANKL-stimulated elevation of intracellular Ca^{2+} exerts its downstream effects on osteoclast differentiation and function first by activating Ca^{2+}-binding proteins.

Since most Ca^{2+}-responsive proteins do not directly bind free Ca^{2+}, a cellular response to the intracellular Ca^{2+} signal first requires binding to an intermediary protein, which then in turn

transduces the signal into downstream effects. The most important of these Ca^{2+} transducers is Calmodulin, a highly conserved 17 kDa protein. Over 50 calmodulin-binding proteins have been identified including kinases and phosphatases, nitric-oxide synthase (NOS), numerous receptors, ion channels, G-coupled proteins, and transcription factors [63].

OSCAR, FcRγ, and DAP12. Despite the evident importance of the calcium–NFATc1 pathway, it remained unclear how RANKL specifically activates calcium signals leading to the induction of NFATc1, since RANK belongs to the TNF receptor family, which is not directly related to calcium signaling. The screening of osteoclast-specific genes has shed light on a novel type of receptor. Osteoclast-associated receptor (OSCAR) is an immunoglobulin-like receptor expressed by osteoclasts, which is involved in the cell–cell interaction between osteoblasts and osteoclasts [64]. OSCAR associates with an adaptor molecule, Fc receptor common γsubunit (FcRγ), which is required for the cell surface expression of OSCAR and its signal transduction [65]. FcRγ harbors an immunoreceptor tyrosine-based activation motif (ITAM), which is critical for the activation of calcium signaling in immune cells. Another ITAM-harboring adaptor, DNAX-activating protein 12 (DAP12), is also involved in the formation and function of osteoclasts. It is noteworthy that mice doubly deficient in FcRγ and DAP12 exhibit severe osteopetrosis owing to a differentiation blockade of osteoclasts, demonstrating that the immunoglobulin-like receptors associated with FcRγ and DAP12 are essential for osteoclastogenesis [65]. However, in the absence of RANKL, the stimulation of these receptors alone is unable to induce osteoclast differentiation, suggesting that these receptor-mediated signals act cooperatively with RANKL but cannot substitute for the signal.

TNFα. Inflammatory bone loss is a significant clinical component in rheumatoid arthritis (RA), periodontal disease, and orthopedic implant loosening, and in all of these cases, tumor necrosis factor alpha (TNFα) is implicated as a primary mediator. Thus, the effects of TNFα on osteoclasts differentiation, and bone resorption have been studied extensively. There is a strong consensus that TNFα and RANKL can act synergistically to induce osteoclastogenesis [66, 67], but it has been more controversial whether or not TNFα alone is sufficient. Furthermore, TNF-generated osteoclast do not resorb bone unless stimulated with IL-1β [68].

TNFα is a potent activator of classical NF-κB downstream of TNFR1. Due to the presence of a death domain in TNFR1, TNFα stimulates pro-apoptotic pathways in addition to the pro-survival pathways that are downstream of classical NF-κB. Thus, the addition of TNFα to osteoclasts or their precursors causes apoptosis only when classical NF-κB is blocked. Thus, NF-κB signaling downstream of TNFα supplies a strong survival signal to osteoclast lineage cells. TNF can also induce the expression of NFATc1, in a p50/p52-dependent manner, albeit at lower levels than RANKL [69], indicating a pro-differentiation role for TNFα as well.

DC-STAMP, a cell–cell fusion regulator, was isolated by a cDNA subtractive screen between osteoclasts and macrophages [70]. DC-STAMP is a seven-transmembrane protein and has been isolated from dendritic cells, IL-4-induced macrophages, and osteoclasts [71, 72]. Interestingly, although the expression of osteoclast differentiation markers was normal, multinucleation of osteoclasts was completely abrogated in DC-STAMP-deficient mice both in vivo and in vitro, indicating that DC-STAMP is specifically required for osteoclast cell–cell fusion rather than differentiation [70]. The absence of cell–cell fusion in osteoclasts resulted in the severe reduction in bone-resorbing activity, which in turn increased bone mass in DC-STAMP-deficient mice [70]. Thus, DC-STAMP plays a role in regulating bone-resorbing efficiency and physiological bone mass. Indeed, DC-STAMP-overexpressing transgenic (DC-STAMP Tg) mice showed accelerated osteoclast bone-resorbing activity and reduced bone mass. Interestingly, although DC-STAMP is not expressed in osteoblasts, osteoblastic activity is upregulated in

DC-STAMP-deficient mice, but it is downregulated in DC-STAMP Tg mice, suggesting that DC-STAMP likely regulates osteoblastic activity through osteoclast cell–cell fusion [73]. Thus, osteoclast cell–cell fusion might be critically involved in bone homeostasis.

Since the expression of DC-STAMP was regulated by NFATc1 [74], osteoclast cell–cell fusion was induced along with the differentiation of osteoclasts. In contrast to the positive regulators of osteoclastogenesis such as AP1 and NFATc1, the negative regulators of osteoclast differentiation have not been fully characterized.

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Bone Matrix Proteins and Mineralization Process

2

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2.1 Bone Matrix Proteins

Bone proteins represent a complex structural entity of organic component of bone extracellular matrix. These biomolecules will be discussed below, starting from collagenic component focusing on collagen type I, the most dominant collagen in bone. Non-collagenous proteins which in turn are divided into gamma-carboxyglutamic acid-containing proteins, glycoprotein, small integrinbinding ligand N-glycosylated proteins and other adhesive proteins containing the Arg-Gly-Asp (RGD) domain recognized by the cells via integrin receptors (Table 2.1), will be then described.

Collagen type I (*COLL-I*) includes approximately 90 % of the entire collagen content of bone and about 80 % of the total proteins present in bone [1]. Other types of collagen, such as types III and V, are present at low levels in bone and appear to modulate the fibril diameter. COLL-I is a member of the wide collagen superfamily which serves as the main source of mechanical strength in connective tissue and the template for matrix deposition and mineralization in the bone [2]. Normal structural and functional COLL-I production and deposition in extracellular matrix need regulation at several steps, and defective synthesis in bone can cause human osteogenesis imperfecta [3]. The collagen molecules are derived from the aggregation of three polypeptide "α" chains, which have the characteristic Gly-XY repeating triplet (in which Gly is glycine, and X and Y are often proline and hydroxyproline) [4]. After their synthesis, each α chain becomes intertwined with two other chains in a triple left-handed helical structure. In particular, COLL-I, initially synthesized as procollagen-soluble precursor, is composed of two α1 chains and one α2 chain containing three distinct domains: a central triple-helical collagenous domain, and N- and C-terminal propeptides. Assembled procollagen trimers undergo several posttranslational modifications including hydroxylation, glycosylation, addition of mannose at the propeptide termini, and formation of intra- and intermolecular covalent cross-links. With the hydroxylation, the chains form a "nucleus" at the C-terminus where they assemble into a triple helix in a zipper-like fashion. This nucleation and "zippering" process must be highly orchestrated and depend on precise alignment of all the chains [5]. When procollagen molecules are secreted into the extracellular spaces, they are converted to collagen by proteolytic cleavage of the N- and C-terminal

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Table 2.1 Bone matrix proteins

Protein	Function
Collagen type I	Serves as template for matrix deposition and mineralization; binds and orients other proteins that nucleate hydroxyapatite deposition
Gamma-carboxyglutamic acid-containing proteins(Gla proteins)	
Osteocalcin	Role in osteoclast recruitment and maturation; it is often used as a marker for the bone formation process; considered as a core of the cross-talk between bone remodeling and glucose metabolism
Matrix Gla protein	Inhibitor of calcification
Glycoproteins	
Osteonectin	Regulates calcium-mediated processes, cell–matrix interactions, hydroxyapatite binding sites, and bone remodeling
Alkaline phosphatase	Decreases the concentration of pyrophosphates (mineralization inhibitor) and increases the concentration of the inorganic phosphate (mineralization promoter)
Small integrin-binding ligand N-glycosylated protein (SIBLINGs)	
Osteopontin	Mediates attachment of bone cells to mineral crystal structure; regulates bone resorption and bone calcification and is active in immunological reactions, tumorigenesis, and angiogenesis
Bone sialoprotein	Binds to cells; promotes the initial formation of hydroxyapatite crystal; stimulates bone resorption by inducing osteoclastogenesis and osteoclast survival and decreasing osteoclast apoptosis
Dentin matrix protein 1	Presents in three distinct segments that control the mineralization; acts as a transcriptional factor for activation of osteoblast-specific genes
Matrix extracellular phosphoprotein	Predominantly expressed by osteocytes; involved in the regulation of both osteoblast and osteoclast activities during bone remodeling, biomineralization, regulation of PHEX (phosphaturic hormone) activity
Other RGD-containing proteins	
Fibronectin	Regulates mineralization binding to other matrix proteins such as collagen
Thrombospondins	Modulate cell–matrix interactions, bind to types I and V collagens; they are potent anti-angiogenic factors; TSP2 expression increases in preosteoblasts and decreases in mature osteoblasts
Vitronectin	Binds to collagen and to heparin and promotes cell attachment, spreading, and migration
Fibrillins	Confer limited elasticity to the bone matrix

propeptides. The mechanism through which the collagen molecules assemble into fibrils is due to their spontaneous alignment. These fibrils provide tensile strength to bone and are composed of collagen helices that assemble parallel to each other in a regular quarter-staggered pattern, creating 68-nm gaps between adjacent collagen molecules. Hydroxyapatite crystals fill these gaps and are responsible for the compressive strength of bone [6].

Importantly, during the process of bone resorption, operated by osteoclasts, the release of small collagen fragments containing hydroxyproline occurs; thus, they can be detected in body fluids as a parameter of bone resorption activity.

2.1.1 Non-collagenous Proteins

Non-collagenous proteins represent 10–15 % of the total bone protein content. These proteins are multifunctional, having roles in organizing the extracellular matrix, coordinating cell–matrix and mineral–matrix interactions, and regulating the mineralization process. This large family of proteins will be discussed below and divided into gamma-carboxy glutamic acid-containing proteins, glycoproteins, small integrin-binding ligand N-glycosylated proteins, and other adhesive proteins containing RGD domain.

2.1.2 Gamma-Carboxy Glutamic Acid-Containing Proteins (Gla Proteins)

These proteins are named after the observation that the vitamin K-dependent, Ca^{2+}-binding, γ-carboxyglutamic acid (Gla) amino acid is a constituent of their molecule. The Gla residues enhance calcium binding so that Gla proteins may function in the control of mineral deposition and remodeling [7]. They include osteocalcin, which is bone specific, and matrix Gla protein, which is also found in many connective tissues [8].

Osteocalcin (*OSTC*), a 6-kDa protein, is synthesized by the cells of the osteoblastic lineage; indeed, its expression has been considered as a marker of osteoblast differentiation in vitro.

OSTC is the second most abundant protein in the bone matrix, and it is highly conserved among all vertebrate species. The biological function of OSTC is probably related to the regulation of bone turnover and/or mineralization [9]. Osteocalcin-deficient mice are reported to have increased bone mineral density compared with normal mice[9], but with age, the mineral properties did not show the changes that occurred in age-matched controls, suggesting a role of OSTC in osteoclast recruitment and maturation [10, 11].

OSTC embedded in bone matrix is released during bone resorption as intact carboxylated molecules and fragments. In fact, part of OSTC, synthesized or derived from resorption activity, could be found in the blood. This circulating OSTC has been widely used in clinical investigations as a marker of bone formation, whereas protein expression as index of osteoblastic phenotype and bone formation in vitro [12]. Furthermore, serum OSTC levels are also considered as a marker of bone turnover rather than bone formation.

Circulating OSTC exists in two forms: carboxylated on 3 glutamate residues and undercarboxylated; recently, it is emerged that the latter form is able to enhance insulin secretion by β-cells, insulin sensitivity, and energy expenditure [13], suggesting that bone cells regulate energy metabolism through an endocrine mechanism and leading to the identification of OSTC, as a core of the cross-talk between bone remodeling and glucose metabolism [14].

Matrix Gla protein (*MGP*) is a small ubiquitous matrix protein containing carboxyglutamic acid, initially isolated from bone [15] but also found in all soft tissues. MGP shares many features with OSTC, but MGP and OSTC do not cross-react and they must be kept distinct [16]. It has been thought that MGP affects differentiation in developing cartilage and bone. In fact, some authors found that MGP overexpression in developing limb leads delayed chondrocyte maturation and blocked endochondral ossification [17]. Its mechanism as inhibitor of calcification is not fully understood, but studies in MPG-deficient mice demonstrated that they develop vascular calcifications and die [18].

2.1.3 Glycoproteins

Many glycosylated proteins with diverse functions are present in bone, and the most well-known among these proteins are osteonectin and alkaline phosphatase which will be examined below.

Osteonectin (*OSN*), the most abundant non-collagenous glycoprotein in bone, can bind to both collagen fibrils and hydroxyapatite. OSN concentration in bone matrix is variable and appears to be inversely correlated with the degree of calcification [19]. Although the role of OSN in bone needs to be better clarified, currently it has been recognized as a protein with a general multifactorial function with particular reference to the regulation of calcium-mediated processes, cell–matrix interactions, hydroxyapatite binding sites, and regulation of bone remodeling [20].

Alkaline phosphatase (*ALP*) is a member of a family of membrane-bound zinc metalloprotein enzymes that catalyze the splitting off a terminal phosphate group from an organic phosphate ester in an alkaline environment (pH 10) [21]. ALP is present not only on the cell membrane and in matrix vesicles, but also in the mineralizing matrices of cartilage and bone [22]. The isoform found in bone, the tissue non-specific alkaline phosphatase (TNAP), is surely decisive for the occurrence of a normal mineralization process as shown by the skeletal defects that develop in congenital hypophosphatasia and TNAP knockout mice. In both cases, in fact, bone is characterized by excessive amounts of osteoid tissue [23]. ALP promotes mineralization by decreasing the concentration of inorganic pyrophosphate, known inhibitor of mineralization, and increasing the concentration of the mineralization promoter, the inorganic phosphate (Pi). Recently, it has become recognized that pathologic calcification of the cardiovascular system follows an osteogenic mechanism [24, 25]. In all these models, expression of ALP is a key part of the process, and presumably acts similarly to its action in hard tissues, i.e., by decreasing the inhibitor of mineralization and increasing Pi levels, which promote mineralization process. In this regard, it has been shown that polyphenols, which are reputed to be cardioprotective, inhibit ALP activity in vascular smooth muscle cells, perhaps inhibiting artery calcification [26].

2.1.4 Small Integrin-Binding Ligand *N*-Glycosylated Protein (SIBLINGs)

Bone cells synthesize different proteins that may mediate cell attachment grouped as members of the small integrin-binding ligand, N-glycosylated protein (SIBLING) family. This family is constituted by osteopontin (OPN), bone sialoprotein (BSP), dentin matrix protein 1 (DMP1), and matrix extracellular phosphoprotein (MEPE). SIBLINGs are defined as small, soluble, and secreted proteins that can be localized through interactions with receptors either on the cell's own surface, enabling autocrine activities, or nearby in paracrine way. They display in their sequence a proline-rich stretch (basic), consensus sites for casein kinase, an arginine–glycine–aspartic acid (RGD) sequence, and (apart for BSP) one or several acidic serine–aspartate-rich MEPE-associated peptides (ASARM), which have a high affinity for hydroxyapatite and appear to be potent regulators of mineralization. RGD motif is the cell attachment consensus sequence that binds to the integrin class of cell surface molecules even if in some cases, cell attachment seems to be RGD independent. The SIBLINGs can engage a number of cell surface integrins. Although SIBLINGs were thought to be functionally restricted to mineralized tissues, recent results show that they are more widely distributed and expressed in non-mineralized normal tissues, upregulated in a number of tumors associated with pathological microcalcifications, and able to metastasize bone. Future investigations should validate the use of SIBLINGs as prominent molecular tools for diagnostic, prognostic, and therapeutic applications in cancer.

Osteopontin (*OPN*) is expressed in bone and bone marrow by mature osteoblasts and osteoclasts and their precursors, as well as by osteocytes. OPN expression is modulated during the various stages of differentiation. Relatively undifferentiated early-stage osteoblasts migrate to the resorbed bone surface and secrete matrix components such as OPN which is recognized

and bound by integrin on other activated osteoblasts (autocrine); here, OPN is immobilized onto preexisting mineral and/or organic moieties of the underlying bone and may act to initiate a new cycle of mineralization at this site. In this way, OPN has the function to mediate attachment of cells to mineral crystal structures; it has been demonstrated that OPN prevents both nucleation of mineral crystal formation and the growth of preexisting crystals [27, 28]. This inhibitory activity requires phosphorylated form of the protein. The production of the highly phosphorylated OPN is increased with osteoblast maturation. In addition to this, OPN may influence osteoclast activity during resorption [29]. The osteoclasts recognize OPN, adhere to the bone surface, and begin to resorb bone matrix. In many situations, OPN appears enriched in biological fluids, including blood, milk, urine, and seminal fluid having elevated levels of calcium; this is also indicative of a role in preventing spontaneous precipitation of calcium salts. Besides regulating bone resorption and bone calcification, OPN is active in diverse biological processes, such as wound healing, immunological reactions, tumorigenesis, atherosclerosis, and angiogenesis. In fact, some authors found that OPN acts as a potent constraining factor on hemopoietic stem cell proliferation, and its overexpression is a feature of hemopoietic malignancies, such as multiple myeloma and chronic myeloid leukemia, although its exact role in the aetiology and progression of these diseases remains unclear. Through osteoblasts and their cell surface, and expressed proteins, including OPN, bone is able to regulate the tissue that resides within it. In doing so, OPN can be considered a bridge between bone and blood [30].

Bone sialoprotein (*BSP*), which is a major non-collagenous extracellular matrix protein in bone, is produced by osteoclasts, osteoblasts, osteocytes, and hypertrophic chondrocytes and has long been identified as an early marker of osteogenic differentiation [31].

The Arg-Gly-Asp (*RGD*) sequence close to the carboxy-terminus of BSP protein is a cell attachment site recognized by $\alpha_v\beta_3$ integrin receptor, while polyglutamic acid regions in the amino-terminus mediate the binding of BSP to hydroxyapatite [32]. Although BSP expression has been shown to be coincident with de novo bone formation, substantial evidences suggested that BSP plays a role also in bone resorption. Some studies showed that BSP significantly stimulates bone resorption in a dose-dependent manner and this stimulation could be partially due to an increase in osteoclast adhesion to bone via its RGD sequence or its acidic sequences [33]. It is also conceivable that it is particularly involved in the process of osteoclastogenesis [34]. It has been suggested that BSP may contribute to the receptor activator of nuclear factor kappa-B ligand (RANKL)-mediated bone resorption by inducing osteoclastogenesis and osteoclast survival and decreasing osteoclast apoptosis. BSP levels are increased in patients affected by bone diseases with high bone remodeling, such as osteoporosis, hyperparathyroidism, Paget's disease, and rheumatoid arthritis, when compared with controls [35]. Furthermore, serum BSP concentrations are significantly higher in postmenopausal women than in premenopausal ones [36]. Numerous studies have suggested that BSP is also involved in the process of bone metastasis though the underlying mechanisms are not perfectly clear yet. There is a significant correlation between high BSP serum values and both the presence and the risk for the subsequent detection of bone metastases. Therefore, serum BSP could be considered as an early marker and a prognostic factor for the development of bone metastases.

Dental Matrix Protein 1 (*DMP1*) is a bone- and teeth-specific protein initially identified from mineralized dentin. Two proteolytic fragments, 37 kDa N-terminal and 57 kDa C-terminal, have been purified from rat long bone and dentin extracts, suggesting that these may be the bioactive forms in vivo. Additionally, the presence of a third chondroitin sulfate-linked N-terminal fragment (DMP1-PG) [37] has been demonstrated and recently correlated with an inhibition function in mineralization [38]. However, what is currently known is that both the highly phosphorylated 57-kDa and 37-kDa fragments could

act as hydroxyapatite nucleators [39]. In addition, the 57-kDa fragment contains almost all functional sequences and domains identified: the RGD motif, the nuclear localization signal, the ASARM peptide, and the peptide functioning as nucleator. DMP1 is a unique molecule that orchestrates mineralization of bone matrix and stimulates osteoblast differentiation during the later stages of their maturation [40]. DMP1 is primarily localized in the nuclear compartment of undifferentiated osteoblasts where it acts as a transcriptional factor for activation of osteoblast-specific genes, such as the osteocalcin gene. During the early phase of osteoblast maturation, Ca^{2+} surges into the nucleus from the cytoplasm, triggering the phosphorylation of DMP1 by a nuclear isoform of casein kinase II. This phosphorylated DMP1 is then exported into the extracellular matrix, where it regulates nucleation of hydroxyapatite. The importance of DMP1 in bone comes from studies in DMP1-null mice, in which it has been shown that vertebrae and long bones are shorter and wider with delayed and malformed secondary ossification centers and an irregular and highly expanded growth plate. Additionally, these mice unexpectedly develop a severe defect in cartilage formation during postnatal chondrogenesis and tooth mineralization defects [41, 42].

Matrix extracellular phosphoprotein (*MEPE*) is a protein predominantly expressed by osteocytes within mineralized bone. This protein is also expressed by differentiated osteoblasts, and its expression is markedly increased during matrix mineralization. Synthetic peptide fragment of MEPE, containing the RGD sequence and SGDG (Ser-Gly-Asp-Gly) glycosaminoglycan-attachment sequence, stimulates new bone formation in vitro and in vivo. MEPE is present in serum, and its levels correlate with bone mineral density and decrease in aged individuals when bone mineral density is low, suggesting a physiological role of MEPE in bone homeostasis [43]. MEPE protein is most likely cleaved by a cathepsin B-like protease to a highly phosphorylated C-terminal acidic serine and ASARM peptide in osteocytes. In vitro, it has been demonstrated that phosphorylated latter peptide inhibits osteoblast mineralization by binding to crystals in bone matrix, and the phosphorylation is necessary for the peptide affinity for crystals. ASARM peptides increase the expression of OPG, in bone marrow stromal cells [44]. MEPE might therefore be involved in the regulation of both osteoblast and osteoclast activities during bone remodeling. Furthermore, specific binding of MEPE to PHEX (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) regulates the degradation of MEPE and the release of ASARM peptides which play a role in phosphate regulation and inhibit mineralization [45] by binding to hydroxyapatite [46]. Because of these properties, MEPE has been considered a bone renal hormone [47].

2.1.5 Other Adhesive RGD-Containing Glycoproteins

Fibronectin (*FN*) is one of the most abundant glycoproteins produced during early stages of bone formation by osteoblasts and accumulated extracellularly at sites of osteogenesis. The molecule is characterized by specific binding sites for heparin and collagen, and FN-cell recognition occurs via integrin receptor.

In vitro studies have shown a key role for FN in the assembly of collagen [48], and it has been demonstrated that osteoblasts produce FN during their proliferation and differentiation at the same time of their collagen type I production [49]. It has also been shown that FN is not only needed during the initial steps of the collagen polymerization, but the continuous presence of FN is also required for matrix integrity [50], suggesting a complex role for this molecule in modulating bone matrix organization. Furthermore, FN may also regulate mineralization in bone [51] by binding to other matrix proteins and modulating their activities. Beside cell-derived FN, a soluble plasma FN has also been found in the bone matrix [52].

Thrombospondins (*TSPs*) are a small family of secreted modular glycoproteins constituted of five members. In bone is predominant TSP2 with

lower levels of other TSPs. In particular, TSP1 and TSP2 have the well-characterized ability to inhibit angiogenesis [53] in vivo, and the migration and proliferation of cultured microvascular endothelial cells (ECs), suggesting that they might regulate blood vessel formation in new bone.

TSP2 has been well investigated in bone, and it has been demonstrated that its expression increases in preosteoblasts when undergoing osteogenic differentiation and decreases as committed osteoblasts undergo terminal differentiation and mineralization. Studies on TSP2-null mice [54] showed increased cortical bone thickness due to enhanced endocortical bone formation. The increase in bone formation in TSP2-null mice is most likely due to higher number of osteoprogenitor cells in their bone marrow. In fact, when TSP2 is defective, proliferation of osteoprogenitor cells enhanced, resulting in an increased osteoblast numbers and bone formation [55]. The role of TSP1 in bone has not been examined as extensively as TSP2. TSP1 expression colocalizes with TSP2 in ossification centers of skull bones formed by intramembranous ossification. TSP1-null mice have no apparent defect in bone mass but show a mild lordotic curvature of the spine. Similar to TSP2, TSP1 expression is decreased in calvarial osteoblasts and long bones of mice overexpressing Fra-1, which is a critical gene for osteoblast differentiation. The role of TSP1 in osteogenic differentiation in vitro has been examined in preosteoblast cell lines and, rather surprisingly, shows the opposite effect of TSP2 [56].

Vitronectin (*VN*) is an RGD-containing protein found at low levels in mineralized matrix. VN is able to bind collagen by means of two functional groups: one adjacent to the RGD sequence and the other adjacent to the heparin-binding domain. It is anchored to the extracellular matrix and promotes cell adhesion, spreading, and migration by interaction with the integrins $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_1$, $\alpha_{IIb}\beta_3$, $\alpha_v\beta_6$, and $\alpha_v\beta_8$ [57]. Upon binding of VN, these integrins activate signaling pathways and regulate cytoskeletal reorganization, intracellular ion transport, lipid metabolism, and gene expression. However, the major VN receptor appears to be $\alpha_v\beta_3$, which is distributed broadly throughout bone tissue and expressed on mature osteoclasts, thereby contributing to the regulation of bone resorption. However, VN-null mice were found to be normal, suggesting that this protein is not so critical and its function can be replaced by alternative constituents of the extracellular matrix [58].

Fibrillins are essential glycoproteins for the formation of elastic fibers found in connective tissue. They are secreted into the extracellular matrix and become incorporated into the insoluble microfibrils. Human osteoblast-like cells in culture were shown to synthesize and secrete fibrillin-1 and fibrillin-2 and to deposit the glycoproteins into the matrix, visualized as a fine fibrillar network. Fibrillin-1 is present in the haversian canals, in the osteocyte lacunae, and in adult human trabecular bone. Fibrillin-containing microfibrils play an ongoing, structural role in mature bone; it has been demonstrated that they possess intrinsic elastic properties, and it is possible that they confer limited elasticity to the bone matrix. Mutations in these genes lead to Marfan's syndrome, which exhibits abnormalities in bone growth [59].

2.2 Mineralization Process

Biomineralization is the process that consists in mineral deposition in extracellular spaces [60]. In bone tissue, minerals are composed of hydroxyapatite [$Ca_{10}(PO_4)_6.(OH)_2$] crystals, made of calcium and phosphate ions (Ca^{2+} and PO_4^{3-}). Osteoblasts, which line the unmineralized organic portion of the bone matrix, synthesize bone protein components and regulate matrix mineralization by releasing small spherical bodies membrane-bound matrix vesicles (MVs), which concentrate calcium and phosphate and destroy inhibitors of mineralization process via an enzymatic way. MVs serve as protected microenvironments in which Ca^{2+} and PO_4^{3-}concentrations can increase sufficiently to precipitate crystal formation. In particular, Ca^{2+} enters into the MVs via an annexin channel, and

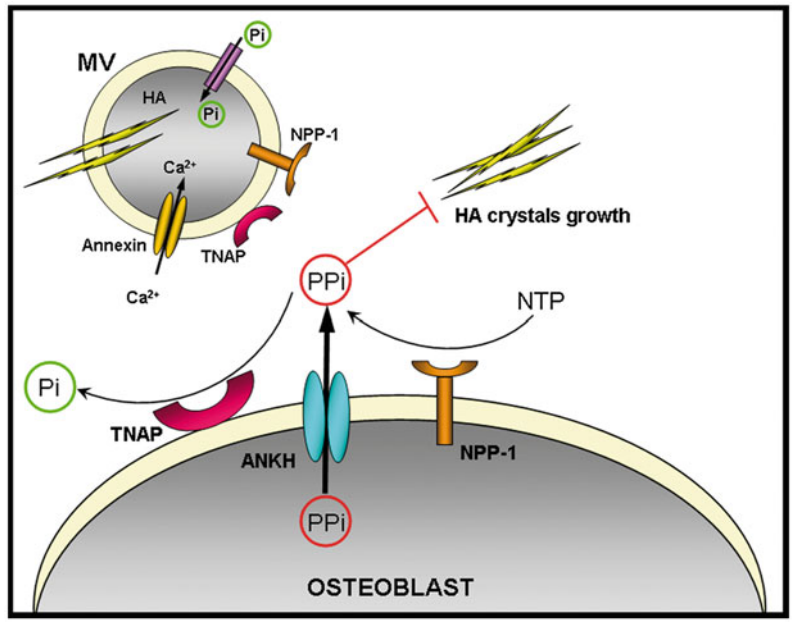

Fig. 2.1 Regulatory signaling pathways operated in controlling local Pi/PPi balance required for physiological bone mineralization. PPi: inorganic pyrophosphate; Pi: inorganic phosphate; NTP: nucleoside triphosphate; NPP1: nucleotide pyrophosphatase/phosphodiesterase 1; ANKH: pyrophosphate transporter; TNAP: tissue non-specific alkaline phosphatase: HA: hydroxyapatite; MV: matrix vesicle

phosphate enters via a Na^+-dependent phosphate transporter to form apatite crystals (Fig. 2.1). Acidic phospholipids and other MV components are thought to nucleate these intravesicular nanocrystals. It is currently believed that the role of MVs in initiating calcification is due to their capacity to regulate, via an enzymatic way, the ratio of inorganic phosphate (Pi) to pyrophosphate (PPi) in the extracellular fluid, while MV lipids and proteins constitute sites for apatite deposition. Inorganic pyrophosphate, which is the primary inhibitor of extracellular matrix mineralization, is formed by the enzymatic action of nucleotide pyrophosphatase/phosphodiesterase 1 (NPP1) and also transported through the membrane by a specific protein (ANKH) into extracellular space; NPP1 and ANKH are localized on the membrane of both MVs and osteoblasts. Moreover, MV membrane is enriched in tissue non-specific alkaline phosphatase (TNAP), which plays the crucial role of restricting the concentration of extracellular PPi to maintain a Pi/PPi ratio permissive for normal bone mineralization (Fig. 2.1). The biogenesis of MVs is still controversial. Some authors suppose that MVs arise by budding from specialized regions of osteoblast microvilli apical plasma membrane enriched in phosphatidyl serine that is important for calcium binding. MVs are surrounded by a lipid bilayer in association with hydroxyapatite crystals although the lipid composition is different from the plasma membrane which they originate. Once formed, MVs are released into extracellular matrix, and although the signals inducing this event are not completely clear, it seems that intracellular calcium and extracellular phosphate may be implied. Mineralization is believed to be a process characterized by an initial formation of hydroxyapatite crystals within MVs and their propagation through the membrane into the extracellular matrix [61]. In extracellular matrix, during early mineralization, apatite crystals become oriented so that their axes are parallel to the collagen fiber axis. It has been thought that small crystals can enter the fibrils probably via the “hole” zones and fibrillar pores, and they further propagate within the fibrils to fill all

available space, resulting in a flexing of collagen molecules away from the fiber axis [62]. Different bone matrix proteins, such as dentin matrix protein 1, bone sialoprotein, and type I collagen, critically contribute to mineralization process. In fact, they may facilitate initial crystal nucleation, sequester mineral ions to increase local concentrations of calcium and/or phosphorus, or facilitate heterogeneous nucleation. Macromolecules also bind to growing crystal surfaces to determine the size, shape, and number of crystals formed. In addition to local factors, systemic molecules play a critical role in regulating mineralization of bone matrix and principal among these is vitamin D important in coordinating calcium and phosphate homeostasis and stimulating osteoblast differentiation and activity [63]. Recently, a vitamin D counter-regulatory hormone, FGF23 [64], has been shown to affect mineralization. Studies in animal models and in cell cultures suggest that excess of FGF23 can negatively affect bone mineralization as a consequence of low phosphorus and vitamin D values (186-175), whereas FGF23 deficiency results in severe hyperphosphatemia, hypervitaminosis D, increased circulating calcium leading to a defective skeletal mineralization [65, 66].

Taking together all these data, we can argue that the process of bone matrix mineralization is very complex and under the control of many local and systemic players, many of which have been well studied, while others need to be better elucidated.

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Bone Remodeling

3

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3.1 Introduction

The skeleton is a relatively dynamic tissue that undergoes significant modifications throughout the life. Its formation starts at the fetal stage and evolves post-natally through modeling and remodeling processes that permit skeletal mass buildup and maintenance [1].

3.2 Bone Modeling

Bone modeling is a process that works in concert with organism growth altering the spatial distribution of bone in coordination with the other tissues [1]. During childhood and adolescence, the muscle mass grows very quickly, altering the load on skeleton that consequently changes its morphology and increases its mass. Therefore, during the body development, the skeleton follows a predetermined morphogenesis through which bone is selectively added or removed from surfaces, hence optimizing its geometry. Thus, modeling can alter the size, shape, and position of a typical long bone cross-section by selectively inhibiting or promoting cellular activity at the resorptive and appositional surfaces. Bone modeling at any surface involves osteoclast activation and subsequent resorption of bone, or it involves osteoblast activation and subsequent formation of bone, but not both at the same location. Once skeletal maturity is reached, bone modeling slows [1]. However, renewed modeling in the adult skeleton can occur in some disease states and in cases where the mechanical loading has been significantly increased.

3.3 Bone Remodeling

Remodeling removes and replaces bone throughout the human life. Bone remodeling is performed by clusters of osteoclasts and osteoblasts arranged as "basic multicellular units" (BMUs). An active BMU consists of a layer of mononuclear cells covering the remodeling area, followed by a group of bone-resorbing osteoclasts on one side, while on the other side, lines of osteoblasts operate bone formation [2]. This process takes place in a specialized structure, the bone remodeling compartment (BRC). The perimeter of this compartment is made up of flattened cells, displaying all the characteristics

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of the lining cells of bone. The BRC generates a unique microenvironment to facilitate "coupled" osteoclast resorption and osteoblast formation and ensures minimal change in bone volume during physiological bone remodeling [2]. The secretion of regulatory factors inside a confined space would facilitate local regulation of the remodeling process. This exclusive spatial and temporal arrangement of cells within the BRC is critical for bone remodeling, ensuring coordination of the distinct and sequential phases of this process: activation, resorption, reversal, formation, and termination.

Activation phase. Remodeling begins when bone cells are activated by local or systemic modulators, mechanical strain, or microcracks. It is thought that osteocyte apoptosis initiates bone remodeling [3]. In particular, under basal conditions, osteocytes secrete transforming growth factor-β (TGF-β), which inhibits osteoclastogenesis. Focal osteocyte apoptosis lowers local TGF-β levels, removing the inhibitory osteoclastogenesis signals and allowing osteoclast formation to proceed [4].

Resorption Phase. Bone-lining cells and osteoblasts respond to parathyroid hormone (PTH) or to signals generated by osteocytes, recruiting osteoclast precursors and promoting osteoclastogenesis into the remodeling site. The activated osteoblasts recruit osteoclast precursors, producing the chemokine monocyte chemoattractant protein-1 (MCP-1) [5], and promote osteoclastogenesis secreting macrophage colony-stimulating factor (MCSF) and receptor activator of nuclear factor kappa ligand (RANKL) [6]. Additionally, in osteoblasts, the expression of osteoprotegerin (OPG), which is an inhibitor of osteoclast formation and activity, is reduced, thus further supporting osteoclastogenesis [6]. The osteoclasts attach to the mineralized bone surface and initiate resorption by the secretion of hydrogen ions and proteolytic enzymes, which can degrade all the bone matrix components. The resorption phase ends in about 3 days with activation of apoptotic pathways that destroy osteoclasts, liberating the remodeling area from the resorbing cells. Signals for osteoclast apoptosis are numerous and include the Fas/Fas ligand system, which is mainly activated by sex hormones [7].

Reversal Phase. Following osteoclast-mediated resorption, the irregular scalloped cavities on bone surface (Howship's lacunae) remain covered with residual undigested collagen matrix [8]; consequently, macrophage-like mononuclear cells cover it. They remove the collagen remnants and prepare the bone surface for subsequent osteoblast-mediated bone formation. The reversal phase lasts about 14 days [9].

Formation Phase. Bone formation is a slow phase, and it takes 3–4 months and completes the remodeling cycle by fully replacing the removed bone with new osteoid that finally mineralizes [9]. During this phase, mesenchymal stem cells are recruited to sites of bone resorption and differentiate toward the osteoblast lineage. The mechanisms involved in the recruitment of osteoblast precursors at the bone formation site and inducing their maturation remain controversial. It was proposed that molecules stored in the bone matrix and liberated during bone resorption, such as bone morphogenetic proteins (BMPs), TGF-β, insulin-like growth factors I and II (IGF-I and -II), could be key signals for recruitment of mesenchymal stem cells to sites of bone resorption [10]. Osteoblast formation could also be indirectly sustained by mechanical strain and PTH signaling, thus suppressing osteocyte expression of sclerostin [11], an osteoblastogenesis inhibitor.

Termination Phase. When an equal quantity of resorbed bone has been replaced by new mineralized matrix, the remodeling cycle concludes. The termination signal(s) that inform the remodeling machinery to stop work are unknown, although osteocyte involvement is emerging [10]. The drop in sclerostin level likely returns toward the end of the remodeling cycle. Once the mineralization is completed, mature osteoblasts can undergo apoptosis, revert back to a bone-lining phenotype or become embedded in the mineralized matrix, and differentiate into osteocytes. The resting bone surface environment is reestablished and maintained until the next wave of remodeling is initiated.

3.4 Bone Formation/Resorption Process During Life and Its Regulation

Bone remodeling differently works in the distinct life phases [12] (Fig. 3.1). In childhood and adolescence, when bone modeling also operates, the rate of formation predominates that of resorption, leading to an outstanding increase in bone mass. In adolescence, pubertal surges of gonadal steroids, growth hormone (GH), and loading are considered critical for the increase in bone mass; this enhance in bone mass is followed by a further slower increase and consolidation of skeletal mineral content until the peak bone mass is achieved at around age 25–35 years and it is higher in men than in women. The achievement of the peak bone mass is fundamental [12]. In particular, it has been demonstrated that lower peak bone density at 25–35 years of age also contributes to risk of osteoporosis and fractures later in life. Several factors regulate peak bone density, including systemic and local factors, dietary intake of specific nutrients, daily mechanical usage, physical activity, and genetic determinants. In adulthood, the activity of bone cells in each remodeling unit is balanced—resorption equals formation—with about 1–2 million active remodeling sites at any time point. In a normal young adult, about 30 % of the total skeletal mass is renewed every year [9]. However, in both sexes, bone loss occurs when resorption exceeds formation (high bone turnover), generally at around age 40, with women losing bone mass more rapidly. After 60 years of age, the rate of bone loss slows but continues for the rest of life. In contrast, men have slower age-related bone loss. In both genders, the age-related reduction in bone mass is due to multiple factors including defective aging osteoblasts, impairment of the GH/IGFs axis, disuse, and increased PTH secretion [12].

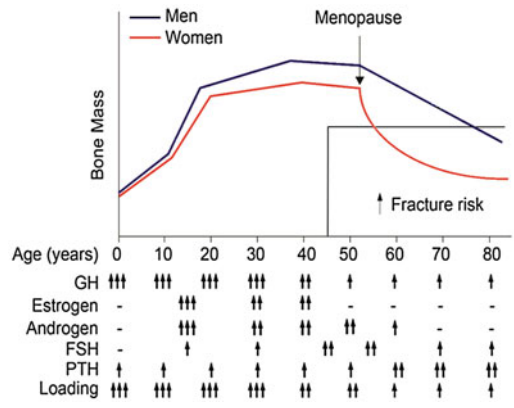

Fig. 3.1 Regulation of bone mass with age in both sexes by growth hormone (GH), estrogen, androgen, FSH, parathyroid hormone (PTH), and loading. The increase in fracture risk is earlier in women than in men, and it is associated with both the higher level of FSH in peri- and post-menopause, and estrogen withdrawal

3.4.1 Growth Hormone

GH, secreted by the anterior pituitary, plays a major role in post-natal longitudinal bone growth owing to its ability to stimulate precursor cells in the epiphyseal cartilage [13]. This hormone also affects the mature skeleton by bone remodeling modulation [13]. These effects are mediated both directly through GH receptor and indirectly by the growth-promoting polypeptides, IGF-I and IGF-II [13]. IGF-I is synthesized mainly in the liver and the majority of it circulates to exert an endocrine action. It is also expressed by bone cells, acting as an autocrine–paracrine factor. Using different mouse models, it has been established that circulating IGF-I plays a pivotal role in the acquisition of bone mass [13]. GH acts on osteoblasts both directly or through IGFs, stimulating the proliferation as well as the synthesis of bone matrix proteins [14, 15]. GH also enhances osteoclastic activity by increasing local IGF-1 production by bone marrow stromal cells [16]. IGF-I, in turn, promotes bone resorption both directly and indirectly. In particular, osteoclasts possess IGF-I receptors [17], which mediate the direct effects of IGF-I. IGF-I also alters the RANKL/OPG ratio [18] in favor of osteoclastogenesis, decreasing OPG synthesis and increasing RANKL expression [18]. GH affects calcium metabolism by rising the levels of 1,25-OH-

vitamin D, through the increase in PTH and IGF-I [13]. The importance of the GH/IGF axis arises from the demonstration that its perturbation has been implicated in growth defects as well as in the pathogenesis of osteoporosis [13]. In particular, several studies have reported reduced circulating levels of IGF in osteoporotic women [13]. Aging is associated with a decrease in the amplitude and frequency of GH production, ultimately leading to a reduction in hepatic IGF-1 synthesis [13].

3.4.2 Sex Steroid

The sex steroid hormones estrogen and androgen are powerful regulators of bone remodeling. They influence positively the growth, maturation, and preservation of the female and male skeletons. In particular, skeletal size and volume are similar in prepubertal girls and boys [19]. However, gender differences in bone growth become apparent during puberty, with men reaching higher peak bone mass. In fact, the male skeleton is characterized by larger size and stronger bones. These skeletal gender differences are attributed to a stimulatory androgen action on periosteal bone formation in men [19]. In women, estrogen favors a greater endocortical apposition. Testosterone and estrogen are crucial determinants in the maintenance of bone mass integrity during adulthood. Indeed, in both genders, gonadal failure is the most important factor for the development of bone loss [19].

Estrogen effects on bone cells. To understand how the differential effects of estrogen on bone might occur and how estrogen might interact with other age-related processes, it is important to review the three fundamental effects on bone metabolism.

a. Estrogen inhibits the activation of bone remodeling and the initiation of new BMUs. In particular, withdrawal of estrogen is associated with increased apoptosis of osteocytes [20]. Recent studies show that serum estradiol levels are inversely associated with serum levels of sclerostin, the key inhibitor of Wnt signaling [21].
b. Estrogen affects osteoclast formation and life span. In particular, it decreases the production of bone-resorbing cytokines, such as interleukin-(IL)-1, IL-6, TNF-α, M-CSF, and prostaglandins by osteoblasts [22].

Estrogen suppresses the activity of mature osteoclasts by direct, receptor-mediated mechanisms [20]. The hormone normally suppresses RANKL production by osteoblasts as well as T- and B lymphocytes [23, 24] and increases OPG production by osteoblasts [25], so that its deficiency leads to an alteration in the RANKL/OPG ratio that favors bone resorption.

Estrogen also increases the production of TGF-β by osteoblast precursor cells [26]. TGF-β induces apoptosis of osteoclasts [27]. Estrogen decreases osteoclastogenesis blocking RANKL/M-CSF-induced activator protein-1-dependent transcription by reducing c-Jun activity [28]. It also promotes osteoclast and their precursors' apoptosis through the activation of Fas/Fas ligand signaling [7]. It favors expression of Fas ligand in osteoclasts and osteoblasts [22].

c. Finally, estrogen is clearly important for the maintenance of bone formation. The effects of estrogen on osteoblasts and their progenitors may be stage specific. In particular, estrogen reduces the self-renewal of early mesenchymal progenitors [29] and the commitment of precursor cells to osteoblast at the expense of adipocyte lineage [30] and prevents osteoblast apoptosis [22]. Estrogen has also been shown to enhance osteoblast differentiation, [22] although data are variable and seem to depend on the system used. Very recently, oxytocin, a neurohypophyseal hormone, has been proposed as estrogen mediator of osteoblast differentiation [31].

Androgen effects on bone cells. Androgens have potent effects on osteoblast formation, and those are differential whether they act on trabecular or periosteal bone. While androgens maintain trabecular bone mass and integrity, they favor periosteal bone formation in men [19]. At the cellular level, testosterone increases the life span of osteoblasts by decreasing apoptosis [32]. Furthermore, androgens stimulate the proliferation of osteoblast progenitors and the

differentiation of mature osteoblasts [32]. The molecular mechanisms of androgen action on bone cells are less well described than for estrogen. However, some evidence indicates that they favor osteoblast proliferation and differentiation by increasing TGF-β and responsiveness to FGF and IGF-II [32–34]. Androgens may also decrease osteoclast formation and bone resorption through increased production of OPG by osteoblasts [35]. The net result is that testosterone favors bone formation. Moreover, testosterone may influence different stages of osteoblast differentiation and may act on osteoblasts differently than estrogen at various skeletal localizations. This last aspect of testosterone on bone formation is also important for the skeletal sexual dimorphism [19].

3.4.3 Follicle-Stimulating Hormone

Follicle-stimulating hormone (FSH) has traditionally been identified with ovarian folliculogenesis and estrogen production. However, it is now known that the peri- and post-menopausal spike in FSH stimulates osteoclastogenesis and bone resorption [36]. During the late peri-menopause, even before estrogen has declined, FSH levels increase. Accompanying this rise, there occurs a quick elevation in the markers of bone resorption and an increase in trabecular damage that deteriorates bone and increases fracture risk [37]. Approximately half of the bone loss over a typical woman's lifetime occurs within the first five years of menopause. Interestingly, much of this loss occurs before significant estrogen declines [37]. The demonstration that FSH effects occurred independently of estrogen came from the finding that haploinsufficiency of FSH in mice resulted in a high bone mass; this increase occurs even though these mice have normal levels of estrogen. FSH stimulates osteoclast formation from its precursors in the presence of RANKL through the Gi2α-coupled FSH receptor, present on both precursors and mature osteoclasts [36]. FSH also stimulates monocytes to produce IL-1β, which in turn activates osteoclasts for bone resorption [37]. Furthermore, the hormone stimulates TNF-α production from the bone marrow precursor macrophages and granulocytes [38]. Likewise, FSH may be responsible for a surge in TNF-α produced in T cells during estrogen deficiency that contributes to bone loss.

3.4.4 Parathyroid Hormone

PTH is the principal regulator of calcium homeostasis and accordingly of bone remodeling since the skeleton represents the major reservoir/deposit of calcium. In response to hypocalcemia, parathyroid glands secret PTH, which acts on different peripheral targets in order to restore normocalcemia. It favors calcium release from bone increasing osteoclast activity. In kidneys, PTH promotes calcium resorption as well as activation of 1,25-OH-vitamin D, which enhances gut absorption of the ion. PTH activates the PTH1 receptor, leading to a wave of transcriptional responses that produce/modulate secretion of molecules exerting both catabolic and anabolic effects on bone. The PTH catabolic effect can both directly and indirectly activate the bone resorptive processes via the stimulation of osteoclast activity [6, 39]. Indeed, it raises the RANKL/OPG ratio by increasing RANKL production and decreasing OPG expression in osteoblasts, thus promoting indirectly osteoclast formation and activity [6]. It has been reported that MCP-1 can also mediate PTH catabolic effect through the recruitment of osteoclast precursors [5]. PTH exerts anabolic effects by direct and indirect mechanisms, resulting in higher bone mass, higher proliferation of bone marrow cells, and deeper extent of osteoblastic differentiation. Indeed, PTH directly enhances IGF-I synthesis by osteoblast [40] and attenuates the adipogenic effect of peroxisome proliferator-activated receptor-γ (PPARγ) favouring osteoblast differentiation [41]. PTH indirectly suppresses the expression of sclerostin, an inhibitor of the Wnt-β-catenin pathway responsible for osteoblastogenesis, thus leading to the increased osteoblast number and activity [42]. T cells expressing PTH1 receptor may be

involved in both anabolic and catabolic effects of PTH through CD40L, a surface molecule of activated T cells that induced CD40 signaling in stromal cells [43]. In particular, the deletion of CD40L on T cells blunts the catabolic activity of PTH in bone by decreasing bone marrow stromal cell number, RANKL/OPG production, and osteoclastogenesis, whereas the T cell–mediated anabolic effect of PTH involves Wnt signaling activation in osteoblasts. In the last years, drugs mimicking PTH anabolic effects have been developed and are used as therapeutic strategy in osteoporosis management.

3.4.5 Wnt/β-Catenin Signaling

Another pathway named Wnt signaling has recently emerged to be important for bone development, homeostasis, and regeneration. Studies with animal models have been shown that changes in Wnt signaling contribute to age-related bone loss [44], and mechanical loading upregulates Wnt signaling in mesenchymal stem cells [45], suggesting that the combination of reduced Wnt signaling and decreased mechanical stimulation with age may contribute to the age-related decline in bone formation. Wnt signaling comprises several ligands, receptors, and inhibitors with bone-specific functions [46]. Activation of Wnt/β-catenin signaling occurs upon binding of Wnt to the 7-transmembrane domain-spanning frizzled receptor and low-density lipoprotein receptor–related protein 4, 5, and 6 (LRP4/5/6) co-receptors. This event prevents an intracellular protein complex consisting of Axin, GSK3ß, and APC from tagging ß-catenin for degradation [46]. As a result, ß-catenin accumulates in the cytosol and can translocate into the nucleus, where it interacts with Tcf/Lef transcription factors, leading to the expression of master genes for osteoblastogenesis. In particular, ß-catenin accumulation favors mesenchymal stem cell commitment for an osteogenic fate [47] and is needed to both promote early osteoblast proliferation and differentiation and suppress osteoclastogenesis [48].

There are several feedbacks which inhibit Wnt signaling, mediated by secreted molecules [46]. These soluble inhibitors include sclerostin, which antagonizes Wnt binding to LRP4-6 co-receptors, the Dickkopfs (Dkks), secreted frizzled-related proteins (sFrps), frizzled-related protein (Frzb), Wnt-1-induced secreted protein (WISE), Wnt inhibitory factor-1 and factor-2 (Wif-1, Wif-2) [46]. The secreted inhibitors, Dkk1 and sclerostin, are particularly interesting, as their increased expression has been demonstrated in many bone-associated diseases. In fact, they are targeted by therapeutic antibodies, which seem to be efficacious and safe in clinical settings.

Dkk1 suppresses Wnt signaling by forming a ternary complex with Lrp5/6 and Kremen (Krm)1/2 [49]. Transgenic mice expressing Dkk1 had fewer osteoblasts and severe osteopenia, whereas deletion of a single Dkk1 allele increased bone mass [49]. Dkk1 also switches mesenchymal stem cells to differentiate toward adipocytes. Moreover, Dkk1 affects the RANKL/OPG axis, in particular Dkk1 blockade leads to the overexpression of OPG [49]. On the contrary, Dkk1 treatment reduced the osteoblast expression of OPG and increased RANKL levels, thus promoting osteoclast formation [49].

The other key inhibitor, sclerostin, the product of SOST gene, is prominently produced by osteocytes embedded in newly formed bone [50]. Mutation or deletion of SOST leads to two rare bone sclerosing dysplasias, as sclerosteosis and van Buchem disease [50]. Sclerostin addition to osteogenic cultures inhibited proliferation and differentiation of mouse and human osteoblastic cells [50]. Moreover, sclerostin was shown to decrease the life span of osteoblasts by stimulating their apoptosis [50]. Mechanical loading decreased SOST mRNA and sclerostin levels, while unloading increased SOST mRNA expression in vivo. Interestingly, SOST knockout mice do not exhibit bone loss after unloading nor canonical Wnt signaling is altered [51]. Several systemic and local factors have been suggested as possible regulators of SOST/sclerostin expression by osteocytes. PTH has been shown to inhibit its expression both in vitro and

in vivo [42], whereas BMP2, BMP4, and BMP26 stimulate SOST expression in osteoblastic cells [50].

3.4.6 Bone Morphogenetic Proteins

BMPs are also important regulators of skeletal development and maintenance and are produced by osteoprogenitor cells, osteoblasts, chondrocytes, and platelets [52]. Several clinical studies demonstrated the efficacy of BMPs in accelerating bone regeneration and fracture healing [52]. The osteogenic potency of the BMPs requires a local and controlled delivery. Moreover, for clinical use of BMPs, their short half-life time should be taken into account. Several delivery systems have been developed to overcome this limitation. BMPs bind to receptor complexes and activate Smad and MAPK pathways, which upregulate the expression of Runx2 and Osterix, thus promoting osteoblastogenesis and bone formation [53]. However, BMP2-4 ligands direct osteoblasts to reduce bone mass via BMPR1A, in part by upregulating sclerostin expression and supporting osteoclastogenesis through the RANKL-OPG pathway. However, this occurs during embryonic bone development [54]. The activity of BMPs is locally regulated by a number of antagonists, which are also important for bone remodeling and may be potential therapeutic targets for osteoporosis. BMP antagonists can be subdivided into molecules that act extracellularly or intracellularly. Extracellular secreted polypeptides, including noggin, chordin, gremlin, twisted gastrulation, and so on, can inhibit the signals by binding BMPs, thereby preventing them to bind their receptors [52], whereas intracellular antagonists intervene with the activation of R-Smads and/or facilitate their proteasomal degradation.

3.4.7 Mechanical Forces

Mechanical loading has prominent influences on bone remodeling. Disuse or lack of loading causes an acceleration of bone turnover, with osteoclast resorption dominating osteoblast formation with the result of a substantial bone mass loss. Disuse of bone (low stress) causes reduced bone formation on periosteal surfaces and increased bone resorption and turnover on endocortical and trabecular surfaces. This type of bone loss has also been observed in astronauts who spend extended periods of time in the microgravity environment of a space station or shuttle. Also, the overuse of bone can increase bone turnover; in fact, the excessive load stimulates bone turnover whose role is to replace and repair damaged bone tissue and this event provides the involvement of osteoclasts which target regions of microdamage and remove compromised bone. The damaged tissue will be then replaced by new bone. If damage accumulates and bone cannot effectively be repaired, microcracks may develop and propagate to form a stress fracture. Overuse injuries are often classified as stress or fatigue fractures and occur as a result of microdamage accumulation and loss of bone stiffness and strength. Mechanical loading influences bone remodeling following a U-shaped curve: As mentioned before, an

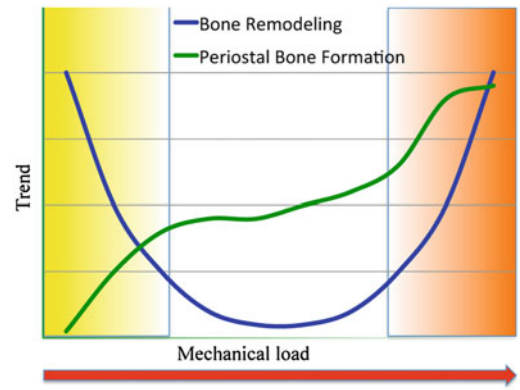

Fig. 3.2 Remodeling increases in states of disuse (*yellow*) and overuse (*orange*).A physiological window falls between the extreme loading conditions, in which bone turnover is low and bone mass is stable. Bone formation at the periosteal bone surfaces is also affected by mechanical loading, but the relationship is different. Periosteal bone formation is very low in states of disuse and increases with increasing mechanical stimulus partially offsetting the bone loss induced by the increased bone remodeling

increase in bone remodeling activity corresponds to a decrease in bone mass. Thus, the central part of the U represents the physiological range in which bone turnover is minimized. The unloading for disuse or microgravity as well as overloading are at the border of the U, indicating a bone remodeling increase. Periosteal bone formation, on the other hand, steadily enhances with increased loading, partially counteracting bone loss in overuse conditions (Fig. 3.2).

The increased bone turnover both in disuse and in overuse events is correlated with osteocyte apoptosis [55] and causes bone loss. The factors that initiate osteocyte death are not known yet but may include direct damage to osteocytes caused by microcracks in the bone matrix (overuse) or lack of convective fluid flow during disuse. However, the mechanical loading influences osteocyte biology. Osteocytes are the most numerous cells in bone. Their abundance and connectivity make them capable to sense the mechanical strains. Osteocytes communicate with the other bone cells and in particular with lining cells on the bone surface through an extensive network of cellular processes connected at gap junctions that allow intercellular cross-talk. Lining cells are ubiquitous on bone surface, and they contain gap junction connections to osteocytes and osteoblasts. Thus, mechanical loads can propagate from osteocytes to bone-lining cells and vice versa. Osteocytes do not respond directly to mechanical strain (deformation) of bone tissue, but sense the extracellular fluid flow variation caused by loading. Bone surfaces are mostly covered with lining cells that can potentially differentiate into mature osteoblasts 2 days after a mechanical stimulus [56] within other 2 days new bone matrix deposition can be observed [57]. Moreover, loading stimulates osteoblast precursor proliferation and differentiation. Mechanical forces also reduce programmed cell death in osteocytes [58] and in active osteoblasts [59], and then, loading may extend the rate of bone mineral matrix deposition for each osteoblast.

It is currently believed that when bones are loaded, the development of forces applied will drive the interstitial fluid surrounding the network of lamellar bone canaliculi, in which pass the osteocyte processes, to flow from regions under high pressure to regions under low pressure. Thus, the flow will get to the osteocyte lacunae, and the increased pressure in the lacunae should act as pumps pushing fluid all along the canaliculus web. This extracellular fluid flow and the interaction between this moving fluid and bone cells are the key to mechanotransduction. Fluid flow along cell bodies and processes produces drag force, fluid shear stress, and an electric potential called a streaming potential (or stress-generated potential). Each of these signals might activate bone cells, although cell culture experiments suggest that cells are more sensitive to fluid forces than they are to electric potential [60]. These signals are sensed by the osteocytes and are for them a strong stimulus to produce in sequence signaling molecules that can regulate osteoclast resorption activity and osteoblast bone formation leading bone remodeling to a new balance. [61]. In particular, the osteocytes can sense bone loading level [62] through their processes that are in contact with canalicular fluid. Osteocyte cell processes are directly attached to the canalicular wall via $\alpha v\beta 3$ integrin, [63] tensile forces acting on these integrin open stretch activated cation channels and induce prostaglandin E2 (PGE2) and nitric oxide (NO) production. The osteocyte secretion of PGE2 stimulates osteoblast bone formation, particularly in the cancellous bone site, while NO inhibits bone resorption. NO inhibits osteoclast activity and differentiation both by suppressing the expression of RANKL and by increasing OPG.

To better investigate the effect of mechanical load on bone cells, an in vitro model using pulsating fluid flow (PFF) has been realized [64]: PFF induces osteocyte secretion of cytokines inhibiting osteoblast proliferation and at the same time stimulating osteoblast differentiation and alkaline phosphatase activity. Moreover, osteocytes, in response to fluid flow, produce soluble factors affecting osteoclast differentiation and activity with the final result to impair bone resorption. The effect of PFF, which mimics mechanical loading, appeared to be

much more effective on osteocyte than on osteoblast. However, also the osteoblasts respond to mechanical stimuli secreting messengers such as prostaglandins and NO, but in bone tissue, they are much less than osteocytes and lining cells. Mechanical stimulus also affects osteoclasts, but this effect is indirect: In fact, loading increases strain also within the bone marrow where are bone marrow stromal cells that as a result of pressure would modify cytokine secretion inhibiting osteoclast differentiation. Hence, when are exposed to strain, bone marrow stromal cells would reduce RANKL expression, which in turn decreases osteoclast differentiation and activity [65]. The final effect of the mechanical loading on bone remodeling is mainly driven by the secretion of molecules produced by osteocytes and bone marrow stromal cells acting on osteoblasts and osteoclasts. Considering the close physical proximity of osteocytes to local osteoblasts and lining cells, it is highly plausible that soluble factors produced by osteocytes act in a paracrine manner on these cells. Therefore, soluble mediators may regulate the properties of neighboring bone cell populations influencing their proliferation and differentiation. Several local and circulating factors, regulating bone remodeling, might amplify or transduce the effects of mechanical loading; these include PTH [24], estrogen [20], sclerostin [51], and IGF-I/II [13].

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Biomechanics and Prosthetic Osseointegration

4

Oreste Moreschini and Simone Pelle

Arthroplasty is a surgical procedure oriented to provide pain-free motion to a joint maintaining stability and restore function to the periarticular soft tissues and muscles that control it. The operation of joint replacement is the result of many improvements in design of prosthesis components, the availability of suitable modern materials, better manufacturing procedure, and the deeper understanding of biomechanics.

The modern total joint replacement is defined by pioneering work of Sir John Charnley; in the 1960s, he paid his attention and study to the development of a total hip arthroplasty consisting of a stemmed stainless steel replacement for the femoral head articulating with a high-density polyethylene acetabular implant, fixed to bone by polymethylmethacrylate (PMMA) cement. Referring to Charnley's "low-friction" arthroplasty concepts, similar total joint designs were developed for most of the other major joints including the knee, ankle, shoulder, elbow, and wrist.

Many improvements in design, materials, and fixation techniques were obtained: modern well-implanted prostheses achieve very high success rates with patients satisfaction in short-term as well as in long-term follow-up. Basic knowledge of the biomechanics of the joints and of functional anatomy is required to surgeon in order to perform properly replacement, to manage the problems that may arise during and after operation, to select the prosthesis components with accuracy, and to suggest patients about physical activities.

4.1 Biomechanics

Orthopedic surgeons, who perform total joint arthroplasties, should be familiar with the functional anatomy and biomechanics, as well as with the function and design principles of the systems available in order to select the proper implant for patients and to achieve optimal functional outcomes.

4.2 Hip

Total hip arthroplasty is actually the most commonly performed surgical joint reconstruction in adult associated with longer implant survivorship.

Successful functional results and long survivorship of hip prostheses are related to respect of biomechanics and to attention of the force acting on the hip joint paid in preoperative planning and during reconstructive procedures.

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In order to describe, the body weight can be represented as a load applied to a lever arm extending from the body's center of gravity (in the midline anterior to the second sacral vertebral body) to the center of the femoral head. The action of abductor muscles operates on a lever arm extending from the abductor insertion on the tip of the greater trochanter to the center of the femoral head; when standing on one leg, it must express an equal moment to hold the pelvis level, and a greater moment to tilt the pelvis to the same side when walking [1].

The ratio of the length of the lever arm of the body weight to that of the abductor musculature approximates 2.5:1, in one-legged stance, the force of the abductor muscles must be about 2.5 times the body weight to maintain the pelvis level. In the stance phase of gait, the load on the femoral head is equal to the forces resulting by the abductors action and the body weight: It is more than 3 times the body weight, and the load on the head during straight leg raising is valued to be about the same. Contact forces across the hip joint during gait range from 3.5 to 5 times the body weight. The load may increase more than 10 times the body weight when running, or jumping [2].

Charnley recommendations for total hip arthroplasty were to shorten the lever arm of the body weight by deepening the acetabulum and to lengthen the lever arm of the abductor mechanism by reattaching the greater trochanter laterally. These techniques based on the original biomechanical principles are currently not relevant with modern prostheses; actual importance is addressed to subchondral pelvic bone preservation and to problems related to the greater trochanter synthesis. Several studies clinically demonstrate that the forces on the implant are lower when the prosthesis hip center was placed in the anatomical position; the ideal total hip replacement reproduces the original center of rotation of the femoral head.

High wear rate of joint surface, evidence of progressive radiolucency, and loosening of components are commonly observed when the hip rotation center was placed in a non-anatomical situation.

Three geometric factors determine the joint replacement with reproduction of rotation center: (a) vertical height (vertical offset), (b) medial offset (horizontal offset), and (c) femoral neck version (anterior offset). The vertical offset of the femoral head is the distance measured to the center of the head from the lesser trochanter; it is important to restore this parameter in order to correct leg length. The distance measured from the center of the femoral head to the femoral shaft axis is the medial offset (Fig. 4.1). This parameter influences strictly the moment arm of the abductor musculature and joint reaction force; reduction in medial offset results in shortening of abductors lever arm and in increased abductor demand and therefore increased loading force on the hip, a lengthening in offset produces high stress on the stem that may lead to fracture or loosening. Femoral neck version is the orientation of the neck in the coronal plane; normal value is 10–15° of anteversion of the neck; restoration of version angle is important in achieving prosthesis stability [3].

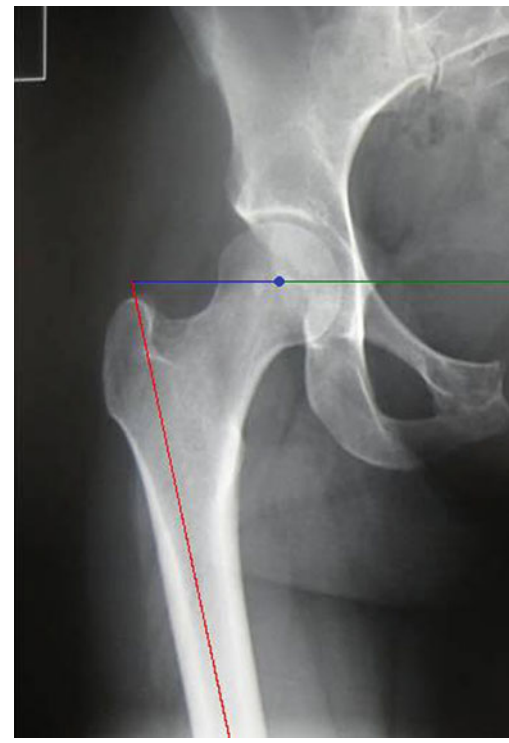

Fig. 4.1 Normal right hip X-ray: femoral shaft axis (*red line*), lateral offset (*blue line*), body weight lever arm (*green line*)

4.3 Knee

Knee motion is more complex than simple flexion and extension; it occurs in flexion and extension, abduction, and adduction, rotation about the long axis of the limb, with a rollback of femoral condyles during flexion [4]. The main factor in the short survivorship and early failure of many knee prosthesis designs should be referred to poor attention to these complex knee motions and their attendant complex stresses. Knee motion is determined by both the joint geometry of the knee and the ligamentous restraints; important evaluations are addressed to the role of posterior cruciate ligament (PCL) in total knee arthroplasty.

The arguments in favor of PCL retention are the greater potential range of motion with effective femoral rollback and the advantage of ligament's function as a restraint to translational displacement of the knee [5]. In PCL-substituting knee prostheses, displacement must be resisted by the prosthetic geometry, with resultant stress transferred to the bone–cement interface; it could suggest higher failure rates in PCL-substituting designs than in PCL-retaining implants because of aseptic loosening. Another argument in favor of PCL retention centers on preservation of PCL proprioceptive role; more physiological and symmetrical gait is observed in patients with PCL-retaining prostheses than with PCL-substituting designs. PCL sparing is also correlated to better function of the patellofemoral joint; PCL-retaining designs do not tolerate much variation in the level of the preoperative joint line while balancing the flexion and extension gaps. Joint line elevation may alter patellofemoral mechanics and result in knee pain and subluxation in postoperative period. Lower alterations are recorded in the relationship of the patella to the joint line with PCL-retaining prostheses. Compelling arguments support PCL substitution. Many authors argue that the PCL is diseased with various forms of contracture; it results in much more difficulties in ligamentous balance. It is unlikely to reproduce normal PCL strain and function in a PCL-retaining knee arthroplasty.

Obtaining a reliable balance of the PCL influences implant survivorship; a too tight PCL in flexion can limit postoperatively the extent of flexion and lead to excessive femoral rollback, which could accelerate posterior tibial polyethylene wear. On the contrary, a too loose PCL may not provide adequate femoral rollback during flexion. It is fundamental to underline the deleterious effect of excessive femoral rollback on component fixation. With knee motion and variation of the point of tibiofemoral, the tibial components alternately undergoes maximal compression anteriorly and posteriorly [6].

Polyethylene wear may be greater with PCL-retaining designs; the tibial articular surface of PCL-retaining implants must be less congruent to the femoral component in the sagittal plane in order to allow femoral rollback. This less-conforming geometry is responsible for higher tibial contact stresses in PCL-retaining prostheses; these could be responsible of accelerated polyethylene wear.

One more argument in favor of PCL substitution is that surgical exposure is simpler with PCL excision; significant deformities can be more easily corrected, especially in stiff knees.

Another factor, which affects knee arthroplasty survivorship, is the restoration of correct limb alignment; malalignment of total knee prostheses seems to be implicated in long-term complications, including tibiofemoral instability, patellofemoral instability, stiffness, accelerated polyethylene wear, and implant aseptic loosening. Normal anatomical axis of the femur and the tibia form a valgus angle of $6 \pm 2°$: Varus or valgus deformity can be determined on the antero-posterior roentgenogram. The mechanical axis of the lower limb is defined as the line on a standing long leg antero-posterior radiogram projecting from the center of the femoral head to the center of the talar dome. This mechanical axis typically projects through the center of the knee joint (neutral mechanical axis) (Fig. 4.2). The knee is in valgus alignment if mechanical axis lies to the lateral side of the knee center. In mechanical varus alignment, the

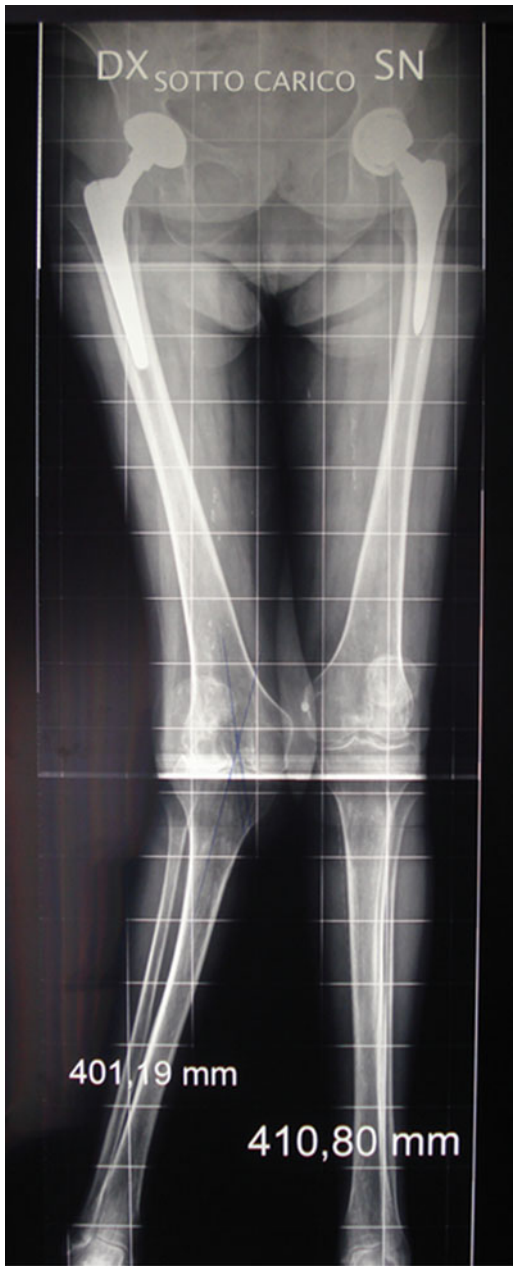

Fig. 4.2 Lower limbs radiograph showing severe right valgus knee deformity in a female patient who underwent bilateral total hip arthroplasty

mechanical axis of the limb lies to the medial side of the knee center.

In knee arthroplasty, the tibial components are implanted perpendicular to the mechanical axis of the tibia in the coronal plane, and the femoral component usually is implanted in 5–6° of valgus, in order to reestablish a neutral mechanical axis of the limb. The rotation of the femoral component influences not only the flexion space but also the patellofemoral tracking. [7]

The primary function of the patella is to increase the lever arm of the extensor mechanism of the knee, improving the efficiency of quadriceps contraction. The modern design of the trochlea in femoral components has been focused on the 1990s. In general, the trochleas have been deepened to resist patellar subluxation with greater areas of contact throughout the range of motion, and lateral flange of the trochlea has been made more prominent.

Patellofemoral stability is guaranteed by a combination of the articular surface geometry and soft tissue restraints. The Q-angle, described by Hvid, is the angle between the anatomical axis of the femur and the line between the center of the patella and the tibial tubercle. Knees with larger Q-angles have a greater tendency for lateral subluxation of patella. Lateral subluxation of the patella in early flexion is resisted primarily by the vastus medialis obliquus fibers because the patella does not contact strictly the trochlea. As the flexion increases, the trochlea and knee constraints play a dominant role in preventing subluxation.

Knee prostheses designs, as well as attention to components implant, reproduction of preoperative joint line height, have improved arthroplasties performances and have decreased significantly the rate of failure.

4.4 Tribology of Joint Prostheses

Tribology is defined as the science of interacting surfaces in relative motion and all effects related. The study of wear, friction, and lubrication belongs to tribology. Low friction, optimal motion, and good transmission of joint loads are important design objectives for prosthetic joints for different reasons. If large shear forces because of high friction are applied to the articular surfaces, the risk of loosening may

increase. Increased frictional shear results in stresses which damage surface; it can produce higher release of wear debris to the surrounding tissue that also increases the risk of loosening.

4.5 Friction

Friction arises from the interaction between moving solids in contact. The friction force is proportional to the load applied to the surface and the coefficient of friction.

The coefficient of friction is the measure of the resistance offered in moving one object over another. It is influenced by different factors: materials and finish of the surfaces of the materials, the load applied on surfaces, the temperature and presence of a fluid as a lubricant.

Normal joints have a coefficient of friction estimated as 0.008–0.02. Several studies demonstrated that the coefficient of friction produced by metal on high-density polyethylene is approximately 0.02, metal-on-metal joints approximately 0.8, and ceramic on ceramic and ceramic on polyethylene are also low [8]. Instead, metal on ceramic produces higher coefficient of friction.

A frictional torque force is produced when the artificial joint moves through an arc of motion. It depends on the frictional forces and by the distance a point on the joint surface moves during an arc of motion. The frictional forces are influenced by the coefficient of friction and the joint surface contact area [9]. Low coefficient of friction is a fundamental element in modern prostheses: Frictional forces are transmitted to the acetabular cup and the femoral stem, the cement–prosthesis or implant–bone interface as forces that lead to destabilize the components. Increasing in frictional torque force should be involved in loosening of prosthesis and in high wear rate.

4.6 Lubrication

Friction can be reduced by lubrication: Interposition of a fluid material between two contacting solids can minimize interaction between them. The extent of fluid film plays an important role in the wear process of artificial joints in vivo. The effectiveness of a lubricant film is defined by film thickness which is dependent on the viscosity of the lubricant, the relative velocity between surfaces, the pressure across the interface, and the surface roughness.

When the thickness of the fluid film is less than or equal to the average surface roughness of the articulating surfaces, boundary lubrication is achieved. This is not an ideal phase; the asperities of the articulating surfaces are in contact. It occurs in rough bearing surfaces, or as a result of third-body formation or protein deposition.

It is improved with better manufacture tolerances of the bearing surfaces. As the implant remain in situ and works, as the surface asperities decrease, as well thickness of the fluid film increases and the articulating surfaces become separated from each other.

The wettability of the material also plays a part in lubrication. This is essentially related to how hydrophobic or hydrophilic it is. The ceramics are the most wettable of the currently used bearings [10].

4.7 Wear

The wear can be defined as the loss of material from the surfaces of the prosthetic joint due to the motion; material is lost in particulate debris. Three types of wear are distinguished: (a) abrasive, the harder material produces furrows in the softer material; (b) adhesive, the softer material is transferred as a thin film onto the harder one, and (c) fatigue, in which repetitive loading produces subsurface cracks or sheets of material delaminated from the surface. The term "three-body wear" refers to a specific mechanism of abrasive wear caused by retention of debris particles between the sliding joint surfaces; these generate additional stress concentrations of the articulating surfaces [11].

Wear is actually considered one of the most significant factors limiting the longevity of total joints. The most important mechanism in total

hip arthroplasties is abrasive and adhesive wear; fatigue wear appears more important in total knee arthroplasties.

The wear is determined by several factors: (a) the coefficient of friction of the materials, (2) the hardness of the materials, (3) the applied load, (4) the sliding distance for each cycle, depending on joint range of motion, and (5) the number of cycles that occur over time [9].

Modern prostheses have very smooth articular surface, but they still present grooves and peaks. The size of the asperities depends on the material and the surface finishing. When the two surfaces slide initially against each other under load, many of asperities are removed, producing high initial wear rate referred to as the "wearing-in" period. The contact area surfaces gradually adapt to each other and the wear rate decreases, reaching a steady state.

Particulate wear debris produces concerning biological consequences which can lead to implant failures because of potential adverse tissue response. Particles consistent with polyethylene debris are routinely identified in the membranes surrounding failed joint replacements. Many authors demonstrated the relationship between the depth of socket wear and the incidence of prostheses components loosening and migration. It is proved that loosening of prosthesis components is the direct result of wear debris macrophage-induced bone resorption at the implant–bone interface [12].

Some knowledge of the characteristics of the various materials and their effects to bone mass is essential for the orthopedic surgeon performing total joint arthroplasties.

Materials properties employed in the manufacturing of bearing surface in joint prostheses have a paramount role in implant performance and survivorship. These include corrosion resistance, strength, ductility, hardness, and particularly frictional characteristics. Frictional characteristics are a result of material wettability, manufacturing variables such as surface finish, and operating conditions such as lubrication. Frictional forces depend on both the material composition and roughness, because both chemical and mechanical interactions may occur.

Osteolysis is a significant cause of aseptic loosening and is cause for the majority of revision surgery. It is due to resorption of bone observed around the prosthetic components. There is a relation between wear and debris formation; osteolysis is reported more commonly in patients with high wear of their implants. These increased osteoclasts activity is induced by immunological response to different debris [13].

There has long been interest in developing bearing materials that exhibit friction and wear behavior similar to that of articular cartilage. Cartilage is an excellent compliant bearing capable of large deformation without failure and low-friction coefficient in synovial joints, less than 0.01.

It appears more than mandatory for physician to have essential knowledge of bearing materials properties in prosthetic implant.

4.7.1 Polyethylene

Polyethylene wear is particularly recognized as a major element limiting the survivorship of arthroplasties; current researches about materials are directed toward strategies to reduce wear [14]. The physical properties of polyethylene affect its rate of wear; molecular weight is correlated with the wear resistance. Manufacturing and sterilization methods may influence molecular weight; oxidation of the polymer before implantation and in vivo contributes to reducing molecular weight. Future improvements in fabrication and sterilization processes may aid in reducing wear rate of polyethylene. Sterilization by autoclaving or by irradiation in the presence of oxygen produces free radicals in the material, exposing the polyethylene to oxidation and making it more susceptible to wear. Actually, polyethylene sterilization is carried out by gamma radiation in an inert environment, typically in nitrogen gas or vacuum [15].

Considerable interest is oriented actually on the improved wear characteristics of highly cross-linked polyethylene [16]. Despite continuing research improving implant materials, the

combination of metal articulating with ultrahigh molecular weight polyethylene (UHMWPE) remains the most commonly used.

It is a tough, extremely chemically inert plastic with good resistance to creep and no biological toxicity.

As mentioned before, the role that particulate polyethylene debris plays in the loosening of total joint prostheses is under increasing scrutiny. Polyethylene wear debris has been demonstrated in strict association with periprosthetic osteolysis around cementless components (Fig. 4.3). The predominant process of long-term prosthetic failure is related to the generation of particulate which causes an inflammatory reaction, osteoclasts stimulation, and subsequent bone resorption around the implant [12].

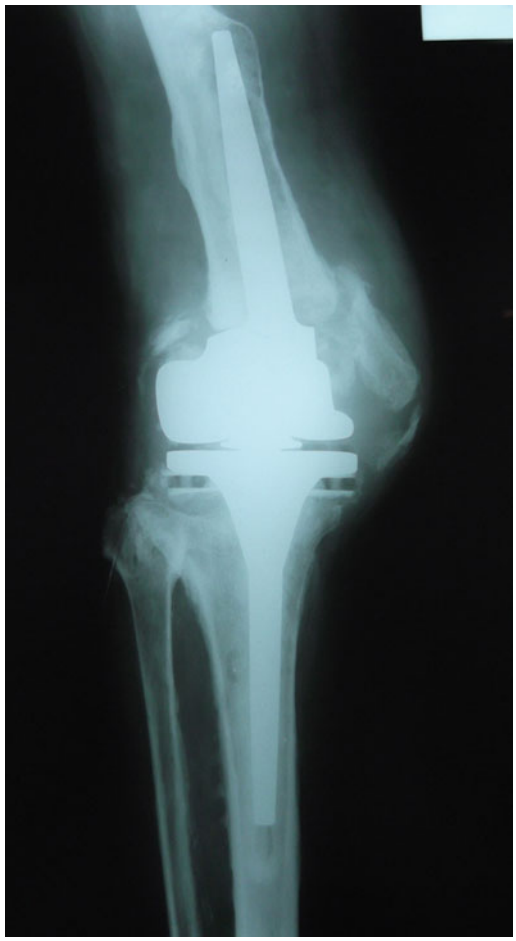

Fig. 4.3 Periprosthetic fracture associated with severe femoral and tibial osteolysis around stemmed knee prosthesis

Different generations of polyethylene debris have been revealed in knee prostheses than in the hip arthroplasties. Surface incongruity, variable loading line by the femoral component, and the greater third-body wear from debris formed in the concavities of the UHMWPE tibial component should be considered: It appears that knees produce larger particles than hips. In general, there is less tendency for the development of osteolysis around well-fixed knee implants than around well-fixed hip implants.

Despite these problems, polyethylene remains a good material for joint prostheses. It should not be replaced by any new polymer in the near future. However, improvements in the manufacturing, sterilization processes, and stockage of polyethylene are necessary to increase wear resistance and reduce particulate debris release and its consequences [17].

4.7.2 Metal

Alternative bearing materials are topics of current researches, including a return to metal-on-metal and ceramic-on-ceramic arthroplasties; perfect articular surfaces in joint prostheses have not been yet recognized. "Hard-on-hard" articulations, like metal on metal or ceramic on ceramic, are being explored as low-wear couples.

The crystal size of a metal is indicative of its quality; it is a major factor in determining fatigue resistance. In general, the smaller or finer the crystal size, the greater the strength and fatigue resistance [18]. Instead, the surface finish of metallic components may be altered by a different process: the oxidative wear (corrosion). Corrosion is a surface electrochemical process that may weaken an implant and also release substantial amounts of metal ions locally and systemically [19]. In fact, on metal surfaces, an oxide film is produced in saline environment of the body, joint motion removes and reforms repeatedly this film with gradual roughening of

the surface itself, weakness of metal structure and release of metallic ion.

Several authors attribute the loosening of implants to an allergic response to local concentrations of chromium, cobalt, or nickel ions [20]. Skin tests with the metal before implantation may have not value because the patient may become sensitized to it only after a local accumulation of metallic particles.

This should be considered particularly in metal-on-metal total hip arthroplasties; more metallic particles were produced by wear in these cases.

Additional concern is represented by long-term harmful effects of metals and the potential carcinogenic effects of metal ions. Some malignant tumors have been reported in the region of total hip arthroplasties were reported. It is unclear whether these tumors were coincidental or induced by some prosthesis material. Most of the tumors have been identified as malignant fibrous histiocytomas, but osteosarcoma also has been reported. Several authors have recorded higher incidence than normal of remote site tumors (leukemias, lymphomas) in patients receiving total joints arthroplasties [21]. However, no clear association between types of implant and incidence of neoplasms has been identified. Considering the great number of total joint replacements performed annually in the world, the tumors may well have been coincidental, but continued surveillance is justified.

4.7.3 Ceramics

In contrast of metal, ceramics are not susceptible to oxidative wear because alumina and zirconia already exist in an oxide stable state; they are chemically inert. In addition, ceramics are substantially harder than metals and therefore more resistant to scratching by third-body debris particles; ceramic heads in hip arthroplasties have shown no change in surface roughness or roundness of the implants. The surface finish of ceramics can be made very smooth: The coefficient of friction of aluminum oxide or zirconium oxide ceramic on itself or on polyethylene is lower than metal on polyethylene, and wear recorded is lower 3–16 times [22].

Even though the greater rigidity compared to metals make ceramics more susceptible to breakage; aluminum oxide ceramic materials are stiffer than metals and consequently do not tolerate non-uniform loading or impact. Malpositioning of a ceramic acetabular component may produce fracture of the ridge from contact with the neck of the femoral component, with production of ceramic debris [23]. Also, it is more demanding to implant ceramic component with perfect congruency; the combination of ceramic on ceramic unforgiven. Because of their stiffness, ceramic articular components cannot deform under load to produce congruency as polyethylene does; the result should reduce contact area and higher surface stresses.

4.8 Load Transfer to Bone, Stress Shielding, and Osseointegration

In addition to wear, the most frequent source of total joint failure is debonding of the implant–bone interface or adverse bone adaptation around the total joint. Because of the difference in material properties of the bone and the implant, an interface is created when the two materials are put together. One of the most important issues in bone–implant interfaces is how load is transferred from the implant to the surrounding bone.

The material prosthesis components are made of, its geometry and size, and the method of fixation influence the pattern in which stress is transferred to bone. A major concern for arthroplasties is that adaptive bone remodeling arising from “stress shielding” will compromise implant support, produce loosening, and predispose to fracture [24]. The term “stress shielding” refers to the reduction in bone density as a result of removal of normal stress from the bone by an implant, for instance, the femoral component of a hip prosthesis. This is because by Wolff’s law, bone responds with remodeling depending on the loads to which it is subjected.

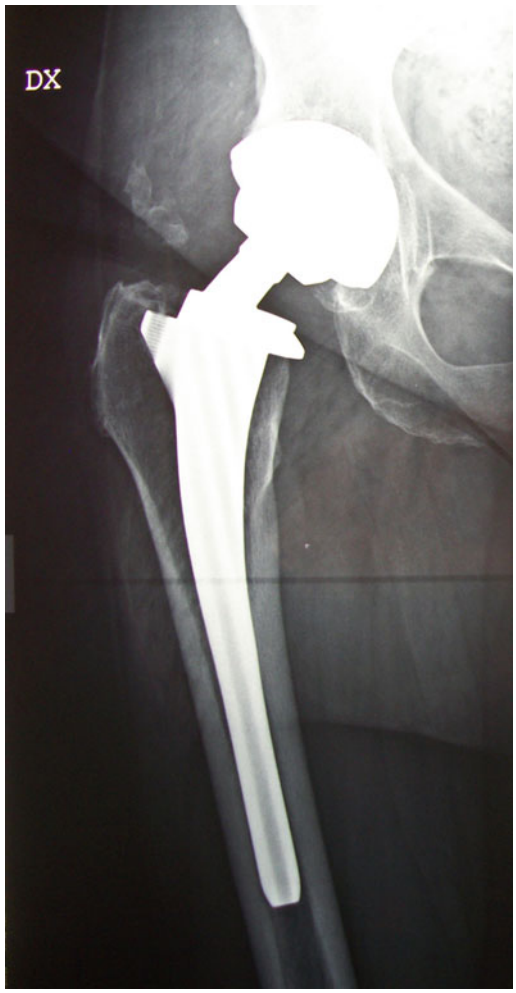

Fig. 4.4 Stress-shielding effect involving femoral metaphysis around hip prosthesis uncemented stem

Therefore, if the loading on the bone decreases, the bone will become less dense and weaker because there is a reduced mechanical stimulus for continued remodeling that is required to maintain bone mass (Fig. 4.4). So, stress transfer to the femur is desirable because it provides a physiological stimulant for maintaining bone mass and preventing disuse osteoporosis.

In the discussion of load transfer and stress shielding effect, the authors will refer to hip arthroplasty which is the joint prosthesis on which detailed and numerous examinations were carried out. In total hip arthroplasty, increasing the modulus of elasticity, the length, the cross-sectional area of the stem decreases the stress in the proximal third of the femur which could produce considerable stress shielding and resorptive surrounding bone remodeling of this region. Cementless stems generally produce more physiological strains than those caused by cemented stems, depending on the stem size and the extent of porous coating. For cementless implant, when a stem is loaded, it produces circumferential or hoop stresses which contribute to primary stability of the prosthesis. Uniformity of hoop stresses depends on uniformity of contact stem with bone in medullary canal; primary stability promotes secondary stability related to bone ingrowth in porous-coated stem.

Three criteria are required in order to obtain bone ingrowth: absence of micromotion (primary stability), strict contact of porous coating to bone, the pores of coatings should greater than 40 mm in diameter. Bone ingrowth provides secondary stability; fibrous tissue ingrowth may provide some stability, but it is not ideal for a real interlock. Motions may cause the development of a smooth membrane (synovial-like membrane) that encapsulates the component without ingrowth and progressively result in loosening and implant failure. If these criteria are met, bone ingrowth at 6 weeks in a wire mesh system produces the same mechanical stability as a bone–cement interface.

Stress shielding of the proximal femur is more pronounced with large diameter and long stems: small increases in stem diameter produce great increments of change in stiffness. Load is preferentially borne by the stiffer structure, and the bone of the proximal femur is relieved of stress. A lower modulus of elasticity (less stiffness) could be advantageous in uncemented hip stems because it would reduce the stress in the component through load sharing with bone and possibly reduce bone remodeling caused by stress shielding [25].

Evidence of more stress shielding is also evident with a press-fit at the isthmus. Extensive porous-coated stems also appear to produce severe stress shielding; localized bone ingrowth can be seen where the stem contacts the cortex, often at the distal end of the porous coating.

Stem configuration shows to affect load transfer to bone: Proximal bone loss is severe in patients with stems of a cylindrical distal geometry that fills the diaphysis and contact strictly the cortical walls.

Many authors showed the existence of a point of equilibrium reached in stress shielding and bone loss, and they stop often progression after a period of 2 years. Accurate care must be taken regarding proximal stress shielding because the adverse clinical implications. The combination of bone remodeling and subsequent osteolysis can predispose to periprosthetic fracture , and revision surgery becomes more complex when femoral bone stock has been lost.

Current investigations are addressed to development of materials with lower modulus of elasticity and with high wear resistance in joint surface, and stem geometries that diminish rigidity in order to reduce adverse periprosthetic stress shielding, bone loss and implant loosening.

4.9 Fixation Methods of the Implants

One of the most relevant surgical issue in joint replacements concerns implant fixation to the bone supporting. Aseptic loosening remains the most common cause of failure in joints prostheses. Three different fixation methods are employed: (a) polymethylmethacrylate (PMMA) cement, (b) use of porous metal surfaces or calcium phosphate ceramic-coated implant to allow fixation to the host bone by bone ingrowth into the implant surface, (c) the use of press-fit designs with heavily textured surfaces intended to achieve fixation by interference fit. The last technique is commonly combined with special coatings of prostheses in order to add secondary stability (Fig. 4.5).

Possible late complications caused by bone resorption from stress shielding, debris particles from the coatings, metal toxicity from the greater exposed surface area of porous-coated implants, have to be proved or rejected as problems.

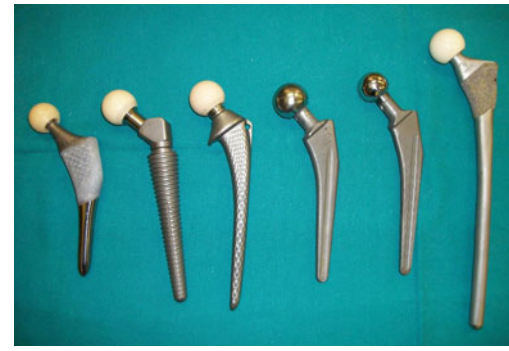

Fig. 4.5 Contemporary and historical femoral components documenting the wide variety of designs with various coatings reflecting different fixation methods

4.9.1 Polymethylmethacrylate Cement

Acrylic cement can be an effective way to satisfy requirements of secure implant fixation to the bone. The clinically significant failures rate of implants secured to bone with PMMA is attributable to the alterations in the cement mechanical properties that can result from handling and mixing techniques [26].

Bone cement is a self-curing form of PMMA produced by polymerization of an initiator contained in a powder and a liquid activator. PMMA bone cement is employed to obtain secure fixation of prosthesis components to bone and to distribute loads evenly from the surface of the components to the bone surface, reducing stresses in the supporting bone. It has limited adhesive qualities; bone cement should not be considered a glue. It is a space-filling, load-transferring material, technically a grout. It does not bond chemically to the surface of metal or to bone components. Some implants are manufactured with a thin layer of PMMA in order to obtain a chemical and mechanical bond of the cement to apply to the precoated implant.

The cement mechanical bond has good resistance to shear forces, parallel to the surface, and lower resistance to tensile forces, perpendicular to the surface. PMMA bonds securely to surrounding bone if it is forced in the interstices of the dry cancellous bone in the low viscosity state. A stable mechanical bond is extremely

important because it prevents motion at the bone–cement interface which can result in poor load transfer and in wear debris generation. These could produce bone absorption, component loosening, and bone fracture.

PMMA is about three times stronger in compression than in tension; it can resist considerably to compression but fails more readily under tension or shear forces. If gaps are left between the bone and the implant surfaces because the cement is not well packed, it may be subjected to shear and tension, and cement mantle may break.

The percentage porosity of manually mixed cement is variable between 9 and 27 %. Large pores in cement are stress risers that adversely affect cement tensile and fatigue properties and promote cracks propagation. Porosity reduction is achieved in the operating room by two techniques: vacuum mixing and centrifugation. Both these methods require additional instruments but are easily performed and require little additional time.

PMMA is a valid prosthesis fixation method, even though local and systemic effects related to PMMA should be considered.

High temperature produced by PMMA polymerization should produce the hypotension that sometimes follows the introduction of PMMA into the femoral canal during hip replacement as the result of peripheral vasodilatation. The monomer entering the circulation seems to be directly involved in myocardial depression. The transient hypotension correlates not with the level of the monomer in the circulation, but rather with a deficit in relative blood volume. Several studies reported fat emboli, myocardial infarction, pulmonary emboli, or possible air emboli after total hip arthroplasties. The local tissue effects of PMMA consist in the coagulation of the tissue proteins induced by the heat of polymerization, occlusion of the nutrient metaphyseal arteries that may produce bone necrosis areas and cytotoxic and lipolytic effects of the non-polymerized monomer.

The good results of cementing relies strictly on the technique, which has been continuously improved over the last decades: vacuum-mixed cements, medullary canal plugs, centralizing elements, and the use of jet lavage to clean the trabecular bone have been shown effectiveness in prolonging the life of cemented prostheses [27].

PMMA bone cement must be used with skill; it is a proven implant fixation method that will be used in total joint arthroplasties for many years to come. It is hoped that current researches will lead cements with better mechanical properties and less adverse effects.

4.9.2 Porous Metal

The clinically significant failures rates of implants secured to supporting bone with PMMA in young and active patients lead to alternative fixation methods development. The use of porous materials has improved the results obtained with cement fixation (Fig. 4.6). Porous coatings considered for promoting osseointegration include ceramics and metals [28]. Porous metal surfaces are created by the sintering of cobalt–chrome powder, or by the diffusion bonding of titanium beads or wire mesh.

The pore size of coatings is determined by the diameter of the powder particles, their packing density, and the sintering technique. In similar way, the titanium wire mesh system, the wires sizes, the density of packing, and the processing methods control pore size. So, porous coatings consist of multiple layers of pore-forming material, creating interconnected open pores which permit bone ingrowth. Porous materials usually have 30–60 % porosity calculated on a volume basis [29]. Other porous metal surfaces can be fabricated by plasma-spraying material

Fig. 4.6 View of the backside of new acetabular components with porous metal coatings

onto the substrate; it results in highly textured surface. Mechanical stress tests demonstrated that with bone ingrowth, porous coatings have the potential of providing better stress distribution and achieve the same mechanical stability as a bone–cement interface after 6 weeks.

However, porous-surface metal implants have potential adverse effects. First of all, the increase in metallic ion release should be considered; the amount of ion released is related to the amount of greater surface area. Porous-coated implants may have a three to seven times greater surface area than smooth implants. Abrasion against bone or cement (fretting) caused by the erosion at the surface of loose components could caused an increase in ion release. As discussed, clinical effects of the release of cobalt, chrome, and nickel ions and metal particulates have not been clearly established.

4.9.3 Calcium Phosphate Ceramics

Increasing interest was recorded over the years in biologically active calcium phosphate ceramic materials in arthroplasties fixation, two materials were widely evaluated: hydroxyapatite (HA) and tricalcium phosphate (TCP) [28]. Neither of these materials exhibits adequate mechanical properties for use as substrate in implant. Thin coatings of these materials on metal represent a biocompatible surface for prostheses demonstrating direct osseointegration in case of strict contact to surrounding bone. In addition, small gaps in implant of prostheses become filled in by bone after surgery. Into porous metal surfaces, such gaps preclude bone ingrowth: This suggests that calcium phosphate ceramics stimulate bone ingrowth.

The optimal thickness of the coating appears to be approximately 50 microns. Thinner coatings may not supply sufficient calcium and phosphate, and thicker layers can be subjected to stress fatigue failure under shear and tensile loads. Calcium phosphate ceramic coatings are applied by a technique of plasma spraying. Manufacturing techniques must be accurately controlled: temperature and mechanism of application of the HA coating affect chemical, mechanical properties and also biological response [30].

Adverse tissue responses to calcium phosphate materials have not been reported, although some investigators suggest that such coatings might be a possible additional source of particulate wear debris.

Considering the growing number of surgeries performed every year and the successful results, joint arthroplasty can be considered the most successful surgery in the history of orthopedics.

Established implants designs and bearing materials have been shown clinical success in great part of patients over long periods. On the other hand, successful preclinical testing is not always related to clinical success.

A continuing need to improve implants and employ new materials is required; however, this process has not to be focused exclusively on benefits and advantages, but also on risks and side effects of developments.

The new developments in bearing surfaces and coating materials are a paramount attempt to bring joint prostheses to the next level and get a further increase as in performance as well in longevity by decreasing the wear degradation and osseointegration problems.

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Material Implant

5

Ciro Villani and Alessandro Calistri

5.1 Introduction

The definition of biomaterial by National Institute of Health (NIH) is any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body.

This definition clearly satisfies the requirements in the orthopedic field where certain diseases such as osteoarthritis, fractures, and tumors require materials to replace bone or cartilage.

Most orthopedic medical devices are used in joint replacement or fracture management procedures, and this is reflected in their global sales, which totaled approximately $12 billion and $1.5 billion, respectively, in 2000 [1].

The treatment of orthopedic diseases has changed considerably over the past decades, allowing patients to live longer and better-quality lives. The introduction of new biomaterials has contributed much to this success.

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5.2 Metal

Several material properties make metals extremely useful as components in orthopedic medical devices. These properties include corrosion resistance, strength, rigidity, stiffness, long fatigue life, fracture toughness, and biocompatibility.

These important material properties have led to the widespread use of metal alloys as load-bearing implant materials.

Metallic materials actually applied in orthopedic surgery include stainless steel (i.e., plates), commercially pure titanium (i.e., plates), and titanium alloy (i.e., intramedullary nails, total joint prostheses). The choice of the type of metal must take account of certain important considerations such as the joint anatomy, the joint mechanical strength, and the characteristics of the metals.

5.3 Stainless Steel

Stainless steel is a metal used in orthopedic implant, which has a low content of impurities. All stainless steels are corrosion-resistant chiefly because of their chrome content and the type of oxyde surface chrome helps to create. Sherman [2] introduced in 1912 this kind of metal for plates and screws. Surgical stainless steel alloys (316L) made with varying amounts of iron, chromium, and nickel are presently used in the manufacture of prostheses. The low carbon (L) in surgical stainless steel diminishes corrosion

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and decreases adverse tissue responses and metal allergies.

Fatigue failure and relatively high corrosion rates make it a poor candidate for the manufacture of modern joint replacement implants [3, 4]. While many implants are still manufactured from this excellent material, its use is relegated mainly to plates, screws, and intramedullary devices that are not meant to be weight bearing for an extended period. Stainless steels without nickel have been recently developed to use them in patient with nickel sensitivity. The Ni-free compositions appear to possess an extraordinary combination of attributes for potential implant applications in the future.

5.4 Cobalt-Based Alloys

Cobalt–chrome–molybdenum is the most important implant alloy used in joint arthroplasty. This alloy has excellent wear resistance than other metallic materials and polymers; biocompatibility and corrosion-resistant as compared to other metallic materials; and high toughness in comparison to ceramics.

5.5 Titanium and Titanium-Based Alloys

Titanium-based alloys have excellent properties for use in porous forms for biologic fixation of prostheses. Levanthal [5] was the first to make use of titanium in surgery.

Titanium and titanium-6 % aluminum-4 % vanadium (Ti-6Al-4V) are known to be biocompatible and corrosion-resistant for this is the most common titanium alloy used in orthopedic implant.

5.6 Ceramic

The first to use ceramic in orthopedics was Rock in 1930, not for joint replacement but like bone substitute (tricalciumphosphate). Sandhaus in 1965 proposed alumina for joint replacement called Degussit AL 23. The ceramic was then reintroduced in 1970, when a rapid development of the application of alumina in orthopedics started, mainly for hip replacement. Alumina was used initially for femoral head and later acetabular cups [6].Zirconia called tetragonal zirconia polycrystals (TZP) was introduced in the end of 1970s [7]. TZP was characterized by a structure of high density, fine grain size and high purity, and twice the strength and toughness of alumina. In 1990, this material had been proved to be biocompatible. The applications in modern orthopedic surgery are femoral heads and insert for acetabular cup.

If these two types of materials are used together in the same prosthetic implant form a mating ceramic–ceramic. The combination, for example, in hip replacement, femoral head, and ceramic insert for acetabular cup, was introduced by different author [7–9] to eliminate the polyethylene wear.

5.7 Characteristics of Modern Ceramics

Theoretically, alumina is 10 times harder than cobalt-chrome [10]; alumina, with a hardness of approximately 2,000 VH (Vickers Hardness), is one of the hardest materials. [11]. This hardness provides improved scratch resistance. Another advantage is the improved lubrication due to its lower wetting angle. This permits better wettability, especially when coupled with the formation of a microfilm of lubrication on the surface of ceramics. In addition, strong bonding between the oxygen and aluminum ions provides extremely good corrosion resistance, leading to better biocompatibility, and because they are inert, there is no concern about allergic reactions [10, 12]. As a result, modern ceramic has much less wear rate compared with other biomaterials [13, 14] These favorable qualities are particularly desirable for implants in high-demand patients, such as young or more active patients [15, 16].

Alumina ceramics are brittle and have no way to deform without breakage [17]. Improvements in ceramic components and design changes have reduced failure rates of THA over the past 30 years. Starting with a failure rate of 1:100 in the initial phase [18, 19], the incidence of ceramic fractures has been reduced nowadays to 1:25,000 [20]. Because of its improved wear characteristics and durability, COC technology has gained widespread popularity. Efforts are continually being made to improve implant design. Nowadays, AMC ceramic material, with its superior mechanical properties and excellent wear behavior, is a promising new material for prostheses. Up until now, no complications have been reported in AMC THA. It is now possible to solve the existing longevity problems currently burdening many total joint systems in young and active patients [21].

5.8 Ultrahigh Molecular Weight Polyethylene

Polyethylene is a material that has a wide variety of molecular and microstuctural differences like molecular weight, degree of branching, crystallinity, and degree of cross linking. This variety of form has different properties.

Ultrahigh molecular weight polyethylene (UHMWPE) possesses excellent sliding properties, high impact strength, high fatigue resistance, and excellent biocompatibility. For over four decades, UHMWPE has been used as one-half of the metal- or ceramic-on-plastic bearing couple in total joint replacement (TJR) components due to its toughness, durability, and biological inertness.

UHMWPE wears at a rate of approximately 0.1 mm/year, but this is variable and influenced by physical activity of the patient, patient weight, size of femoral head (32 vs. 28 mm), roughness of the metallic counterface, and oxidation of the UHMWPE. Most medical devices are sterilized by exposure in gamma radiation. In the first half of the 1990s became widely known in the orthopedic device industry that this method to sterilize implants was causing break the chains of UHMWPE. It can reduce the molecular weight with loss of ductility and a decrease in strength. The final effect is more susceptible to wear. Sterilizing the polyethylene with gamma radiation in an inert gas such as nitrogen or argon actually made the polyethylene much stronger.

5.9 Joint Replacement Interface

5.9.1 Ceramic-on-Ceramic

Boutin [22] reported the first experience of ceramic-on-ceramic (COC) on total hip arthroplasty (THA) in 1970. Early and midterm COC THA clinical outcome reports from the initial experience in the USA have been encouraging [23, 24]. At a minimum of 18.5-year follow-up, Hamadouche et al. [25] reported minimal wear, limited osteolysis, and a low rate of complication with COC THA.

However, some important disadvantages of early-generation COC articulations have been reported. Early ceramic component materials were of large grain size and contained a lot of impurities, resulting in unacceptable component fracture rates [15, 26] For instance, relatively high rates (up to 13 %) of component fracture in the first-generation ceramics have been reported in the literature [27].

Although the second-generation ceramics has been much improved, the reported fracture rate is still up to 0.014 %. [28, 29] With the development of manufacturing processes such as hot isostatic pressing, laser etching, and proof testing, the modern ceramic component material which is now produced has better characteristics (the third-generation ceramic Biolox Forte [Ceram Tec Medical Products, Plochingen, Germany], approved by the US FDA in 2003) [30, 31].

The average size of the grains has been reduced from 3.2 to 1.8 mm, and the bending strength has been increased to 580 MPa for alumina ceramics [32].

The third-generation alumina ceramics commercialized today benefit from all of these improvements, and the fracture rate has been reduced to 0.004 % [33]. Compared to the old alumina ceramic in previous clinical studies, for which the 10-year survival rate was 90.8 %, third-generation, highly purified alumina has an almost 100 % 10-year survival rate [34].

The ceramic materials that are mainly used in total hip and knee arthroplasty can be divided into alumina, zirconia, and composite ceramics. Other ceramic surface modifications, including oxidized zirconium, diamond-like carbon, and titanium nitride as well as the nonoxide ceramics, silicon nitride and silicon carbide, are hardly used or are in development [35].

5.9.2 Metal-on-Metal

The metal-on-metal (MoM) articulations in THA were widely used between 1960 and 1975. The McKee–Farrar and other first-generation prostheses failed at a high rate because impingement caused early component loosening. The problem of early component loosening was corrected by improved component design and better manufacturing quality. Second-generation MoM total hip replacements (THR) have experienced short and medium-term success as assessed by Harris hip scores and patient self-assessment [36].

Today, MoM technology is used in total hip implants and hip resurfacing implants. Current designs have attempted to correct and improve the design flaws of earlier implants, which included poor manufacturing tolerances, inadequate clearances, early impingement, poor material selection, and increased failure rates [37]. MoM bearing couples have advantages over implants that use PE. The most important advantage is the considerably less linear and volumetric wear shown. Hip simulator testing has shown repeatedly that a MoM bearing has considerably less wear than a metal-on-PE couple [38, 39].

As with any other bearing articulation, there are disadvantages in the use of metal-on metal articulations. Concerns continue to exist regarding the production of metal ions, biologic concerns resulting from prolonged exposure to elevated metal ions, issues of hypersensitivity, implant-specific issues, and the challenge of appropriate patient selection [40]. The popularity of MoM bearings, for instance, as used in up to 35 % of the primary total hip replacement procedures performed in the U.S. MoM bearings is attractive, as they have less wear than metal-on-polyethylene bearings, thereby minimizing debris-associated failures. In addition, their mechanical properties allow thin-walled acetabular components so that large femoral heads can be used. Furthermore, MoM bearings allow hip resurfacing procedures that help to preserve femoral bone stock, which is highly desirable for young patients. For current MoM bearing hip replacements, which almost always involve austenitic cobalt–chrome–molybdenum (CoCrMo) alloys, a fair amount is known about the metallurgy far below the sliding contact region (microns away) [41].

Although the metal plays an important role in load bearing, there must also be some lubrication mechanism within the human body; otherwise, the wear rates would be prohibitive, and severe metal toxicity would be common. Protein in the surrounding fluid is known to play a critical role for MoM replacements [42, 43].

The evolution of second-generation MoM components brought improvements in metallurgy and geometry, including carbon content, method of fabrication, heat treatment, radial clearance, sphericity, surface finish, functional arc, fixation surface, and head size. Enhanced stability afforded by large heads and low wear made MoM an attractive bearing choice. Although early results with second-generation MoM devices were promising, concern has mounted with unexplained pain, implant design—related failure, aseptic loosening, metal ion release and systemic distribution, metallosis, pseudotumors, and hypersensitivity reactions [44, 45].

These delayed hypersensitivity reactions have been described as aseptic lymphocyte-dominated vasculitis-associated lesions and/or lymphocyte-dominated immunologic answer. [45, 46]

5.9.3 Metal-on-Ceramic

To improve long-term results of THR, hard-on-hard bearings, as COC and MoM are often used. The main issue associated with ceramic remains its brittleness, which could lead to clinically relevant failure rates (0.004 % head fracture [33] and 0.22 % liner fracture [17]). Although in the case of metal implants, ions present in the serum and their potential toxic effects both locally and systemically are a cause for concern [47], to avoid the breakage of the ceramic insert on one hand and to reduce ions release on the other, an innovative hybrid hard-on-hard bearing was introduced where a ceramic head is coupled with a metallic insert [48].

The emphasis on the encouraging short-term results of this hybrid coupling might lead to a new intraoperative, worst-case scenario: the use of a ceramic-on-metal (COM) coupling with components not specifically authorized to be coupled. This medical malpractice, involving different bearings material, is traceable throughout clinical reports [49, 50].

Considering that a differential hardness might reduce wear, compared with the ceramic gold standard, we hypothesized that COM hip components, not specifically authorized to be coupled, would reduce wear compared with a COC bearing. We also wondered whether in the context of two different COM diameters, a larger femoral head would reduce wear. Finally, we investigated whether geometrical mismatch, due to the different roundness measurements, would correlate with the wear behavior of all specimens.

5.9.4 Ceramic-on-Polyethylene

Catastrophic polyethylene failure is an uncommon complication of ceramic-on-polyethylene THA because of the favorable tribological characteristics of these implants.

The correct inclination of the acetabular component is necessary to prevent accelerated polyethylene wear in THA, even though favorable articular bearing surfaces have been used (e.g., ceramic-on-polyethylene coupling). If the cup appear well waxed and fairly oriented on follow-up radiographies, the early detection of severe polyethylene wear may permit a revision of only the femoral head and acetabular liner. One possible long-term complication of THA is breakage of the cementless, metal-backed acetabular component. In THAs with metal heads, it has been related to catastrophic polyethylene failure with complete wear-through of the polyethylene liner and metal shell [51, 52].

The wear rate of acetabular polyethylene in ceramic-on-polyethylene articulations has been reported to be lower than that of metal-on-polyethylene implants in both hip simulator and in clinical studies.

Despite these favorable tribologic characteristics, catastrophic polyethylene failure and cup breakage have been reported even in THAs with ceramic–polyethylene bearing surfaces.

One bearing surface option for total hip arthroplasty (THA) uses a ceramic femoral head articulating with a polyethylene liner. Several studies have suggested that ceramic systems exhibit superior wear characteristics compared with traditional metal–polyethylene systems. Both systems have long-term complications, including aseptic loosening, dislocation, and infection.

Another less common but very significant complication is catastrophic failure of the acetabular component, which has been reported in ceramic and metal systems.

The frequency of catastrophic failure has not been well studied, and previous attempts to quantify rates have been extremely variable (0.29–10.9 %).

Component wear leading to osteolysis and implant loosening remains a significant problem in THA. Submicron polyethylene debris generated by wear stimulates the process of osteolysis.

Coupling a ceramic head with the more conventional ultrahigh molecular weight polyethylene acetabular component liner may be an

alternative to reduce the rate of ceramic component fracture while maintaining the wear characteristics associated with ceramic–ceramic bearings. ceramic–polyethylene couples had excellent short-term to midterm clinical results. However, it should be noted that ceramic–polyethylene couples did not offer sufficiently low linear wear rates to theoretically prevent osteolysis in longer term follow-up. The properties of cross-linked polyethylene may provide a more acceptable reduction in wear rate .

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Part II
Images Techniques, Conventional RX, CT, MR, Bone Scintigraphy, Periprosthetic DXA

Role of Conventional RX, CT, and MRI in the Evaluation of Prosthetic Joints

6

Carlo Masciocchi, Francesco Arrigoni and Antonio Barile

6.1 Introduction

Imaging of joint prostheses is a specific competence of the radiologist in strong collaboration with the orthopedic surgeon, and it is correctly interpreted provided that the medical specialists involved are well aware of the type of prosthesis employed, the implantation technique, and the clinical status of the patient. With the technological development, a great variety of prosthetic devices has become available, designed to fit all body districts, sometimes even personalized according to the anatomical characteristics of the patient.

The most prevalent joint replacements are those of the hip and the knee. This study mostly focuses on these types of intervention; nevertheless, the concepts expressed can also be applied to other body districts.

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6.1.1 Preoperative Imaging

The hip—The preoperative imaging of the hip must be performed by the radiologist in strong collaboration with the operating orthopedic surgeon, who has to study the anatomical features of the patient.

Plain film is the first-choice technique to obtain initial assessment and measurements. It is performed on the anteroposterior (AP), including the third superior of the femur, and latero-lateral (LL) projections.

The radiological evaluations include the skeleton (presence and degree of osteoporosis), and the search for congenital (dimorphisms) or acquired diseases (osteophytes, geodic formations, modification of the femoral head, displacement, etc.).

The choice of the prosthetic devices to be implanted will be made on the basis of the following measurements:

- Femoral neck angle: It extends medially between the femoral diaphysis and the femoral neck axes, at about 125°–135°.
- Femoral offset: It is the distance from the center of the femoral head to a line bisecting the long axis of the femur (the distance is measured on the line perpendicular to this one). It is not an absolute measurement and its range is quite wide: 24.7–55.2 (Dolphain et al. Acta Orthop Belg 2002). The higher this value, the higher the joint range of motion and functionality. This distance must never be reduced, because its width guarantees the prosthetic stability.

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- The line tangential to the ischiatic tuberosities: The intersection with the lesser trochanters bilaterally must be at the same level. It helps define discrepancies between the levels of the legs.
- The acetabular angle of Sharp: The angle formed between the anterior acetabular cilium and the line tangential to the ischiatic tuberosities. Normal range is about 38 ± 4°. It measures the acetabular coverage.
- The center-edge angle of Wiberg: It provides information about the femoral head, and it is obtained drawing a line perpendicular to the one bisecting the femoral heads and another one tangential to the lateral acetabular edge. The resulting angle has to range from 20° (young patients) to 40° (adult patients). A value under 20° is indicator of hip dysplasia.
- Acetabular depth measurement: It is measured by drawing a line perpendicular to the one extending from the super-external point of the acetabulum to the superior edge of the pubic symphysis. The acetabular depth is the measurement between the intersection and the most internal point of the acetabular fundus. Normally, it ranges between 7 and 18 mm.
- Acetabular protrusion index or Kohler's line: It lies between the internal edge of the ileum and the medial ischiatic edge. The acetabular head lying within this line is a sign of coxa profunda.
- Canal to calcar isthmus ratio or CC ratio: It is the ratio of the width of the channel lying 10 cm caudally to the lesser trochanter to the width of the one located at the level of the lesser trochanter. A too low ratio indicates the presence of a narrow channel, which may complicate the prosthetic implantation.

Additional two measurements can be obtained with CT (on axial images):

- Alpha angle: It is the angle formed by two lines both originating from the femoral head medially, the one following the femoral neck axis and the other extending to the head–neck junction. If superior to 55°, this angle indicates the presence of a femoroacetabular impingement of the CAM type.
- Anteversion angle of the femoral head: It is formed by the line passing through the center of the femoral head and the neck axis and from the posterior intercondylar line of the femur. V.N. 18° (±6).

Computed tomography (CT) and MRI are employed for the presurgical assessment in case of prosthetic implantation for coxarthrosis. They are useful for assessment of diseases affecting the surrounding soft tissues and in the presurgical procedures in patients with fractures, where plain film is not diriment.

In case of fractures, plain film first and CT secondly are useful in the assessment of the site of the fracture, particularly when the latter occurs in an implanted body district, possibly leading to complications such as prosthetic instability.

When the fracture involves the lesser and greater trochanters is usually stable. When the fracture occurs at a lower level, in the stem, it is unstable. It is also important to evaluate the quantity of bone around the prosthesis. The distal fracture must be treated as a diaphyseal fracture.

Knee—Plain film represents the first-choice technique to preoperatively assess the knee. The employed projections are the following:

- Under load anteroposterior projection including hip and ankle. This helps to assess the lower limb mechanical axis. This projection is a line passing from the center of the femoral head to the center of the ankle (ankle mortise); there is a correct load transmission, provided that this line bisects the knee. An additional measurement is that of the femorotibial angle: Under normal conditions, the lines passing through the femoral and tibial diaphyses form an externally open angle of about 170°–175°; angles inferior to 180° are sign of slightly valgus knee. Inferior angles are sign of pathologically valgus knee. Superior angles are sign of varus knee. This measurement has also a part in the assessment of dysmetric lower limbs.
- LL and specific projections for the patella to assess possible presence of arthrosis, osteopenia, and other diseases, the awareness of

which is important to decide the type of prostheses to be implanted.

Decisions on the prostheses to be implanted can be made on the basis of these measurements and on second-choice investigation techniques, in selected cases, depending on particular patient requirements.

Shoulder—The shoulder arthroplasty is indicated for humeral fractures and chronic shoulder diseases. There are different types of prosthesis: hemiarthroplasty (humeral prosthesis without replacement of the glenoid), total shoulder arthroplasty (humeral and glenoid prosthesis), and reverse shoulder replacement (humeral cup prosthesis with glenosphere implantation). The hemiarthroplasty is indicated in particular in cases of osteonecrosis with a preserved glenoid, proximal humerus fractures, cuff-tear arthropathy, and inflammatory arthropathy with massive cuff tear or insufficient glenoid bone stock. Total shoulder arthroplasty is indicated in case of primary or post-traumatic osteoarthritis, inflammatory arthropathies, and osteonecrosis with an affected glenoid and is important to remember that the total shoulder arthroplasty has to be implanted only if there is not a massive rotator cuff tear. The main indication for the reverse shoulder replacement is the osteoarthritis of the shoulder with massive irreparable cuff tear, but also the failure of previous arthroplasty. Preoperative imaging evaluation includes radiography and CT. A standard preoperative three-view radiographic series of the shoulder is essential and should include a true anteroposterior view. This view is most important for assessment of the shape of the glenoid margin. The role of the CT (acquisitions with thin slices and reconstructions in the most representative plans) is very important to study preparatory the joint anatomy of the patients and the feasibility of the implant.

6.1.2 Post-operative Imaging

Plain film is the first-choice technique and often sufficient for an accurate evaluation of the prostheses. The other second-choice techniques, such as MRI and CT, are useful for assessing the patients in case of complications, but are limited by the presence of artifacts caused by the metallic prostheses, which may degrade the imaging of the adjacent portions (Fig. 6.1). The rule for the post-surgical evaluation is to be aware of the type of implanted prostheses and employed techniques, information provided by a strong collaboration with the orthopedic surgeon.

Whatever the body district implanted, the first purpose of the post-operative imaging is the evaluation of the correct positioning of the prosthesis. As a consequence, the first post-operative imaging needs that the same radiographic projections be employed, as performed prior to surgery. The comparison of the previous with the current measurements is important to evaluate whether the patient has regained the same pre-surgical anatomical relationships, as well as the correct alignment of the prosthetic devices and the recovery of the physiological axes, the latter in particular for the knee (Fig. 6.2).

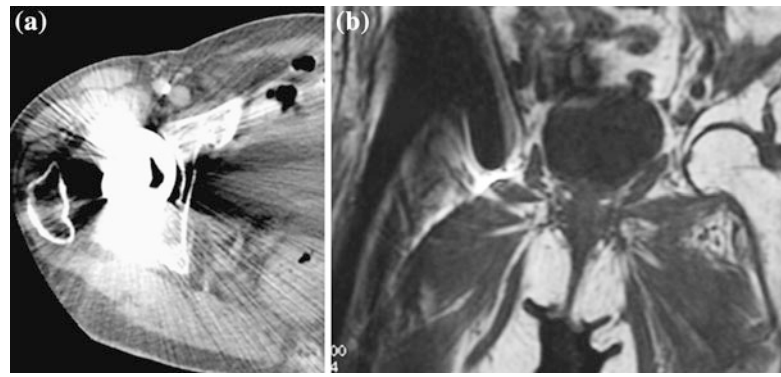

Fig. 6.1 Metal artifacts in CT (**a**) and MRI (**b**)

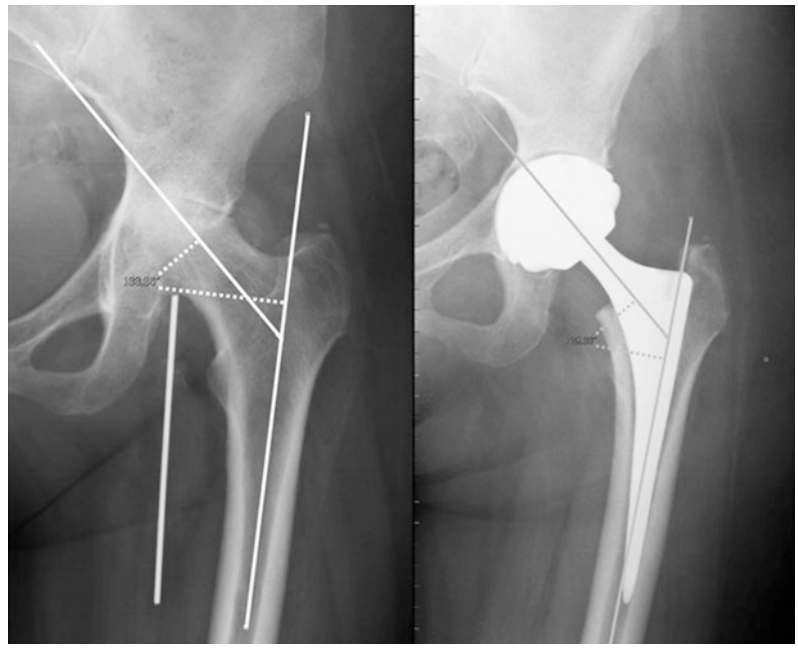

Fig. 6.2 Maintenance of the physiological angles

It is important to verify that the prosthesis does not impinge to the surrounding structures (a typical example is represented by the oversized prosthetic tibial plateau which impinges to the neighboring tendons causing inflammation of the anserine bursa) (Fig. 6.3).

Subsequent radiological follow-up is useful to verify that the prosthesis maintains its position and functionality. Plain film still remains the first-choice technique, also in presence of the two main complications typical of prosthetic implantation: loosening (Fig. 6.4) (with possible periprosthetic fractures) and infection.

Hip—Besides being complete (acetabular or femoral) or only femoral, hip prostheses can be cemented or uncemented and the latter present a porous component that induces the periprosthetic growth of bone and the prosthetic adherence to the adjacent bone (Fig. 6.5). Hence, for the assessment of prosthetic loosening and possible presence of fracture, the medical specialists must bear in mind both the prosthetic characteristics and the original status of the patient. The prosthesis is cemented to guarantee a major longevity, but cement can induce osteolysis. Higher periprosthetic lucency around the bone–cement interface is observed in case of loosening of cemented prostheses (Fig. 6.6). There are no established criteria to define prosthetic loosening. However, it is commonly recognized that a

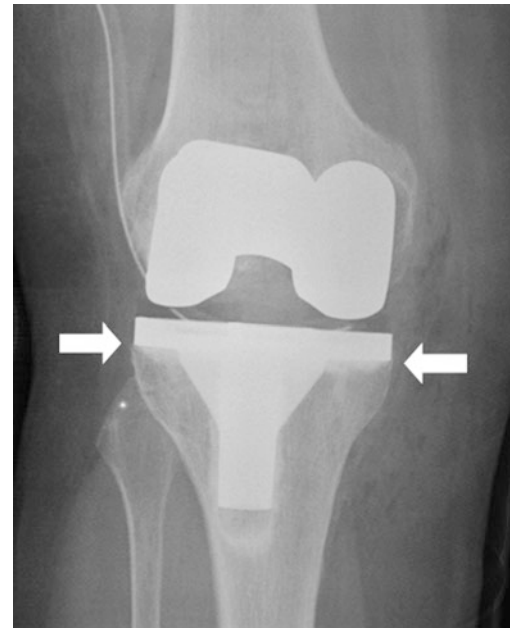

Fig. 6.3 Good positioning of prosthesis without impingement of tibial component with the surrounding structures

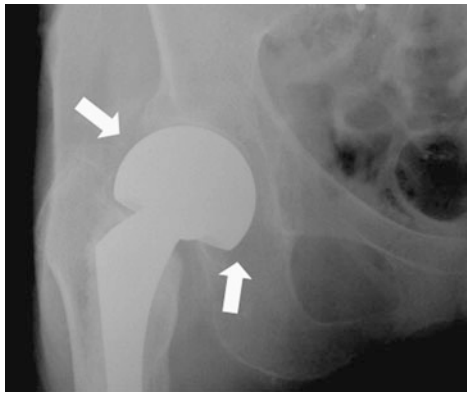

Fig. 6.4 Loosening and subsequent anteversion of the acetabular component

radiolucency of at least 2 mm may be suggestive of prosthetic loosening, particularly at femoral level, less at the acetabular one. Different criteria are adopted for uncemented prostheses. A radiolucency thickness measuring at least 2 mm is considered pathological when observed around the porous portion of the prosthesis; up to 2 mm, it is considered normal, particularly along the prosthetic stem, as well as the presence of cortical hypertrophy. The most reliable sign of prosthetic loosening remains in both cases the presence, at subsequent controls, of a progressive radiolucency. Another sign is the presence of periprosthetic areas of osteolysis caused by the prosthetic materials inducing granuloma formation. Three periacetabular zones and 7 adjacent to the femur have been defined to study the radiolucency. Other less employed techniques for assessment of prosthetic loosening are arthrography, useful for evaluation of contrast medium periprosthetic effusion (false positive, however, may be sometimes due to the presence of communications with the bursa), and the intra-articular injection of local anesthetic.

Knee—A great variety of prostheses is available also for the knee. The most employed ones are those formed by femoral, tibial, and sometimes also patellar components. An indicator of loosening is represented by increased radiolucency evaluated at tibial level in 7 zones. The presence of ill-defined resorption areas is a possible indicator of infection. Fluoroscopy is useful in the knee, more than in the hip, for assessment of the bone–prosthesis interface.

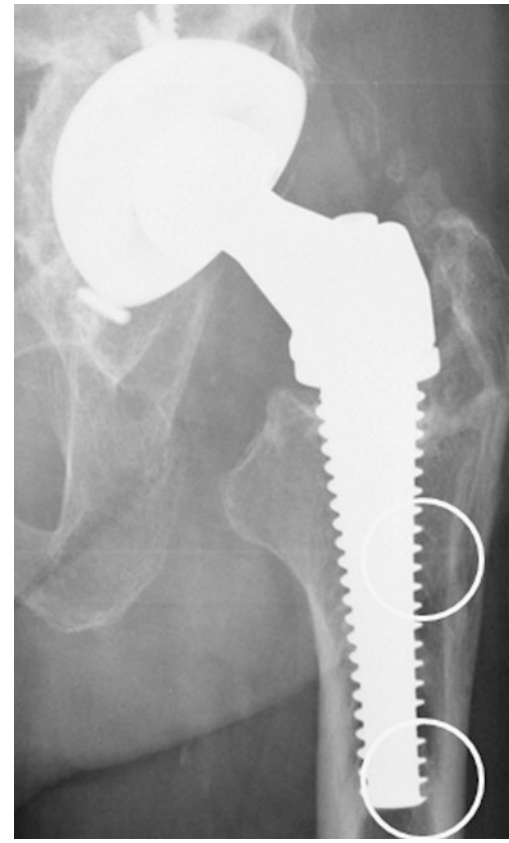

Fig. 6.5 Growth of new bone around the implant, a sign of stability

Infection is the second major complication occurring with a calculated incidence ranging between 1 and 3 %. Plain film represents the first-choice examination technique although its findings are aspecific. When infection is limited or at an early stage, in fact, plain film findings may result negative or show small areas of bony rarefaction possibly associated with periosteal reaction. In addition to more specific clinical and diagnostic examinations, MRI and CT are employed, but are limited by the presence of metal-induced artifacts. However, they are useful in assessing the extension of the infection to the adjacent soft tissues. Ultrasound allows evaluation of the adjacent soft tissues and is of

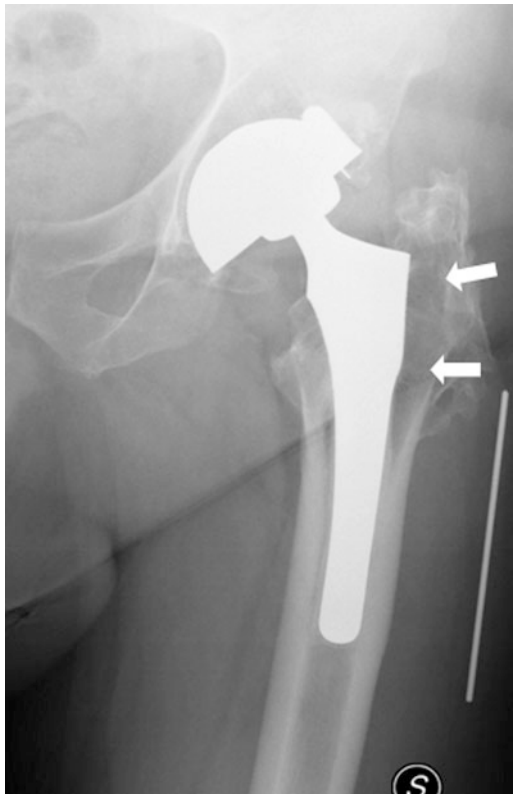

Fig. 6.6 Large area of periprosthetic lucency

great help in case a biopsy should be performed. Nuclear medicine is useful to analyze functionality and is not degraded by metallic artifacts. Scintigraphy is reliable in detecting the presence of complications (failed joint replacement), but does not help differentiating between prosthetic infection and aseptic loosening. Combined scintigraphy and marked leukocytes provide 90 % accuracy, selectively detecting inflammatory phenomena through the leukocytes, and represent the technique of choice for the study of infection of implanted joints. Positron emission tomography (PET) is gaining a role in this field, but important breakthroughs are expected with the development of new radioactive tracers specific for bony lesions.

Shoulder—Generally, the reverse shoulder replacement (Fig. 6.7) is performed due to osteoarthritis of the shoulder. The main complication is loosening, infection, and fractures. As in the other districts, the radiographic signs

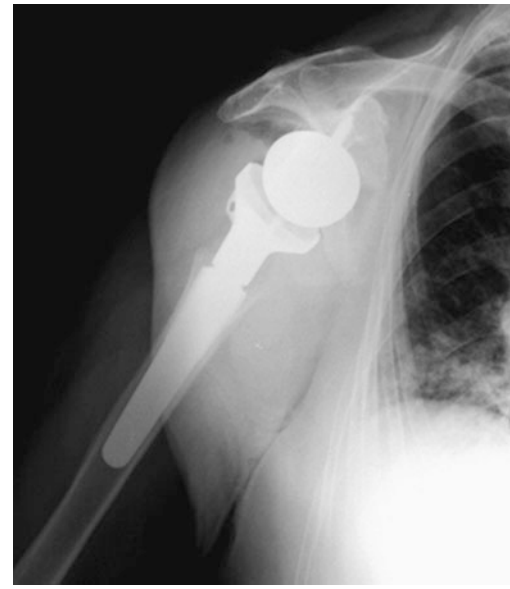

Fig. 6.7 Reverse shoulder replacement

of loosening are a lucent line around the components (especially in controls seriate in time), but also the displacement of the prosthesis (for example, the tears of the rotator cuff do not contain the prosthetic humeral head that will tend to rise upward). However, the loosening is a complication that involves most frequently the glenoid component. Another typical complication of the shoulder prosthesis is the impingement that can arise from incorrect positioning of the prosthesis with a segment elevation between the top edge of the prosthesis and the upper margin of the greater tuberosity. A characteristic compliance of the reverse shoulder replacement is the inferior glenoid impingement that can lead to scapular erosion: The humeral component in fact can bump against the bone of the glenoid (which is medial to the glenoid prosthetic component) and erode the latter and lead to loosening of the glenoid component.

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Role of Nuclear Medicine in Prosthesis Surveillance

7

Mauro Liberatore

The materials of which the prostheses are made are studied extensively elsewhere in this book. A brief mention to this subject, however, must also be made in this chapter, because some constitutive characteristics of the prostheses have important reflexes on scintigraphic findings. Prostheses are usually made of metal (cobalt–chromium or titanium) and plastic (high molecular weight polyethylene). The attachment of this hardware to the bone can be assured by surgical cement (polymethylmethacrylate) or by new bone formation itself around the prosthesis, avoiding the use of the cement. The latter condition requires application of hydroxyapatite to the prosthetic surface or, alternatively, the use of prosthetic materials with a porous coating. In cemented prostheses, normal marrow cells are observed at the cement–bone interface, while in cementless porous-coated prostheses, most of the pore space is occupied by endostal bone and the remainder by normal marrow cells. In the cementless nonporous-coated prostheses, a partially mineralized fibrous tissue can be found around the prosthesis [1].

Nowadays, joint replacement is a widely used surgical procedure that has led to improved quality of life for a large number of people suffering from advanced joint diseases. It has been estimated that about 700,000 hip and knee arthroplasties are performed every year in the United States alone [2]. Furthermore, it is reasonable to presume a further increase in this number due to increased life expectancy in the Western countries. While these surgical procedures, in the vast majority of cases, are successful, some complications can occur, such as aseptic loosening, dislocation, infection, fracture, and hardware failure. A number of these complications are relatively rare and easily diagnosed by plain radiography, while differentiation between aseptic loosening and infection can be more difficult. Symptoms and signs of early infection are not specific: the erythrocyte sedimentation rate, increased leukocyte count, and protein C-reactive levels are neither sensitive nor specific, and the standard radiographic appearance of infection can mimic that of aseptic loosening. Although joint aspiration with Gram staining and culture is considered the definitive diagnostic test, its sensitivity is variable ranging from 28 to 92 %. Its specificity is more reliable ranging from 92 to 100 % [2, 3]. Plain radiographs are neither sensitive nor specific, and computed tomography and magnetic resonance imaging, even if more sensitive for detecting osteolysis, can be limited by the artefacts caused by the implanted metallic prosthesis. Since clinical and radiographic signs of the two conditions may overlap in a significant number of cases, radionuclide imaging

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plays a significant role in the study of these complications.

Aseptic loosening of the prothesis is the most common reason for revision surgery. About 25 % of all prostheses demonstrate, sooner or later, evidence of loosening [2]. Inappropriate mechanical load, fatigue failure at the bone–prosthesis or cement–prosthesis interface, and implant motion can cause this complication. However, the most frequent cause of this complication is an inflammatory reaction caused by the fragmentation of prosthetic components [4]. The shedding of microscopic particles of these materials, due to the wear of hardware, probably attracts and activates phagocytic tissues cells. However, enzymatic digestion of these particles is particularly difficult, leading to a continuous inflammatory stimulus, which produces secretion of pro-inflammatory cytokines and proteolytic enzymes responsible for bone and cartilage damages. The development of a pseudo-membrane with a variable cellular composition has been reported: histiocytes are the most common isolated cells (95 % of specimens), but also giant cells are very frequent (80 %) as well as lymphocytes and plasma cells (25 %), while neutrophils are present only in about 10 % of specimens [5–8]. A similar condition leads to osteolysis, corresponding to radiographic appearance of periprosthetic lucency, loss of supporting osseous tissues, and eventually loosening of the prosthesis.

Infection is the third most common reason for revision arthroplasty, but is, perhaps, the most serious complication. Its frequency ranges from 1 to 2 % for primary implants and from about 3 to 5 % for revision implants [9]. This complication can develop within the first months, but also years after surgery. From the histopathological point of view, the inflammatory reaction found in the infected prosthesis can be similar to that present in aseptic loosening except for the presence of neutrophil leukocytes, which are almost absent in aseptic loosening and always abundantly present in infection.

Distinguishing infection from aseptic loosening of a prosthesis is extremely important, since infection often requires multiple admission (removal of infected hardware followed by a long course of antibiotic treatment and a revision arthroplasty), while aseptic loosening requires only one hospital admission and a single surgical intervention (single-stage exchange arthroplasty). Thus, a false-positive case (lack of specificity of the diagnostic tool) can produce unnecessary, multiple, and expensive surgical procedures, while a false-negative case (lack of sensitivity of the diagnostic tool) results in additional surgical intervention, since undiagnosed infection will turn into failure of the revision implant. Radionuclide imaging usefully contribute to the evaluation of symptomatic prosthesis suspected of infection by several scintigraphic methods.

7.1 Bone Scintigraphy

Bone scintigraphy is based on the administration and the study of skeletal uptake of phosphates and phosphonates labeled with 99mTc. This uptake reflects bone turnover and, therefore, bone metabolic activity. This scan is an easily available and inexpensive diagnostic tool, and its role in the evaluation of painful joint replacements has been extensively studied over the years. This scan is extremely sensitive for detecting bone changes around prosthetic joints, since, like all scintigraphic methods, it provides functional rather than anatomic information. Several authors reported that bone scan is a useful method for detecting joint replacement failure, but that it is not sufficiently specific for assessing the cause of the failure. Aliabadi et al. found that bone scintigraphy can accurately detect prosthetic loosening, but cannot distinguish aseptic from infected loosening [10]. Some investigators based their attempt to differentiate aseptic loosening from infection on the periprosthetic uptake patterns of the radiopharmaceutical [11]: focal uptake was considered indicative of aseptic loosening, while diffuse periprosthetic uptake around the femoral and acetabular component was associated with infection. Different results were obtained by other authors, who found diffuse periprosthetic

uptake associated with both the conditions [12] or reported that a similar uptake pattern was sufficiently specific, but insensitive to infection [13]. It has been reported (and could be concluded) that, focusing the analysis only on aseptic, loosened prosthesis, bone scan can be considered both sensitive and specific [14]. In reality, the problem is more complex, because the uptake of the radiopharmaceutical depends on bone mineral turnover, which increases in a number of conditions besides infection, producing increased periprosthetic activity. Furthermore, it is well known that asymptomatic hip replacements are associated with several uptake patterns of the radiopharmaceutical. These patterns partially depend on the time elapsed from surgery and also on the modality of attachment of prosthetic implant. Usually, up to about one year from surgery, the periprosthetic uptake is very variable independently of the presence of surgical cement. After this period, while the majority of asymptomatic patients with cemented hip replacement have a normal uptake pattern, about 10 % of these patients present increased periprosthetic uptake [15] (Fig. 7.1). This increased uptake beyond one year from surgery is even more frequent when porous-coated hip prostheses are implanted [16, 17].

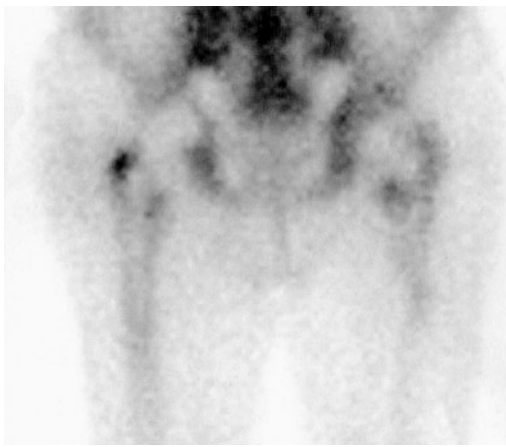

Fig. 7.1 Bone scintigraphy in posterior view. Aseptic loosening of the right hip prosthesis. The left prosthesis was painless. Significant uptake of the radiopharmaceutical can be seen around both the prostheses

The study of total knee replacement by bone scintigraphy is perhaps more problematic than that of hip prosthesis. In fact, it has been reported that 60 % of femoral and 90 % of tibial components show increased periprosthetic uptake more than 12 months after surgery [18, 19]. Serial bone scans performed in asymptomatic patients for a period of two years after implantation of total knee prostheses demonstrate that even if periprosthetic activity generally decreased over time, there was significant variability patient-to-patient [19]. These authors proposed the use of serial scans to actually asses the significance of increased periprosthetic uptake.

On this basis, the results obtained by further studies showing low accuracy of bone scan in assessing infection of total knee replacement are not surprizing [20, 21].

Bone scintigraphy can also be performed evaluating not only late images (reflecting bone osteometabolic activity) but also early phases of the scan (vascular and blood pool phases). A similar study is currently called 3-phase bone scan. This different approach does not seem to produce better results in diagnosing prosthetic infection, as reported in Table 7.1.

As can be seen, the clinical usefulness of bone scintigraphy in the evaluation of painful prosthetic joints can be considered low, due to the low values of its diagnostic accuracy. It does not seem possible with a single scan to differentiate aseptic loosening from either infection or normal post-operative appearance. For both cemented and porous-coated hip and knee replacements, bone scan is more useful in excluding prosthetic pathology when it is clearly negative. Due to its high negative predictive value, this scintigraphy can be used as a screening test or in association with other radionuclide studies.

7.2 Combined Bone/Gallium Scintigraphy

The property of gallium-67 of accumulating in both septic and aseptic inflammations has been known for about 40 years. Early investigations

Table 7.1 Reliability of 3-phase bone scintigraphy in the assessment of prosthetic infection

Author and year	Type of prosthesis	N° of prostheses	Sensitivity (%)	Specificity (%)	Accuracy (%)
Magnuson et al. [41]	Hip and knee	49	100	18	53
Levitsky et al. [42]	Hip and knee	72	30	86	68
Palestro et al. [20]	Knee	41	67	76	–
Love et al. [21]	Hip and knee	150	76	51	62*

* In the same study, the accuracy value of simple bone scintigraphy was 50 %

regarding the role of this radionuclide in musculo-skeletal infections showed variable values of accuracy. In 1979, Reing et al. carried out a study on 79 joint replacements, comparing bone and gallium-67 scintigraphies in diagnosing infection [22]. The sensitivity and specificity values obtained for bone and gallium-67 scans were 100, 15, and 95, 100 %, respectively. These findings suggested that gallium-67 imaging may significantly increase the accuracy of radionuclide diagnosis of infected joint replacement. Rushton et al. in a comparative study of bone and gallium-67 scans reported that gallium-67 accumulated in all the 13 infected prostheses they studied, whereas none of the 18 patients with aseptic loosening of prosthesis showed abnormal gallium-67 uptake (100 % accuracy) [23]. Other authors found 80 % accuracy values [13, 24], while Aliabadi et al. reported that gallium-67 scan is only 37 % sensitive, but 100 % specific [10]. In order to improve the accuracy of both bone and gallium-67 scans, the two studies are often interpreted together according to standardized criteria [25]. According to this approach, the scan is positive for infection when the spatial distribution of the two tracers is incongruent or when this distribution is spatially congruent but the gallium-67 uptake is higher than that found on the bone scan. The test is negative for infection when the gallium-67 scan is normal, independently from the bone scan results or when the spatial distribution of the two tracers is congruent, but the gallium-67 uptake is lower than that found on bone scan. Finally, the scans have to be considered dubious for infection when spatial distribution and intensity of uptake of the two radiotracers are congruent.

This combined interpretation, however, does not significantly increase the accuracy over either study alone. In fact, while Tehranzadeh et al. reported a 95 % accuracy for combined studies [26], the majority of the authors found less satisfactory results, as shown in Table 7.2.

In conclusion, on the basis of the above reported accuracy values, it can be affirmed that combined bone/gallium-67 imaging interpretation, produces only a slight accuracy improvement in comparison with bone scan alone.

7.3 Labeled Leukocyte Scintigraphy

From the physio-pathological point of view, indium-111-labeled leukocytes should be the most specific tracer for detecting infection, since they are always abundantly present in the histopathological specimen drawn at the site of prosthetic joint infection. Most of the early reported results, however, can be considered disappointing. A possible explanation of similar contradictory results may be found in the different methods used for image interpretation. All the methods shown in Table 7.3 are based on a comparison of intensities between periprosthetic region and another region used as reference point or merely on the presence of any periprosthetic activity. Labeled leukocytes accumulate in bone marrow, and even if bone marrow is more present in axial skeleton and proximal humeri and femurs, its distribution is characterized by significant inter-individual variability. Furthermore, orthopedic hardware can give rise to localized marrow expansion [27–29], and other systemic diseases can also cause generalized bone marrow

Table 7.2 Reliability of combined bone/gallium-67 scintigraphy in the assessment of prosthetic infection

Author and year	Sensitivity (%)	Specificity (%)	Accuracy (%)
Merkel et al. [43]	66	81	77
Gomez-Luzuriaga et al. [44]	70	90	80
Kraemer et al. [45]	38	100	81
Love et al. [21]	75	59	66

expansion. Thus, similar conditions can make it difficult to correctly distinguish eventual alteration of marrow distribution from uptake really due to infection. Poor accuracy of above-mentioned results depends on the fact that the intensity of labeled leukocyte accumulation is not a useful criterion to obtain a correct diagnosis of infection.

In order to improve accuracy of labeled leukocyte scans, combined leukocyte/bone scan was tested, assuming incongruent images with the two tracers as positivity criterion. As shown in Table 7.4, inconsistent results were obtained. In particular, some authors reported a significant increase in sensitivity (from 45 % with leukocyte scan to 85 % with leukocyte/bone imaging) against a slight drop in specificity (from 100 to 85 %) [30]. Further experiences gave similar results, showing higher specificity values of combined scans in comparison with leukocyte scan alone (95 vs. 50 %) and only small decrease of sensitivity (88 vs. 100 %) [31].

On the other hand, lower accuracy of the combined scintigraphies was found by other investigators. Studying total knee replacements, Palestro et al. reported that sensitivity and specificity of combined scans were not significantly better than those of a leukocyte scan alone (67 vs. 89 % and 78 vs. 75 %) [20]. Only slight improvement of accuracy was obtained with combined leukocyte/bone scintigraphy by Love et al. (from 64 % with leukocyte scan to 70 % with leukocyte/bone imaging) [21]. Furthermore, incongruent leukocyte/bone images were observed in 15 % of asymptomatic patients with porous-coated hip arthroplasties [16]. Such

Table 7.3 Diagnostic reliability of labeled leukocyte scintigraphy in the assessment of prosthetic infection

Author and year	Type of prosthesis	Criteria for classifying images as positive	Sensitivity (%)	Specificity (%)
Pring et al. [46]	Hip and knee	Periprosthetic activity at least as intense as normal marrow	100	89.5
Magnuson et al. [41]	Hip and knee	As above	88	73
McKillop et al. [24]	Hip and knee	Any type of periprosthetic activity	50	100
Wukich et al. [30]	Hip and knee	Focal increase of activity compared with adjacent bone marrow activity	100	45
Johnson et al. [31]	Hip and knee	Any type of periprosthetic activity	100	50
Palestro et al. [32]	Hip	Any type of periprosthetic activity, regardless of intensity	100	23
Palestro et al. [32]	Hip	Periprosthetic activity more intense than the controlateral hip	23	63
Palestro et al. [20]	Knee	Any type of periprosthetic activity, regardless of intensity	89	50
Palestro et al. [20]	Knee	Periprosthetic activity more intense than the controlateral hip	89	75

Table 7.4 Reliability of combined leukocyte/bone scintigraphy in the assessment of prosthetic infection

Author and year	Type of prosthesis	Sensitivity (%)	Specificity (%)
Mulamba et al. [47]	Hip	92	100
Merckel et al. [48]	Hip and knee	86	100
Pring et al. et al. [49]	Hip and knee	100	66
Palestro et al. [20]	Knee	67	78
Cuckler et al. [50]	Hip and knee	60	73

incongruence, not dependent on the presence of an infection, is probably due to the different distribution of the tracers (marrow uptake for leukocyte and bone uptake for diphosphonate). Several conditions can affect both these distributions or only one of these, with unforeseeable effects.

Labeled colloids used for bone marrow imaging (such as 99mTc-Sulfur colloid) and labeled leukocyte have a very similar distribution in the bone marrow in normal subjects and also in patients with marrow abnormalities. Combining bone marrow with leukocyte imaging, congruent images are obtained, except in the case of osteomyelitis, which strongly attracts white blood cells, producing incongruent uptake patterns. On the basis of these criteria, Palestro et al. used leukocyte/marrow imaging in patients with painful hip replacement, obtaining a sensitivity of 100 % and a specificity of 98.7 % for the diagnosis of infection [32]. These authors in another study, regarding painful knee prostheses, found that these combined scans produce more accurate results than bone scintigraphy alone, leukocyte imaging alone, and combined leukocyte/bone imaging in diagnosis of infection [20]. Love et al. studied, with leukocyte/marrow imaging, 59 painful lower extremity joint replacements and reported sensitivity, specificity, and accuracy values for prosthetic joint infection of 100, 91, and 95 %, respectively [33]. These authors, more recently, investigating 150 failed joint prostheses, found that sensitivity, specificity, and accuracy of leukocyte/marrow imaging were 96, 87, and 91 %, respectively. Furthermore, the test resulted more accurate than bone (50 %) bone/gallium-67 (66 %), and leukocyte/bone imaging (70 %). From a practical point of view, leukocyte scan should be performed first, since if no periprosthetic activity is found on this scan, the marrow scan need not be performed. Alternatively, simultaneous dual-isotope acquisitions can also be performed, with significant advantages from the point of view of the comparison and interpretation of the images.

In addition to the 111-Indium,, leukocytes can be labeled with technetium-99m with satisfactory results. This method, avoiding the execution of bone marrow imaging, contemplates the acquisition of images at various time points. The early images should reflect the uptake of leukocytes in the marrow, while late images reflect the uptake due to the infection (Fig. 7.2). With this approach Pelosi et al. obtained satisfactory results, with an accuracy of 75 % using a visual analysis and of 95 % using a semi-quantitative analysis [34]. If one were to perform, however, even after technetium-99m-labeled leukocyte scan, the bone marrow scintigraphy, it is necessary to carry out marrow imaging at least 72 h after leukocyte scintigraphy. In conclusion, scintigraphy with labeled leukocytes, if based on a positivity criterion that takes into account the normal distribution of bone marrow rather than the intensity leukocyte uptake, is the most reliable method for diagnosis of prosthetic infection. This scan can be performed labeling cells with indium-111 and comparing the findings with bone marrow imaging obtained by technetium-99m-sulfur colloid. Alternatively, the labeling can be performed with technetium-99m, evaluating normal marrow activity and infection by multiple time-point analysis.

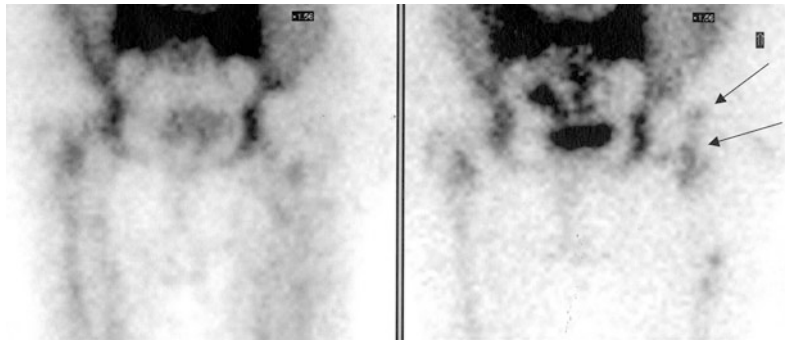

Fig. 7.2 99mTc-labeled leukocyte scan at 30 min (*left*) and 20 h (*right*) after labeled cells administration, in a patient with infection of left hip prosthesis. The appearance of two areas of increased uptake of the radiopharmaceutical (*arrows*), which was not present in the *left image*, can be seen on the *right image*

7.4 Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography

In recent years, fluorine-18-fluorodeoxyglucose positron emission tomography (18F-FDG) has been widely utilized in diagnosing prosthetic joint infection due to its advantageous characteristics (high resolution of PET images, availability, and rapid completion of the examination) and some disadvantages of leukocyte imaging (time-consuming separation and labeling of cells, direct contact with blood). The obtained results, however, seem to be inconclusive, mainly because of differing methods for image interpretation. In fact, some authors have used as a criterion of positivity, the increased uptake at the bone prosthesis interface, resulting in sensitivity, specificity, and accuracy values of 90, 89.3, and 89.5 %, respectively, for prosthetic hip infection and of 90.9, 72 and 77.8 %, respectively, for prosthetic knee infection [35]. Other authors have argued that accuracy of the test does not depend on the intensity of the uptake, but on the location of the uptake. In particular, the presence of activity at the bone–prosthesis interface along the shaft of the femoral component of a hip prosthesis is sensitive (92 %) and specific (97 %) for infection [36]. Further experiences confirmed that periprosthetic uptake patterns on PET images are able to differentiate infection from aseptic loosening, while intensity of uptake does not permit such a diagnosis [37]. On the contrary, Manthey et al. found that differential diagnosis between aseptic loosening and infection is possible by analyzing both intensity and pattern of uptake (96 % accuracy) and that the presence of activity around the femoral head and neck (the exact opposite of what was stated by others) are suggestive of infection [38]. Considering only intense periprostatic activity, Stumpe et al. found 18F-FDG-PET significantly sensitive, but not specific, with an overall accuracy of 69 %, which resulted in lower than that obtained with bone scan [39].

Using several different criteria for interpretation of 18F-FDG images, Love et al. reported that the most accurate criteria (71 %) for diagnosing infection is the presence of activity on the bone–prosthesis interface, with a target to background ration greater than 3.6:1 for hip replacement and 3.1:1 for knee replacement [33]. This study, however, demonstrates that the accuracy of leukocyte/marrow imaging in the same patients was 95 %, showing that 18F-FDG cannot replace leukocyte/marrow imaging in differentiating aseptic loosening from infection. Similar results were obtained by Mayer-Wagner et al., who, with 18F-FDG, found sensitivity and specificity values of 67 and 83 %, respectively, for the diagnosis of prosthetic infection [40].

7.5 Conclusions

In the evaluation of painful joint replacements, nuclear medicine plays essentially the role of differentiating aseptic loosening from infection of the prosthesis. Some partial analogies between the pathophysiological frameworks of these two conditions make nonspecific tracers of inflammation unreliable. The bone scan, due to its excellent negative predictive value, can be used as an initial screening test, since no tracer uptake reliably excludes infection. Labeled leukocyte scan combined with marrow imaging or based on multiple time-point analysis to evaluate the normal marrow activity is the scintigraphic method of choice for diagnosing infection.

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Periprosthetic DXA

8

Carlina V. Albanese

8.1 Introduction

The first studies on measurement of periprosthetic bone mass started at the end of the 1980s. The single-photon absorptiometry (SPA) devices were soon abandoned due to the low spatial resolution. Also the devices for dual-photon absorptiometry (DPA) were limited in terms of spatial resolution, scan times, and poor precision; therefore, the application in the orthopaedic field was stopped after a few studies [1]. The introduction of dual-energy X-ray absorptiometry (DXA) marked a decisive turning point, so that these facilities were implemented on the first specific analysis software to measure the bone mineral content (BMC) and the bone mineral density (BMD) in the proximity of metal implants by their automatic insulation through recognition of extreme density outside the normal range of bone [2]. Additionally, the algorithms detect the bone-to-soft tissue and bone-to-implant interfaces, and the effects of heavily attenuating implants can be excluded. At the beginning of the first DXA applications, the methodological issues to evaluate accuracy and precision of the densitometric parameters were tested, and thereafter various analysis protocols for the study of bone remodeling around different stem design of cemented and uncemented prosthesis implants were proposed. After having obtained many encouraging results, the application of DXA technique in the orthopaedic field of research was gradually extended to different areas of interest and in particular to study:

- preimplantation bone characteristics;
- reaction of the bone to implant metal;
- periprosthetic bone stock;
- influence of stem design and different weight-bearing regimes after implant on bone remodeling;
- longitudinal evaluation of time-related bone remodeling after implant.

Periprosthetic bone loss is one of the most common complications of total hip arthroplasty (THA) and total knee arthroplasty (TKA). The aseptic loosening of prostheses and periprosthetic bone loss are thought to be consequences of both stress-shielding and an inflammatory process induced by foreign-body particles. Loss of periprosthetic bone mass can compromise the outcome of arthroplasty and may predispose to loosening and migration of prosthesis, periprosthetic fracture, and to problems in revision arthroplasty [3, 4]. Several diagnostic tools are available in the clinical diagnosis of failed arthroplasty (see Chaps. 6–7), but most of these

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techniques are insensitive, nonspecific, and imprecise for the determination of quantitative changes in bone mass about metallic prosthesis [5–10].

Qualitative data on periprosthetic bone can be obtained with magnetic resonance imaging (MRI), computed tomography (CT), and radiography. Scintigraphy is a sensitive but nonspecific technique for diagnosing loosening. MRI will often provide better anatomical details for preoperative planning in extensive deep collections although the portion of the image adjacent to the prosthesis will be degradated by metal artefacts [5]. Recently, it was reported that CT shows more and larger periprosthetic lesions than radiographs around an ankle prosthesis, and they recommend adding CT imaging to postoperative follow-up after total ankle arthroplasty for patients with suspected or known periprosthetic lucencies on radiographs [6]. Other prospective studies showed that quantitative evaluation of periprosthetic bone remodeling using quantitative CT allows an accurate analysis of bone structures with a consistent reduction in soft tissue and metal artefacts [7, 8]. However, these CT studies do not describe the method used to position the region of interest (ROI) to minimize the operator's intervention during the monitoring of periprosthetic BMD, and no data are available related to the precision of measurements performed. At the present time, owing to the high radiation dose required for CT imaging and the high cost of utilizing these technologies, the method is restricted to research purposes. Standard radiographs give direct information on prosthetic position and bone morphology, and they were applied to evaluate loosening and bone remodeling after prosthesis implant [9], but as reported by Engh et al. [10] are not very sensitive in the quantitative evaluation of periprosthetic bone resorption. In fact, although the method can precisely monitor the geometric qualities in the bone, bone mass changes of less than approximately 30 % are difficult to visualize. Furthermore, the radiographic features did not correlate well with clinical outcome [2]. This may reflect a true lack of correlation or might result from poor precision and accuracy of radiographic assessment.

Changes not already visible on standard X-ray films can be detected early with DXA [2, 3]. The measurement of bone mass, since the first studies, was an indirect index of redistribution of the mechanical load induced by a particular prosthetic design and of the resulting biological response of bone [2, 11]. Using DXA periprosthetic software, it is possible to both quantify the host bone response in the presence of a prosthesis stem and relate it to its specific design, and study the dynamics of bone–prosthesis interaction. A cementless stem provides excellent results in long term if it has a good primary stability, which in turn ensures a good osteointegration (secondary stability). It is well documented that the more uniform is the transmission of forces from the stem to the bone, the smaller will be the phenomena of stress-shielding. Moreover, the more is the transmission of forces along the stem the greater is the stress-shielding [12, 13]. Periprosthetic bone resorption may be reduced in the absence of other complications, the longevity of the implant avoiding the prosthesis aseptic loosening. From this and other well-established scientific evidence was born and expanded with the passing of years the interest in the field of orthopaedic applications of the DXA technique. Although the periprosthetic DXA can be applied to evaluate different prosthesis joints such as humeral head [14] and spine [15], the majority of studies are currently conducted on hip and knee implants. This chapter summarizes the basic principles of periprosthetic bone densitometry and its clinical applications in the management of hip and knee arthroplasty in the light of a brief review of the literature and our own experience.

8.2 DXA Technique and Periprosthetic Software

DXA technique. Currently, DXA is the most widely accepted method for measuring periprosthetic bone mass for its accuracy, reproducibility,

and low invasiveness [2, 16–18]. This technique uses X-ray absorption to determine the amount of bone in specified skeletal regions. DXA is commonly used for monitoring bone changes related to ageing, metabolic disorders, drug therapies, etc. Because X-ray tubes produce a beam that spans a wide range of photon energies, the beam must be narrowed in some fashion in order to produce the two distinct photoelectric peaks necessary to separate bone from soft tissue. The major manufacturers of DXA systems in the United States have chosen to do this in one of two ways. GE Healthcare of Madison, WI, and Norland Corp./Cooper Surgical Company, Ft. Atkinson, WI use rare-earth K-edge filters to produce two distinct photoelectric peaks. Hologic Inc., Waltham, MA, uses a pulsed power source to the X-ray tube to create the same effect. In these devices, the metal removal analysis algorithms are available. The amount of bone in the beam path is calculated as BMC in grams. BMC is then divided by the projected area of the region scanned, and this is reported as the BMD in g/cm^2. BMD thus provides an "area density", representing bone concentration in a given region, corrected for size of that region. The DXA output is therefore similar to the AP projection in conventional radiography where a three-dimensional structure is imaged in two dimensions. The radiation dose is low (< 5 mrem/scan) [7], and scan time is very fast ranging from 4 to 12 min in relation to the equipment used. Phantom tests have shown that DXA is accurate for determining periprosthetic BMD with an error below 1 % [2].

Periprosthetic software. The DXA scan of sites containing metal is taken in a similar fashion as scanning other bone sites. Because the bone dimensions, such as the cortical shell, are considerably smaller than in the equivalent spine or hip regions, higher spatial resolution is needed. The metal removal software excludes the contributions of the heavily attenuating metallic implant, measuring BMD solely on the periprosthetic bone. Specialized algorithms automatically detect bone–soft tissue and bone–implant interfaces. This is necessary since precision results are better if the computer algorithm is allowed to define the edges of the bone or metal regions compared with manual exclusion. Once the metal-excluded bone region has been defined, the bone map is broken into regions small enough to be sensitive to local bone adaption but large enough to have adequate precision usually not less than 1 cm^2. There is no periprosthetic single ROIs analysis protocol that is universally accepted. To study periprosthetic hip, the most popular are the Gruen zones, originally defined for radiographic assessment of bone quality [19]. These seven regions are typically to be good compromises between precision and sensitivity. That is, smaller regions will have lower precision but higher sensitivity. However, different protocols of analysis have been proposed to adapt them to the study of different stem design [11, 20] and to evaluate bone remodeling around different metal joint prostheses [21–23]. Lunar GE Orthopedic software measures BMD on the medial and lateral sides of hip implants using an automated region of ROI positioned according to Gruen zones to minimize the operator's intervention (Fig. 8.1). Lunar has also included an optional cement exclusion boundary layer to aid in removing the effects of overestimation due to cement around prostheses [16]. Hologic metal removal and Norland software include a general ROI analysis that allows the user to create ROIs of arbitrary size and location, including the Gruen zones (Fig. 8.2). These softwares also allow for the mirror image of the analysis ROIs to be superimposed onto the contralateral femur (Fig. 8.3), which can be useful in different research applications, for example to compare operated versus unoperated limb or to compare different length prostheses (Fig. 8.4). The periprosthetic algorithms are most commonly used to analyse bone stock surrounding hip, knee arthroplasties, and spine fusions.

Accuracy. In bone densitometry, accuracy describes the degree to which the measurement of bone density reflects the true bone density. In other words, if the bone in question was removed from the body, measured, and then ashed and assayed, the true bone density could be determined. The accuracy error is usually described as %CV that describes the proportion

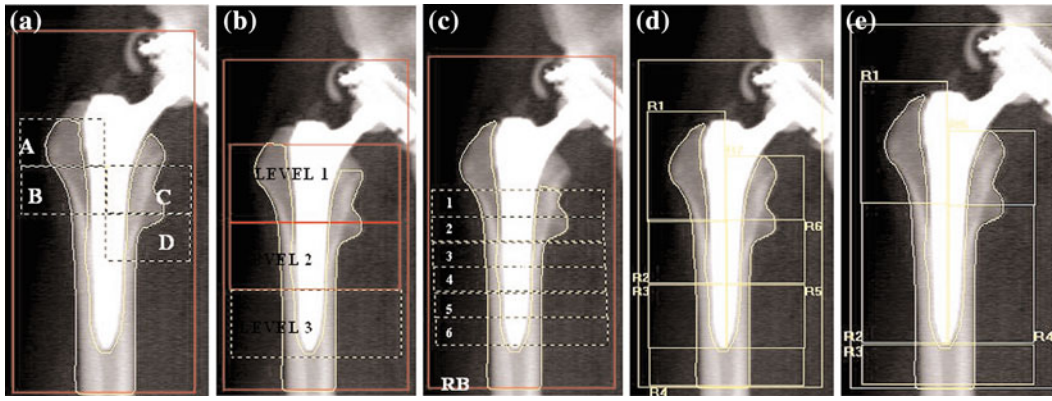

Fig. 8.1 A few example of periprosthetic DXA protocols of analysis after total hip arthroplasty, proposed by various authors. (**a**) Kiratli et al. [2]; (**b**) Engh et al. [26]; (**c**) Kilgus et al. [17]; (**d**) Trevisan et al. [11]; (**e**) Albanese et al. [20]

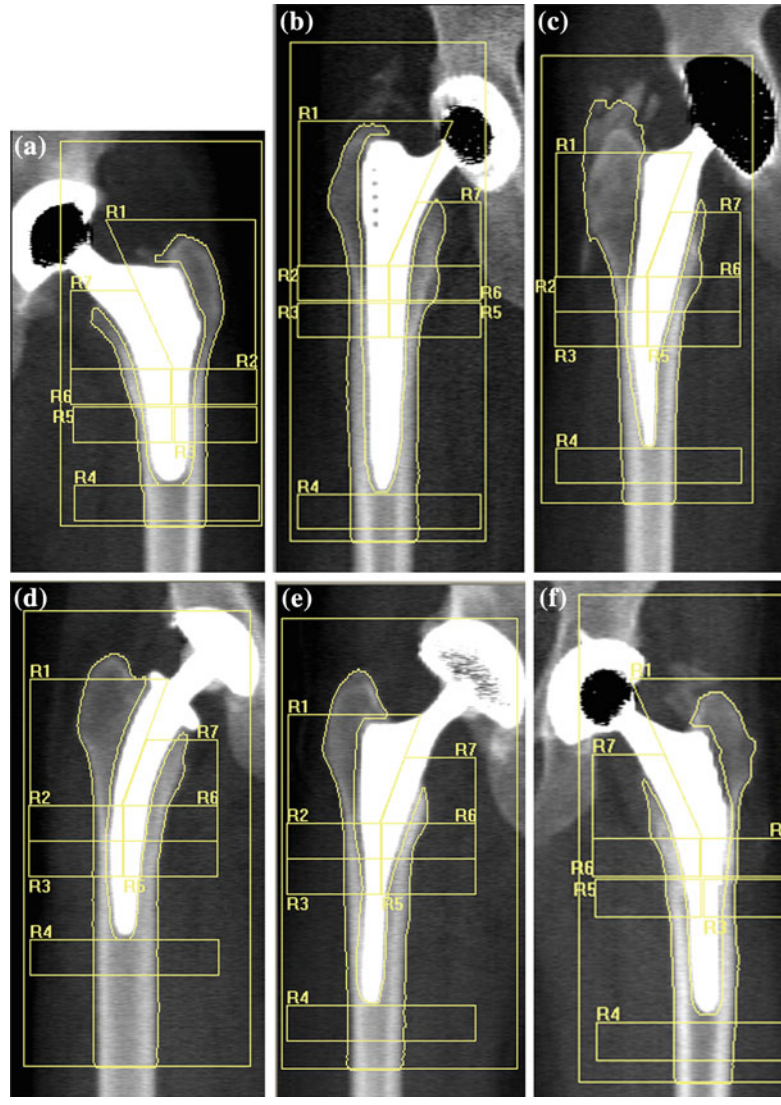

Fig. 8.2 Periprosthetic DXA was used to compare bone mass after uncemented THA of a custom-made stemless design (**a**) with five groups of conventional cementless implants: Alloclassic (**b**), Mayo (**c**), CFP (**d**), IPS (**e**) and ABG (**f**). The adaptive bone changes of the proximal femur 3 years after implantation were evaluated. To allow the comparative analysis of prosthesis with different length of the stem, ROI 3 and 5 are placed more proximally with respect to standard Gruen analysis protocol [33]

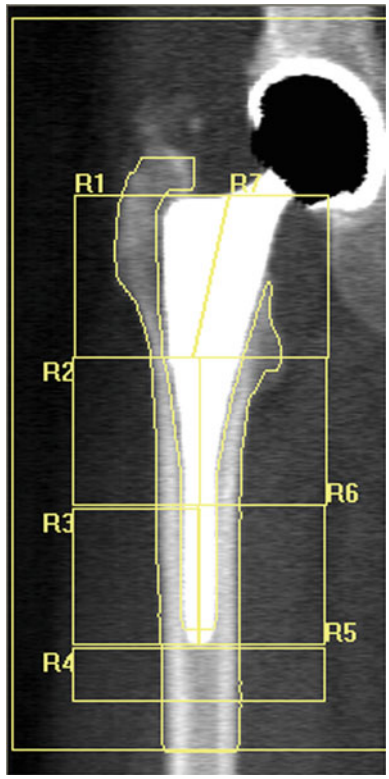

Fig. 8.3 Periprosthetic DXA: example of 7-ROI protocol of analysis according to Gruen zone

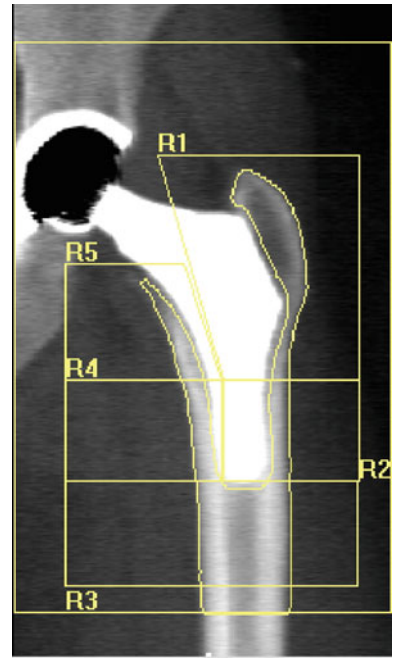

Fig. 8.4 Type 1 custom-made femoral implant featuring an extremely short distal stem. DXA images of the proximal femoral periprosthetic analysis with 5 regions of interest: R1–R5, [20]

by which the individual measurements vary from the mean value as a percentage that is synonymous with "true BMD". Therefore, lower values of %CV are better than higher because of the %CV describing the variability of the measurement about the true BMD. Different factors may affect the accuracy. It was reported that bone cement infiltration into bone and the cement mantle around the prosthesis may affect accuracy because they determine an artificial increase in BMD [3]. A study on implanted cadaver femora reported [24] that positioning of patients is essential to obtain reliable results. Rotation of the femur about its longitudinal axis altered the BMD measurement. The largest variations with rotation were in region 7, the calcar and lesser trochanter: 15° internal rotation caused a 24 % difference compared with neutral rotation. This is important as it is in this area where marked bone remodeling and resorption occur after joint replacement [13].

Precision. Precision is the ability to reproduce the measurement when it is performed under identical conditions when there has been no real biological change in the patient. Monitoring periprosthetic bone after stem implantation provides insight into the pattern of stress redistributions that occur after implant insertion [3, 4], so the precision error of bone density testing assumes great importance when the technique is used to follow changes in bone density over time in this specific context. Like accuracy, precision is usually described as %CV. Again, the smaller the %CV is, the better the precision of the technique. Accuracy is far less important than precision. This is because it is the magnitude of the difference between measurements that is of interest.

Different factors may affect the DXA periprosthetic scan reproducibility. The precision relies on the quality of the scanner, the quality of the analysis software [25], mode of scan analysis in the case of cemented prosthesis [21], position of scanned limb [22], and the homogeneity of

positioning of the patients at follow-up investigations [23]. The in vivo precision error of periprosthetic BMD measurement ranges from 1 % to 7.5 % depending on the ROI and type of the prosthetic stem [17, 24, 26]. Cohen et al. [24], in a study designed to evaluate the DXA accuracy, reported that the most significant factor affecting reproducibility was rotation of the femur. They found a CV variation of 2, 2.7, and 1 % using a hydroxyapatite phantom, an anthropomorphic phantom specimen, and in repeated measurements on implanted cadaver femora, respectively. In patients, the precision error was 1.1–4.5, depending on the ROI and rotation of the femur particularly in the region of calcar (ROI 7 according to Gruen analysis).

8.3 Periprosthetic Hip

The preoperative application of DXA, in THA to prospectively evaluate implant primary stability, is started from the observation that the efficiency of a prosthesis stem and the type of fixation are dependent on the degree of mineralization of the bone in which the prosthesis is implanted [27]. In case of poorly mineralized bone, the cemented prostheses are more suitable while in well mineralized bone with a potencially higher long-term mechanical quality, uncemented prostheses are better suited. DXA has been extensively used to evaluate the bone remodeling pattern associated with uncemented or cemented femoral stem implants. Bone cement alone or mixed with radiopaque substances such are barium or zirconium is the cause of artefacts in BMD measurements. Uncertainty remains as to whether mixed or alone cement should be included or excluded from analysis of ROIs when measuring BMD around cemented femoral implants. This had led various authors to study mainly prostheses fixed without cement [1, 2, 8, 12, 13, 17, 18].

Wilkinson et al. [21], in a study aimed at determining the effect of bone cement on the measurement of BMD in femoral ROIs after THA, reported that manual exclusion of cement from femoral ROIs increased the net CV from 1.6 to 3.6 % and decreased the measured BMD by 20 %. They concluded that manual removal of cement may be of use in population studies but of limited value in the monitoring of individuals. The main reason for this poor precision lies in the difficulty of consistently removing the same amount of cement from baseline and subsequent analyses. Venesmaa et al. [28] in a prospective 5-year study were likewise unable to distinguish cement from bone. However, it can be assumed that the density of the cement mantle does not change with time [16]. Therefore, to estimate long-term changes in periprosthetic bone density after cemented THA, BMD should be measured in the immediate postoperative period because all the BMD changes found during follow-up reflect the periprosthetic BMD measured baseline.

Uncemented prostheses, ensure high primary stability that on one hand reduces the risk of stress-shielding (loosening of the prosthesis) and on the other promotes the progressive bone integration between bone and prosthesis for direct adhesion. The evaluation of preoperative BMD makes it possible to obtain precise information about the mechanical quality of bone in the individual patient [28]. Patients with low preoperative BMD risk lose more bone near the prosthesis. Bone loss may make revision surgery more complicated or predispose to periprosthetic fractures. It was also shown that results obtained from “standard femoral DXA”, can be used to provide the surgeon with useful data about the mechanical characteristics of certain areas of the femur involved in the fixing and support of the prosthesis, in particular the subtrochanteric region of the lesser trochanter that corresponds to the diaphyseal portion, bearing the maximum stress after insertion of a stem [29].

One of the most interesting and widely studied applications of DXA in orthopaedics is the evaluation of the changes of periprosthetic bone mass during the follow-up (secondary stability), also in relation to the design of the prosthesis stem. This application is started following the observation, in some patients of a marked demineralization in the proximal regions of the femur after implantation of a cemented or

uncemented prosthesis that influenced the mechanical stability of the implant [30, 31].

In long-lasting implants, the persistence of the phenomenon of stress-shielding and bone ageing, which is manifested by the endosteal enlargement and reduction in cortical thickness, are also additive potential causes of failure of the anchorage between bone and prosthesis. The survival of an implant, therefore, depends on a number of factors, such as the mechanical stability achieved, the bone integration with the bone that hosts it, the stem type used, the surgical procedures adopted, and the bone quality [32].

DXA, along with other standard diagnostic methods (conventional radiography, bone scintigraphy, CT, and RM), has contributed substantially to being able to respond to questions relevant to the evaluation of the survival of the prosthesis. The measure of bone stock, from the first studies performed with DXA, has indirectly resulted in a measure for the redistribution of the mechanical loading created from a particular prosthetic design and the consequent biologic response [2, 11]. Bone response seems to differ between different stem designs and type of fixation. Thus, bone densitometry has an important role assessing new prosthesis designs. Over the years, different protocols of analysis have been proposed in order to evaluate the bone redistribution around the implant with regard to specific stem designs obtaining satisfactory results about accuracy and precision [2, 10, 11, 16, 17] and clinical outcome.

Figure 8.1 shows the main application models proposed by various authors in the evaluation of bone changes after hip arthroplasty using DXA technique. In a cross-sectional multicenter clinical study [33], we have used a modified Gruen protocol of analysis to evaluate BMD changes in the periprosthetic bone of five femoral uncemented conventional implants compared with a custom-made stemless implant proposed by Santori et al. [34, 35]. The study was aimed at evaluating the effect on bone remodeling of the proximal loading device with metaphyseal geometry (lateral flare). In order to compare a shorter stem implant to longest stems,

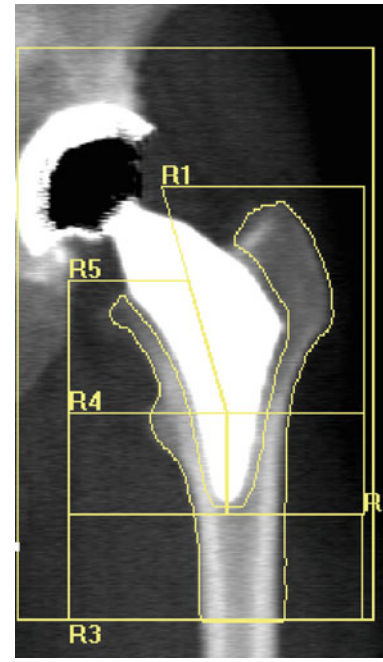

Fig. 8.5 Type 2 custom-made femoral implant featuring an almost complete absence of the stem. DXA images of the proximal femoral periprosthetic analysis with 5 regions of interest: R1–R5, [20]

six ROIs were placed more proximally and one under the tip (Fig. 8.2) with respect to the standard Gruen analysis protocol (Fig. 8.3). The short-term precision error was 1.8 %. The precision varied from 1.0 to 2.9 %, depending on the ROI. The short implant showed better strain distribution, resulting in a more favorable pattern of bone remodeling in the ROIs known to be at high risk of bone loss (calcar and greater trochanter). A similar finding was reported [20] when a short implant was compared to ultra-short custom-made femoral stem (Figs. 8.4, 8.5), and to another short-stem design with the same rationale [36]. In this study, a five-ROI protocol of analysis was proposed to test the flexibility of DXA in adapting the protocol of periprosthetic analysis to the specific requirements of new implant designs and its sensibility in the evaluation of the biological response of bone to changes in implant shape. The reproducibility was consistent with the literature [12, 25], ranging from 2.8 to 3.4 % in the implanted hip

and from 2.5 to 3.7 % in the contralateral unoperated hip. Recently, Lazarinis [37] in a prospective cohort study on the short collum femoris-preserving stem showed that substantial loss in proximal periprosthetic BMD cannot be prevented by the use of a novel type of short, curved stem, and forces appear to be transmitted distally. They reported a precision error between 1.1 and 5.7 % for the seven ROIs that were studied. However, the DXA images allow us to observe that the dividing line between zones 6 and 7 was not correctly placed in the mid-line of the lesser trochanter. Furthermore, the ROI 6 (that entirely includes the lesser trochanter) has been positioned too close to the bone tissue. These factors may be the sources of variability in the assessment of bone loss. These methodological considerations were allowed by the fact that the authors showed their protocol of analysis as a DXA printout image. However, despite a great variability of the periprosthetic protocols of analysis proposed in the literature, most of the published investigations reported instead of the "real bone densitometry images" [13, 20, 21, 33, 35, 36] a "schematic drawing" [2, 12, 24, 38–40] of their DXA analysis. This could generate some remarkable differences with respect to the actual analysis performed using the DXA metal/removal or orthopaedic software, thus not allowing the readers to both evaluate the reported results and reproduce the described protocol.

8.4 Periprosthetic Knee

DXA periprosthetic analysis software was applied to total knee artroplasty (THA) less than in hip prostheses. DXA was mainly used for the assessment of bone remodeling of the tibial plate and/or of the femoral condyles after TKA. The first report of local bone mass measurements after TKA was by Seitz et al. [41] using a CT device in a longitudinal study. They observed a significant reduction in the trabecular bone mass and in the cortical thickness around the tibial component immediately after the implantation. The application of QCT, after the initial enthusiasm, has been little used for artefacts due to the presence of metallic implants. Traditionally, the results of TKA have been evaluated by postoperative assessment of clinical parameters such as knee function, stability, range of motion, pain and plain radiographs. Plain radiographs can be used to assess implant position and knee alignment to evaluate bone–prosthesis and bone–cement interfaces, and to provide evidence of infection, loosening, or subsidence. However, the quantitative evaluation of periprosthetic bone density is unreliable in plain radiographs. Robertson et al. [42] showed the superiority of DXA compared to other methods in assessing changes in bone mass after TKA. DXA is a precise and reproducible method for assessment of changes in periprosthetic bone following TKA [43, 44]. However, the precision relies on the quality of the scanner, the quality of the analysis software, and the homogeneity of positioning of the patients at follow-up investigations [45, 46].

The applications of DXA to knee prostheses implies several differences from the protocols used for hip prostheses. A first substantial difference concerns the scarcity of soft tissues around the knee compared to the hip. A thin layer of soft tissue may be responsible for errors in the measurement of BMD or BMC. When using computer programs that are developed for different anatomical regions, it is necessary to imitate the expected tissue-equivalent density by use of tissue-equivalent material. Rice, nylon, or water bags are commonly used to trick the software into running in automatic mode and to avoid air gaps when these are not expected by the software. Recently, a specific "knee program" was proposed instead of traditional spine-mode DXA software that seems to alleviate the use of tissue aids and makes clinical use much simpler. However, it is currently only available for use in clinical research [47].

A second aspect concerns the placement of the limb, which is of crucial importance in TKA. It is well known that the DXA does not measure the volumetric density but only the surface density. Therefore, small movements of the femorotibial axis are able to jeopardize the

reproducibility and accuracy of the test. In the case of studies in PA projection, the knee must be carefully aligned to the longitudinal axis (0° rotation). The use of a heavy-duty polyethylene leg brace to fix the knee in full extension and neutral rotation has been advocated in analysis protocols [43, 44] and has also been shown to improve the precision of scans in a small-scale setup [45]. However, due to pain and swelling, TKA patients often have a temporary extension deficit of the operated knee. Baseline BMD scans are usually performed within the first week after surgery, when many patients may not be able to fully extend the knee, which is often possible in later follow-up scans. The clinical reliability of the suggested fully extended leg position is therefore questionable. Stilling et al. [22] found that flexion deficiency (range 5–30°) is a problem for two-thirds of patients in the first days after TKA surgery, and that even small changes in knee flexion (range 5–15°) substantially influence the periprosthetic bone density measured in the proximal tibia. They tested the clinical reproducibility of BMD measurements in the proximity of stemmed tibia components with a generally applicable foam positioner that would ensure neutral leg rotation and 25° degrees of flexion. A high degree of precision with CVs between 1.8 and 3.7 % for the most and least precisely assessed ROI is in accordance with other reports [43, 48]. However, even with a leg positioner at hand, a dedicated protocol must be available, and the positioning of the lower leg and knee must be meticulously handled to obtain high-precision scans over a long period of time by several technicians, which are the typical conditions in clinical studies.

Finally, the extension of the bone–prosthesis interface in hip prostheses is quite large, and this allows an accurate analysis of the established ROIs. In TKA, this space is greatly reduced since the extension of the prosthetic components can significantly reduce the area to be examined.

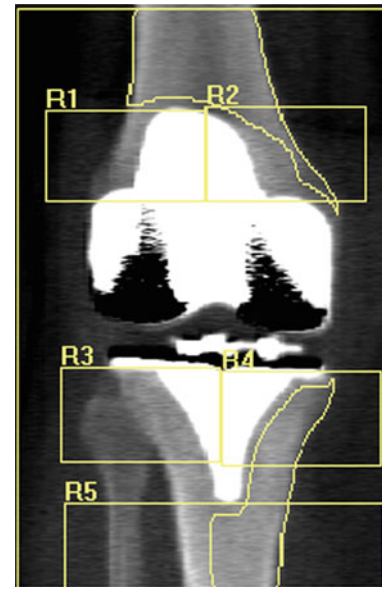

Fig. 8.6 Periprosthetic DXA after TKA. Example of 5-ROI protocol of analysis. The ROIs are manually placed to allow the assessment of bone mass around femoral and tibial components of the prosthesis. The bone of the fibula was excluded from the analysis

Soininvaara et al. [49] reported an average precision error of 3.1 % in femoral ROIs and 2.9 % in tibial ROIs after TKA. In the prosthesis-free control knees, CV% were similar: 3.2 and 2.5 %, respectively. They found the best precision in the femoral diaphyses above the implant (1.3 %), whereas the least reproducible BMD was determined in the patellar region of the TKA knees (6.9 %). However, three smaller ROIs in the distal femur showed slightly lower BMD precision (3.2–5.4 %) compared with the larger ROI 8, which enclosed the area of all three ROIs (1.9–2.6 %). This is consistent with previous findings: the smaller the area examined, the greater is the intrinsic system variability in evaluating the relevant BMDs [2, 24, 43]. Figures 8.6, 8.7, 8.8, and 8.9 show several densitometric analysis protocols in the study of bone remodeling of the knee after TKA.

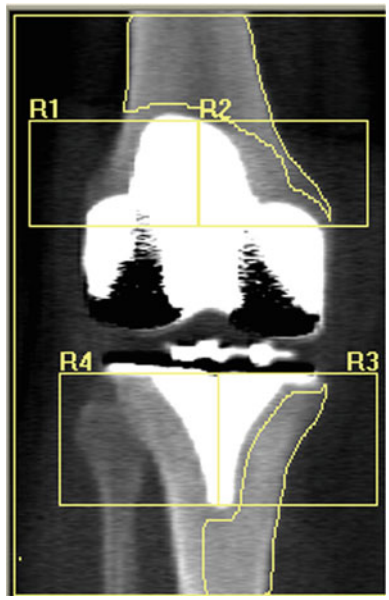

Fig. 8.7 Periprosthetic DXA after TKA. Example of 4-ROI protocol of analysis. The ROIs are manually placed to allow the assessment of lateral and medial bone mass around femoral and tibial components of the prosthesis. The bone of the fibula was excluded from the analysis

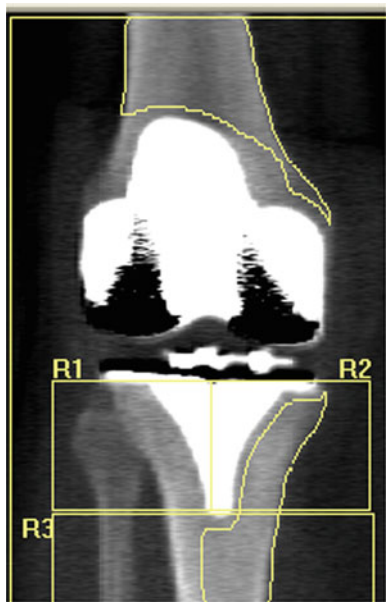

Fig. 8.8 Periprosthetic DXA after TKA. Example of 3-ROI protocol of analysis [22]. AP densitometry analysis of a right tibia (implant) with software-automated metal removal (*white*) and bone edge detection (*white line*). The bone of the fibula was excluded from the analysis

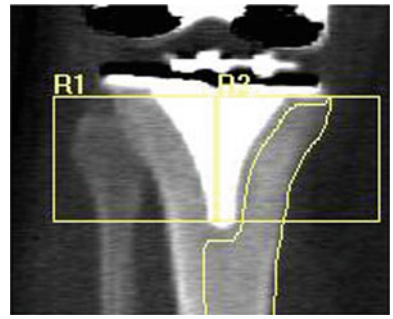

Fig. 8.9 Periprosthetic DXA after TKA. Example of 2-ROI protocol of analysis. The ROIs 1 and 2 are manually placed to allow the assessment of lateral and medial bone mass around tibial component of the prosthesis. The bone of the fibula was excluded from the analysis

8.5 Conclusions

Bone densitometry has far-reaching implications for orthopaedic practice and research. As the clinical survival of joint arthroplasties is clearly associated with the quality of surrounding bony i.e., BMD, it is important to measure bone strength and quality after arthroplasty. Small bone mineral changes around prostheses can be measured using DXA with special software algorithms providing a feasible method for monitoring over time. Furthermore, DXA requires only a small volume of bone to detect potential changes of BMD. Therefore, DXA is appropriate for the evaluation of bone mass adjacent to cemented or cementless prostheses and provides both the accuracy and the precision required to detect and quantify bone mass and remodeling around prostheses.

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Part III
Prosthetic Joints of Foot and Ankle, Hip, Knee, Shoulder, Elbow, Wrist and Hand

Foot and Ankle

9

Davide Edoardo Bonasia, Laura Bruno, Lorenzo Morino and Raul Cerlon

9.1 Introduction

Total ankle replacement (TAR) was initially attempted in the 1970s, but poor results and high failure rates with first-generation implants led to considering TAR inferior to ankle fusion until the early 1990s [1]. By that time, newer designs which more closely replicated the natural anatomy of the ankle showed improved clinical outcomes. Currently, even though controversy still exists about the effectiveness of TAR compared to ankle fusion, TAR has shown promising mid-term results and should no longer be considered an experimental procedure, but a reasonable alternative to arthrodesis in selected patients. When performing TAR, a thorough knowledge of the ankle anatomy, pathologic anatomy, and biomechanics is needed together with a careful preoperative planning. These aspects are essential to obtain durable outcomes. This chapter describes the most common TAR implants, surgical procedure, and the imaging techniques used pre- and postoperatively.

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9.2 Type of Prosthesis

First TAR implants were constrained, cemented, and required extensive bone resection both from the tibia and from the talus. Due to these characteristics, early loosening was a common complication and was attributed to the inability to dissipate the rotational forces produced because of the changing rotational axis of the ankle joint. However, first-generation unconstrained implants did not produce any better results due to the extra strain placed on surrounding soft tissues, as a result of the lack of constraint. Therefore, most of the second-generation implants overcame these problems by using semi-constrained designs. Second-generation implants pay particular attention to reproducing normal ankle anatomy, joint kinematics, ligament stability, and mechanical alignment [2].

Currently, there are more than 40 different TAR designs available on the market and most of them consist of 2 metal components and a polyethylene liner. Both fixed and rotating polyethylene liner designs are available, with the tendency of preferring rotating platform implants, in order to reduce components' wear. Almost all modern ankle replacements are now cementless, using porous bead coatings, normally covered in hydroxyapatite to encourage bone ingrowth, and require minimal tibial and talar bone resection. Most implants are designed to be implanted with an anterior approach to the ankle joint, but some newer implants require a lateral trans-malleolar approach.

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9.3 Preoperative Imaging

Preoperative imaging assessment of the patient is fundamental for the planning of surgery, in order to evaluate the ankle joint anatomy and deformity, as well as to choose the appropriate type and size of the prosthesis.

9.3.1 Traditional Radiography

Weight-bearing anteroposterior, lateral, and mortise views of both ankles are required. The rearfoot alignment (Cobey/Saltzman) view (Fig. 9.1a) is essential to evaluate the ankle joint and identify any calcaneal-to-tibial deformities. This view is obtained with the patient standing on an elevated platform, a cassette positioned 15° anteriorly inclined from vertical and the X-ray beam oriented perpendicular to the film, aimed at the ankle. In case of diaphyseal deformities, anteroposterior and lateral views of the leg (Fig. 9.1b) are required together with weight-bearing long-leg X-rays.

In the **coronal plane views**, different measurements can be obtained, including the lateral distal tibial angle (LDTA), the tibial–talar angle, and the calcaneal tibial alignment. The LDTA (Fig. 9.2a) is formed by the distal tibial articular surface and the anatomical axis of the tibia and measures 89° ± 3° [3, 4]. A decreased LDTA represents a varus deformity. The tibial–talar angle (Fig. 9.2c) is defined by the tibial and talar articular surfaces of the ankle joint. When the tibial–talar angle is >10°, the joint is defined incongruent (unstable) [5]. The calcaneal–tibial alignment (measured on the Cobey/Saltzman view) is useful to confirm any varus or valgus deformities as well as to assess every talar compensation (inversion and eversion) to an abnormal LDTA. The subtalar joint can compensate 15° of eversion and 30° of inversion [4].

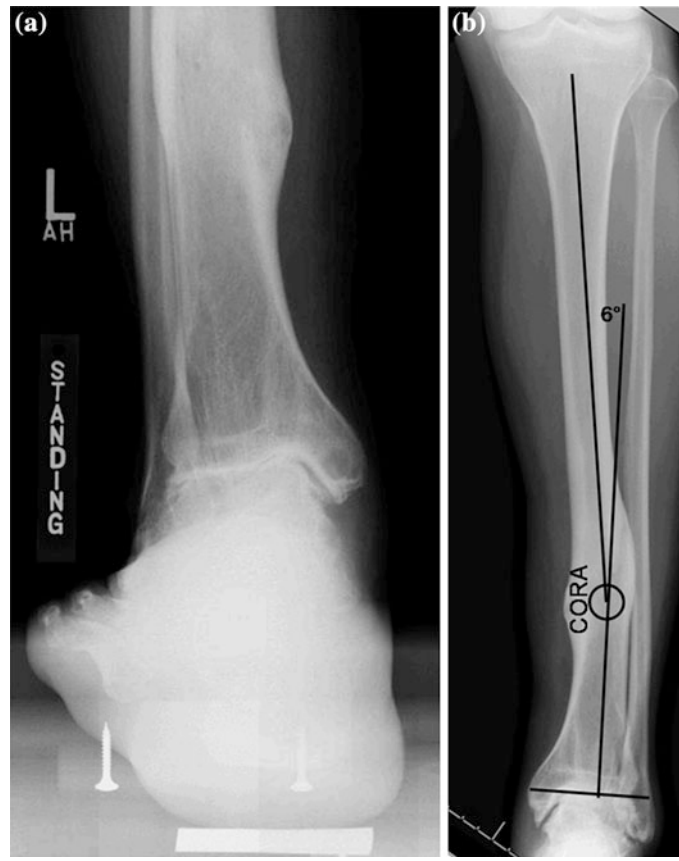

Fig. 9.1 Left posttraumatic ankle arthritis. **a** Cobey/Saltzman view. **b** Anteroposterior radiograph of the left leg showing a varus deformity, with center of rotation of angulation (CORA) located at the distal third of the tibia. With permission from: Bonasia et al. [3]

Evaluation of subtalar joint compensation and range of motion is important because tibial realignment (with osteotomy or TAR) may unmask a subtalar deformity. If this distal (rearfoot) deformity is not addressed, further symptoms may develop [4]. In the **sagittal plane**, the anterior distal tibial angle (ADTA) should be measured. The ADTA is formed by the mechanical axis of the tibia and the joint orientation line of the ankle in the sagittal plane and measures 80° ± 3° in the normal lower extremity (Fig. 9.2b) [4]. An increased ADTA represents a recurvatum deformity.

If an abnormal ADTA or LDTA is present (sagittal or coronal deformity), the center of rotation of angulation (CORA) is measured. The CORA is the intersection of the mid-diaphyseal line and the line starting from the middle of the joint and perpendicular to the abnormal ADTA or LDTA (Fig. 9.3) [3]. The CORA can be located at the joint line level (usually due to anatomical joint line malalignment or to ankle degeneration) or proximally (usually due to tibial deformities/fractures). Malalignment and instability should be thoroughly evaluated in the preoperative planning. Both can lead to edge-loading of the implant, polyethylene wear, progressive deformity, and high early failure rates.

9.3.2 Computed Tomography

Computed tomography (CT) provides accurate information about bone stock. It is not routinely performed in primary TAR, but it is often required in case of severe deformities and revision surgery and in some cases of rheumatoid arthritis.

9.3.3 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is not routinely used preoperatively in TAR, but can be performed in case of avascular necrosis of the talus in order to confirm the diagnosis or to assess its severity and to evaluate soft tissue conditions.

9.4 Implantation Technique [3]

The patient is positioned supine, with a bump under the hip and a tourniquet on the proximal thigh. After antibiotic prophylaxis, a mid-line 10-cm skin incision centered on the joint line is performed. The superficial peroneal nerve is identified and protected throughout the whole

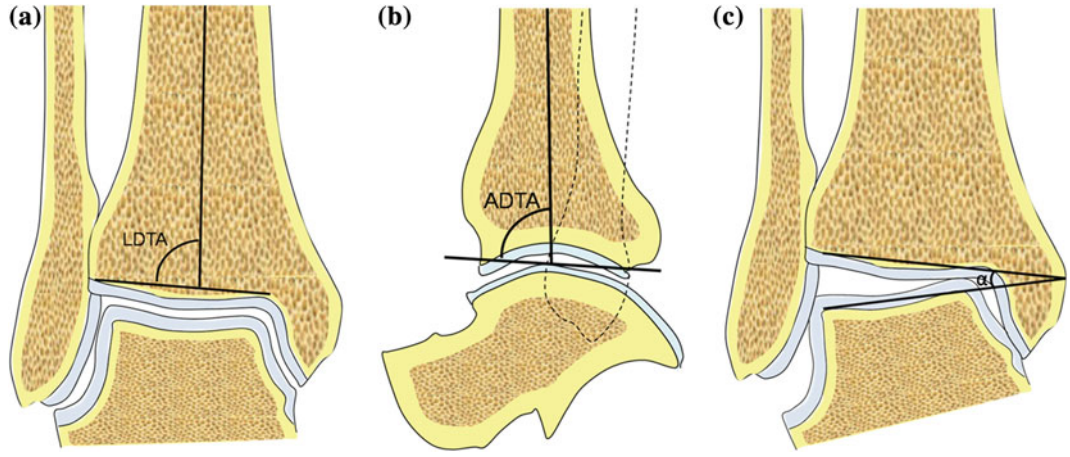

Fig. 9.2 Preoperative measurement. **a** The LDTA is formed by the distal tibial articular surface and the anatomical axis of the tibia (normal values 89° ± 3°). **b** The ADTA is formed by the mechanical axis of the tibia and the joint orientation line of the ankle in the sagittal plane (normal values 80° ± 3°). **c** The tibial–talar angle (α) is defined by the tibial and talar articular surfaces in the ankle joint; if it measures >10°, the joint is defined incongruent. With permission from: Bonasia et al. [3]

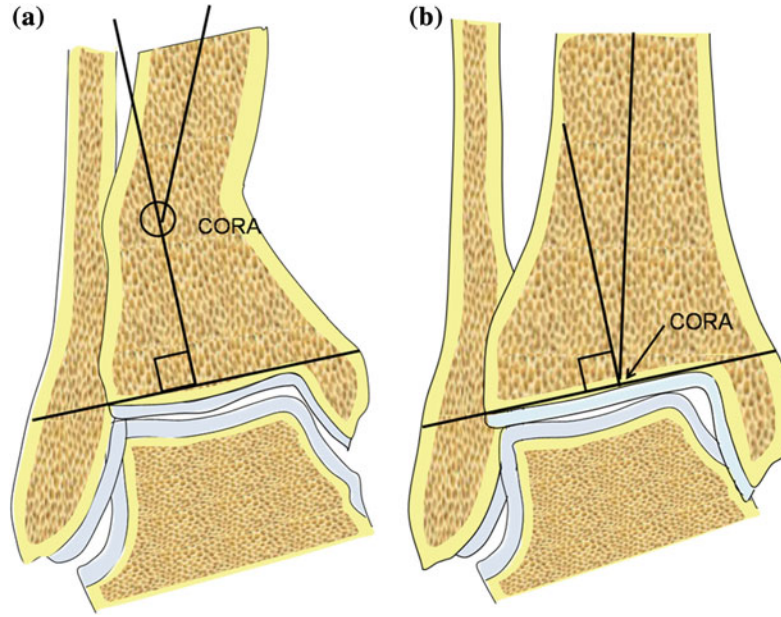

Fig. 9.3 The center of rotation of angulation (CORA) is the intersection of the mid-diaphyseal line and the line starting from the middle of the joint and perpendicular to the abnormal ADTA or LDTA (LDTA in this figure). The CORA can be located proximally at the tibia (**a**) or at the joint line level (**b**). With permission from: Bonasia et al. [3]

procedure. The joint is approached through the bed of the tibialis anterior tendon or the extensor hallucis longus, and the neurovascular bundle is retracted laterally. Once in the joint, it is fundamental to achieve a correct soft tissue balancing and restore a correct tibio-talar alignment, in order to position the tibial and talar components perpendicular to the plumb line of the body. Therefore, a careful debridement of the osteophytes, synovial tissue, and redundant capsule is carried out. The medial and lateral gutters need to be debrided as well.

In a *congruent varus* (*or valgus*) *ankles*, the tibial cut is then performed to neutralize the LDTA and to have a reference for talar tilt reduction. In the valgus tibial deformity, more bone should be removed medially compared to laterally and vice versa in the varus tibial malalignment. The talar tilt is then reduced by subperiosteal deltoid ligament release with a Cobb elevator. If this is not sufficient, the tibialis posterior tendon is released as well.

In *incongruent varus* (*or valgus*) *ankles*, the LDTA is normal and no neutralizing cuts are necessary. The talar tilt is reduced with intra-articular and extra-articular soft tissue procedure, as described above.

In case of *severe varus or valgus deformity* (*i.e., rheumatoid patients*), tibial and talar bone cuts are necessary to realign the joint, with the "sculpturing technique" [6]. When performing tibial cuts with the talus still tilted, it is important to have TAR instruments that allow talar cut independent of the tibial one. Then, soft tissue procedure can be performed to achieve a rectangular space between the tibial and talar cuts.

At this point, bone cuts are completed and trial components positioned. With the trial components, ROM and stability should be checked. If limited dorsiflexion is achieved, and this is not due to component malpositioning, a percutaneous Achilles' tendon lengthening is indicated and can be performed. If stability of the implant is not satisfactory from varus tilt, reconstruction of lateral ligaments may be necessary. Generally, if the implants are placed in anatomical alignment, with an appropriate poly spacer, instability is uncommon. If ligamentous stabilization is required, this can be performed, as for ankle instability, with anatomical repair (Broström [7] or Gould [8]), with or without auto/allograft augmentation, or with non-anatomical reconstruction tenodeses (i.e., Watson-Jones [9], Evans [10], Chrisman and Snook [11]

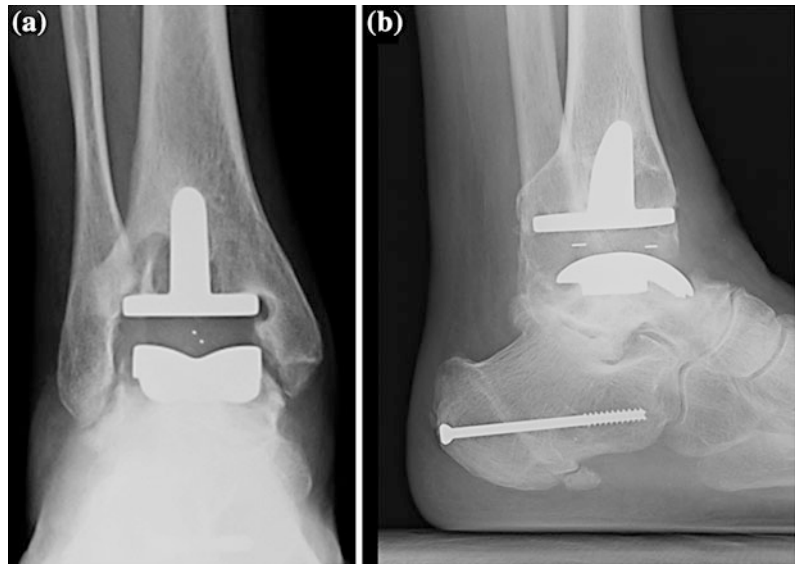

Fig. 9.4 **a** Anteroposterior and **b** lateral views of simultaneous total ankle replacement and calcaneal osteotomy. Note the marked signs of osteolysis around the tibial component, without loosening

procedures). Once a correct soft tissue balancing is obtained, definitive TAR components can be implanted.

Occasionally, despite these measures, hindfoot malalignment persists and requires correction with a separate hindfoot procedure (calcaneal osteotomy, subtalar fusion) that can be performed concomitantly or as staged second procedure.

The wound is then closed over a suction drain, which is removed on the first postoperative day. The postoperative regimen is dictated by combined bony procedures (arthrodesis or osteotomy). If only TAR and soft tissue procedures are performed, the patient is immobilized in a walking plaster cast for 4–6 weeks. Weight-bearing is usually allowed with crutches, unless markedly poor bone quality is identified. Then, the plaster is removed, free range of motion and weight-bearing as tolerated are allowed.

9.5 Follow-up

Postoperative imaging is fundamental to evaluate the correct positioning of the implant and complications that may occur during the follow-up (Fig. 9.4a, b). Standard follow-up includes clinical and standing X-ray (anteroposterior, lateral, and mortise views of the ankle) control 40 days after surgery, then repeated 6 months later and yearly thereafter.

Failure is defined as persistent pain with radiological signs of loosening of the implant [12]. TAR can fail because of infection, mechanical failure, or aseptic loosening. Aseptic loosening may be associated with extensive bone loss [13]. Initial investigations include a full blood count, erythrocyte sedimentation rate and level of C-reactive protein and standing plain radiography of the affected ankle. Radiological signs of loosening are radiolucent lines around the components, or malposition and subsidence of one or both of them, cavitation at the tibial component interface or migration of the components.

Component migration can be assessed through comparison of prosthesis alignment on sequential radiographs. Implant alignment is assessed through angular measurements of the angle between the anatomical axis of the tibia and the articular surface of the tibial implant on the AP radiograph; the angle between the anatomical axis of the tibia and the articular surface

of the tibial component on the lateral radiograph; and the angle formed by the talar component and the talar neck [14, 15]. Conventional radiography does not show a high sensitivity since the appearance of infection can be variable, besides radiographs are normal in most patients.

Standard radiographs are also useful to detect bony impingement, which may be the cause of persistent pain after TAR.

In spite of the past limitation due to metal artifacts, nowadays CT and MRI are useful tools to assess periprosthetic bone and soft tissues (Fig. 9.5).

Ultrasound is useful to detect joint effusions, soft tissue fluid collections, and in some cases synovial hypertrophy and inflammation (aided by the use of color and power Doppler). The more advantageous use of ultrasound, however, is to guide intervention such as joint aspiration. Joint aspiration is a useful confirmatory test showing sensitivity and a specificity ranging from 67 to 82 % and from 91 and 95 %, respectively [16, 17].

Nuclear medicine studies are extremely useful in evaluating prosthetic complications. Bone scan, performed with technetium-99 m (Tc-99 m)-labeled diphosphonates, is highly sensitive in detecting complications of lower extremity prosthetic joint surgery (Fig. 9.6). Both infection and aseptic loosening may show increased uptake on delayed images, but the test is not specific mostly in the early postoperative period [18]. Furthermore, even in the absence of complications, persistent periprosthetic activity has been shown to be increased for up to 2 years because of continued postoperative reparative osteoblastic activity, and performing the bone scan as a three-phase study does not improve the accuracy of the test. As a matter of fact, the blood pool images may also show increased activity in both aseptic loosening and infection. Despite the overall accuracy of bone scintigraphy in evaluation of the painful prosthetic joint is about 50–70 %, this study has a high negative predictive value and a negative bone scan excludes both loosening and infection [17]. Therefore, it may be used as an initial screening test in conjunction with other diagnostic tests.

Sequential bone/gallium imaging is often performed along with a bone scan and the studies are interpreted together, but it is nonspecific and offers only a slight improvement over bone scintigraphy alone and is of limited value in differentiating prosthetic joint infection from other causes of prosthetic failure.

Labeled leukocyte (white blood cell [WBC]) imaging has been proposed as the radionuclide procedure of choice for diagnosing prosthetic infection. Bone scan combined with indium-

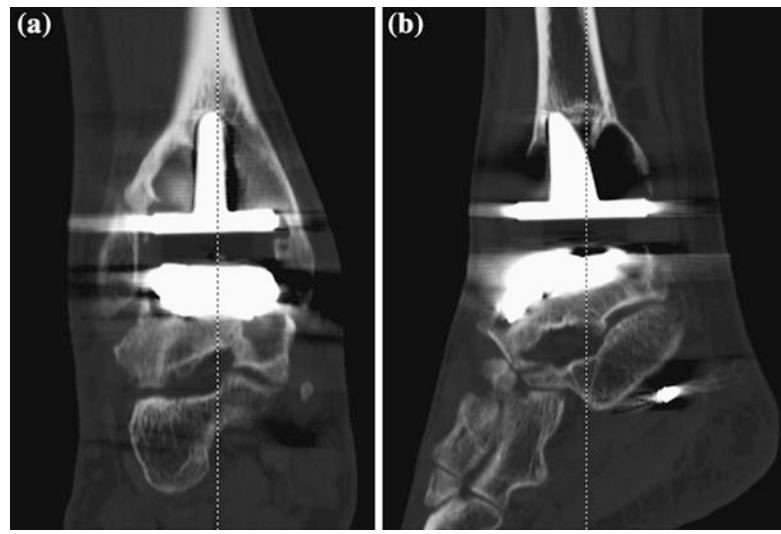

Fig. 9.5 **a** Coronal and **b** sagittal views of simultaneous total ankle replacement and calcaneal osteotomy. Note the marked signs of osteolysis around the tibial component, without loosening

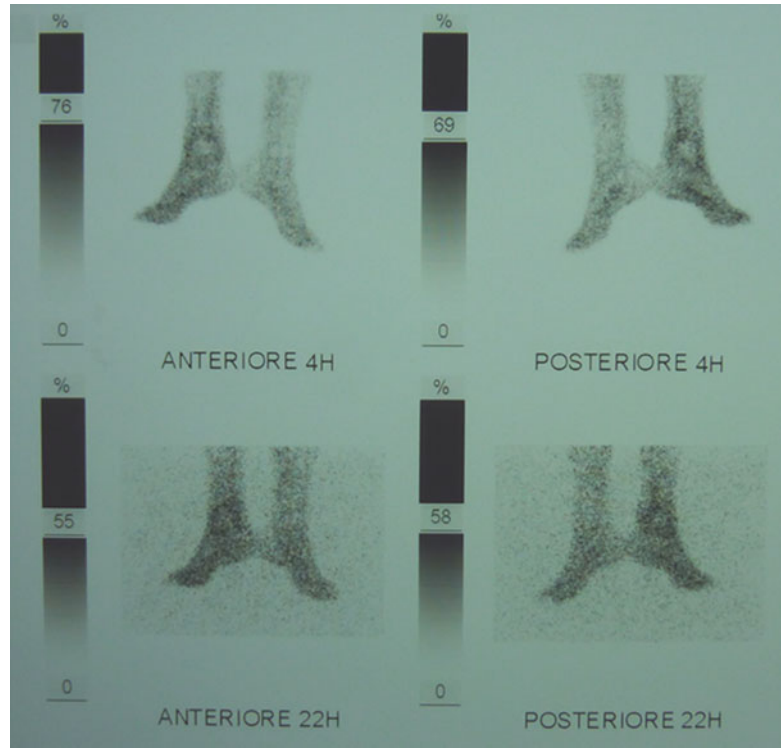

Fig. 9.6 Bone scan with technetium-99 m (Tc-99 m)-labeled diphosphonates in infected TAR. Note the increased uptake on *the right side*

111-labeled WBC has a low sensitivity and specificity, but both are increased when a Tc-99 m sulfur colloid marrow scan is done in addition offering the accuracy up to 95 % [19]. The principle of combined WBC/marrow imaging is based on the fact that both WBC and marrow images reflect radiotracer accumulation in the reticuloendothelial cells, or fixed macrophages, of the marrow. Normal individuals and in those with underlying marrow abnormalities show either a similar or spatially congruent distribution of marrow activity on WBC and marrow images. Osteomyelitis, including prosthetic joint infection, which stimulates uptake of leukocytes but suppresses uptake of sulfur colloid, results in spatially incongruent images.

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been reported to be effective for diagnosing prosthetic joint infection, since studies have shown sensitivity and specificity of 100 and 86 %, respectively, in limited numbers [19]. FDG is transported into cells via glucose transporters, but unlike glucose, it is not metabolized and remains trapped within the cell. Normal bone marrow has only a low glucose metabolism under physiologic conditions, whereas the infection shows an increased FDG uptake due to increased expression of glucose transporters in inflammatory cells and increased affinity of these glucose transporters for deoxyglucose. Degenerative bone changes usually show only faintly increased FDG uptake compared with infection. In spite of the fact that FDG-PET has generated considerable interest because of its advantages, studies have concluded that PET offers no benefit over standard three-phase bone scans so far [18].

The emergence of hybrid modality imaging using integrated single-photon emission computed tomography (SPECT) and PET with computed tomography (SPECT/CT and PET/CT) may also have a contributing role for more accurate assessment of joint replacement complications, especially combined with new radiotracers [18].

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Hip: Type of Prosthesis and Implantation Technique

10

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10.1 Hip Arthroplasty

Hip replacements are among the most common orthopedic procedures.

When a total hip replacement is performed, the arthritic damaged hip joint is removed. The ball-and-socket hip joint is then replaced with an artificial implant.

A total hip replacementimplant has three parts: the stem, which fits into the femur; the ball, which replaces the spherical head of the femur; and the cup, which replaces the worn out hip socket. Each part comes in various sizes to accommodate various body sizes and types (Fig. 10.1).

At present, there is a wide range of prostheses with different new types of articulations such as metal on metal and ceramic on ceramic instead of metal on polyethylene, based on new scientific research and availability of improved metal alloys, which may reduce the wear up to 1/4,000.

The use of exchangeable neck/ball (modular prosthesis) in primary as well as revision surgery has enhanced the surgeons amatory to create a stable prosthesis in most conditions and facilitates future revision surgery.

In some designs, the stem and ball are one piece; other designs are modular, allowing for additional customization in fit.

The stem could be implanted with cemented or uncemented technique.

Over the past 40 years, there have been many improvements in the materials and the methods used to hold the femoral in place. Today, the most common used bone cement is an acrylic polymer called polymethylmethacrylate.

From 1980s, new implant designs were introduced to attach directly to bone without the use of cement. In general, these designs are larger and longer than those used with cement.

From the results of Implants National Registries, it seems to be that the uncemented technique is more indicated for younger patients. However, final decision regarding implant selection should be based on the quality and anatomy of the patient's bone as well as on expected functional demands and expected life span of the patient.

All these issues have an impact on the choice of component fixation and, above all, on the choice of bearing surfaces.

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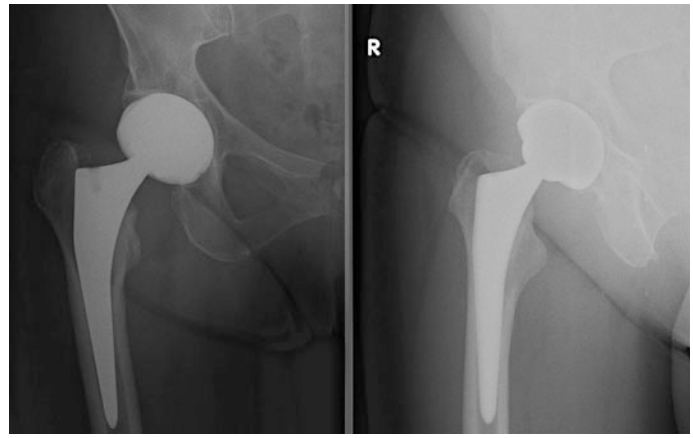

Fig. 10.1 Hip arthroplasty

The patient's bone type/quality, the presence of bone loss on the acetabular or the femoral side as well as the presence of shortening or deformity are all factors that may influence the final decision to opt for cemented or cementless fixation and to determine whether additional augmentation or bone grafting will be required. Several rating systems for bone quality have been reported. The Dorr classification (Fig. 10.2) has the advantage of simplicity and reproducibility and is of practical value in the clinical setting. According to this system, cemented femoral components are often advocated for Type C bone. Severe osteoporosis is associated with increased risk of intraoperative fracture, both femoral and acetabular, necessitating great care in the preparation and insertion of the components. In this setting, the bone quality may be such that the use of cemented component(s) may be preferable to achieve a stable and durable construct.

In the instance of THA after previous proximal femoral fracture or osteotomy where the hardware has been removed, the most distal screw hole should ideally be bypassed by at least two and a half times the diameter of the bone at that level to reduce the risk of periprosthetic fracture. This may then require that a revision-type long-stem femoral component be used in the primary setting.

Developmental dysplasia of the hip poses additional technical challenges. This is particularly seen in Crowe Types III and IV hips in which augmented acetabular reconstruction using metal and/or structural bone graft may be required. In addition, distortion of the femoral anatomy may require the use of either a fully modular femoral component to allow for correction of excessive femoral neck anteversion or even potentially a custom femoral component.

The tribology of materials is the main role in the follow-up of long-term implants. In recent years, technology has led to strong developments in this surgery developing more resistant materials and then determining a lower failure rate.

Nowadays, the aseptic loosening, normally due to the implants' wear, represents more than 75 % of the failures in prosthetic surgery of the hip.

The coupling materials available are as follows:

10.2 Metal on Metal

These are fabricated from a harder cobalt–chromium alloy and thus consist of a metal-on-metal couple. This new combination creates a differential hardness between the two moving parts. This differential hardness determines that the metal is likely to release less particles into the body and wear less over time. In all hip prostheses, the femoral head wears quicker than the acetabular shell (except the metal-on-polyethylene ones (hard-on-soft)). The difference in hardness is a major advantage over the previous

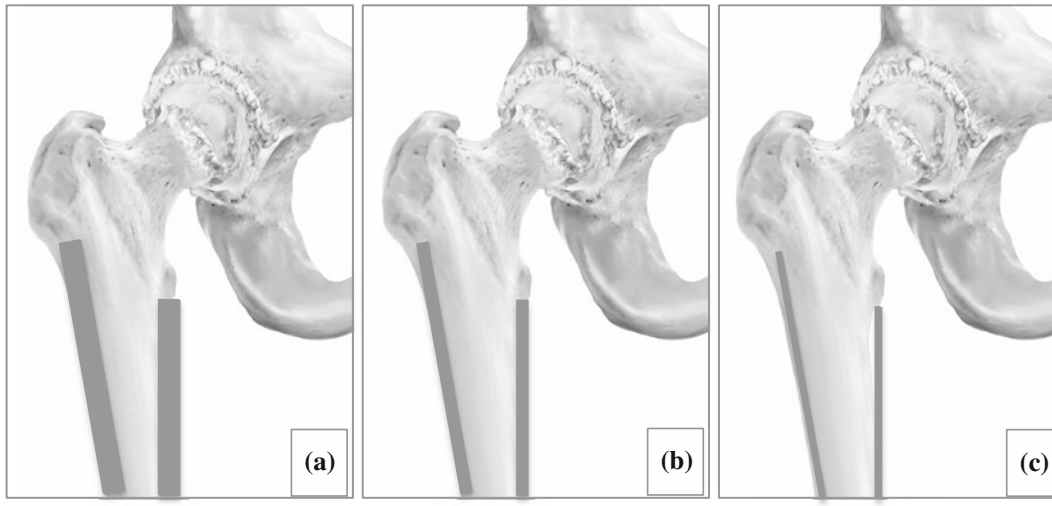

Fig. 10.2 Dorrr femoral bone classification. *Type A narrow canal* with thick cortical walls (champagne flute canal). *Type B* moderate cortical walls. *Type C wide canal* with thin cortical walls (stove-pipe canal)

metal-on-metal prostheses and even more over the metal-on-polyethylene prostheses.

The metal-on-metal bearings are hard without being brittle and they are more resistant to scratching and wearing. There is a debate on the effect of metal ions released by the couple; the potential effect of these ions is not clear yet, but research is being done on that subject.

10.3 Ceramic on Ceramic

Ceramic-on-ceramic (COC) has been an excellent alternative bearing surface for total hip arthroplasties (THA) in young, high-demand patients with end-stage arthritis of the hip.

Ceramic material has been used for THA in Europe for 40 years with variable results.

Hamadouche et al. described minimal wear, a low rate of complications and limited osteolysis with COC THA after 18.5 years of follow-up. On the other hand, the revision rate in Europe and the USA from 1988 till 1996 varied between 3 and 44 %.

Subsequently, new generations of C–o–C BIOLOX-delta bearings were developed, eliminating this risk and presenting the superior tribological properties of ceramics.

As it is demonstrated, the reinforcing mechanism is fully activated within a region of a few micrometers. For the macroscopic performance of the material, it is very important that immediately at the beginning of crack initiation, the reinforcing mechanisms are also activated. Regarding this mechanism, one should keep in mind that the average distance between the reinforcing zirconia particles is approx. 0.3 mm, i.e., similar to the grain size. Thus, the reinforcement is activated immediately when any microcrack is initiated. This is of particular interest for the significant advantage of ZTA (BIOLOX®delta) under severe wear conditions.

10.4 Ceramic–Metal on Polyethylene

Polyethylene acetabular cups coupled with metal or ceramic femoral heads remain the most popular bearing combination in the hip. In the long term, the polyethylene cups wear and the micron

and submicron wear particles result in osteolysis and loosening. Particles accumulate in periprosthetic tissues until a critical volume and concentration is reached, which results in osteolysis. Patients have different levels of reactivity to polyethylene particles and particle concentrations in tissues are dependent on access. It is important to reduce polyethylene wear rate in order to extend the osteolysis-free lifetime.

10.5 Hip Resurfacing

Increasing number of total hip replacements in young patients in recent years is accompanied by an increased number of revision operations due to excessive wear of the polyethylene in the young active patient, leading to osteolysis and loosening of the prosthesis. For this reason, there has been extensive research to find alternative bearings with better wear properties to cope with this tremendous devastating problem.

In conventional hip replacement surgery, the femoral head and a portion of the femoral neck are completely removed and replaced with a stemmed prosthesis, which is inserted into the medullary canal of the upper femur.

Hip resurfacing procedure shapes the femoral head and recaps it with a metal surface replacement. This preserved the normal bone of the upper femur and allows normal mechanics and weight-bearing loads across this area. Normal load forces through the bone of the upper femur keep the bone healthy and strong. The acetabulum of the hip joint is also resurfaced.

Surface hip arthroplasty (Fig. 10.3) has become more important in treating younger patients for osteoarthritis in the new century.

The resurfacing technique in the past, namely the Teflon prosthesis of Charnley and metal-on-polyethylene prosthesis of Wagner or Tharies prosthesis, is based on failure of the design and material properties of the implants, rather than failure of the resurfacing concept.

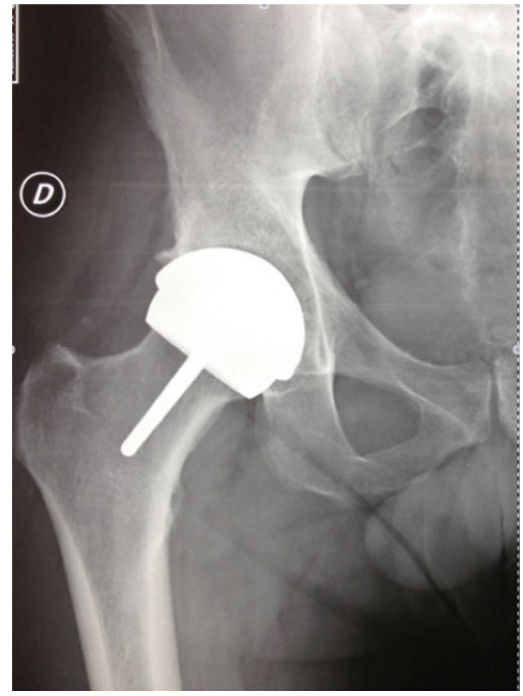

Fig. 10.3 Hip resurfacing

Due to a perfect operation technique, an up-to-date knowledge and fabrication of metal-on-metal articulations, the resurfacing technique is doing extremely well with clinical and radiological follow-up for more than 10 years.

The overall results were consistent with data produced from registry and high specialization centers in that the clinical outcome of large male patients was extremely encouraging, whereas the survival of the smaller joints was less satisfactory.

10.6 Hip Revision

Hip revision surgery, which is also known as revision total hip arthroplasty, is a procedure in which the surgeon removes a previously

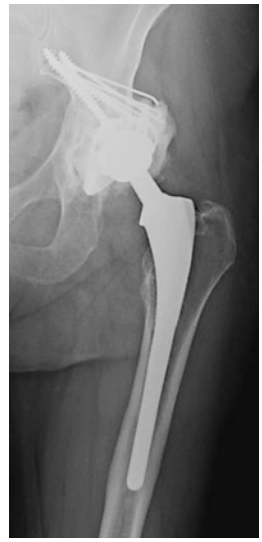

Fig. 10.4 Hip revision arthroplasty

implanted artificial hip joint, or prosthesis, and replaces it with a new prosthesis. Hip revision surgery may also involve the use of bone grafts. The bone graft may be an autograft, which means that the bone is taken from another site in the patient's own body, or an allograft, which means that the bone tissue comes from another donor (Fig. 10.4).

Hip revision surgery has three major purposes: relieving pain in the affected hip, restoring the patient's mobility, and removing a loose or damaged prosthesis before irreversible harm is done to the joint. Hip prostheses that contain parts made of polyethylene typically become loose because wear and tear on the prosthesis gradually produces tiny particles from the plastic that irritate the soft tissue around the prosthesis. The inflamed tissue begins to dissolve the underlying bone in a process known as osteolysis. Eventually, the soft tissue expands around the prosthesis to the point at which the prosthesis loses contact with the bone.

In general, a surgeon will consider revision surgery for pain relief only when more conservative measures, such as medication and changes in the patient's lifestyle, have not helped. In some cases, revision surgery is performed when X-ray studies show loosening of the prosthesis, wearing of the surfaces of the hip joint, or loss of bone tissue even though the patient may not have experienced any discomfort. In most cases, however, increasing pain in the affected hip is one of the first indications that revision surgery is necessary.

Other less common reasons for hip revision surgery include fracture of the hip, the presence of infection, or dislocation of the prosthesis. In these cases, the prosthesis must be removed in order to prevent long-term damage.

10.7 Approach to the Hip Joint

The hip joint can be approached in many ways, and therefore, many different exposures have been described. There are advantages and disadvantages to each, and there is a great deal of controversy among hip surgeons as to which is the "best." All surgeons have a favored surgical approach, and it is a testament to the success of the procedure that all of them generally produce good results.

Surgical approaches to the hip joint can be classified in many ways. One simple classification is based on the direction of approach. The common approaches used based on this classification are the anterior, direct lateral, and posterior.

10.8 Anterior Approach (Heuter)

The first hip arthroplasty performed through this approach was by Robert Judet in 1947. Judet referred to the surgical approach as the "Heuter Approach" referring to Heuter Volkmann and the approach for drainage of a tuberculosis hip abscess. The reasons for Judet's choice of this approach for hip arthroplasty are several: (1) The hip is an anterior joint, closer to the skin anterior than posterior. (2) The approach follows the anatomic interval between the zones of enervation of the superior and inferior gluteal nerves lateral and the femoral nerve medial. (3) The approach exposes the hip without detachment of muscle from the bone.

Position The patient is placed supine on a standard operating table or on a Trauma Judet Table.

Technique The skin incision begins 2 cm below the anterior–superior iliac spine and extends distally for approximately 8 cm in a linear fashion between the tensor fascia lata and the Sartorius. This interval can be identified by palpation. The subcutaneous tissue is reflected to the level of the fascia. The Sartorius and tensor fascia lata muscles are identified and the fascia investing these two muscles is split longitudinally. Splitting the anterior fibers of tensor muscle helps protect against injury to the lateral femoral cutaneous nerve. The tensor is separated from the Sartorius by sharp and blunt dissection. The Sartorius is reflected medially, the tensor laterally. Further exposure is straightforward and is usually done by palpating the femoral head and exposing the capsule by blunt dissection. The ascending branch of the lateral circumflex artery and vein do cross the field and must be ligated or cauterized. At the level of the hip joint, the gluteus medius and tensor fascia are further reflected laterally. The attachment of the reflected head of the rectus femoris is observed at the superior aspect of the acetabulum and must be incised. Excising the anterior capsule the hip joint is accessed.

Internervous plane Lies between the Sartorius (femoral nerve) and the tensor fasciae lata (superior gluteal nerve).

Dislocation Extension and external rotation of the hip.

Closure Suturing of the subcutaneous tissue and the skin.

Advantages Preservation of the vascularity, stability following the procedure with less chance of dislocation and good access to the acetabulum are the key advantages of this approach. The approach limits muscle cutting and separation, the extensors and the abductors are kept intact along with the medial circumflex femoral artery and its branches.

Disadvantages The main limitation of this approach is the limited access to the proximal femur. Some encourage using a fracture table to get a better approach to the femur. Injury to lateral cutaneous nerve can occur.

10.9 Direct Lateral Approach (Hardinge)

Direct lateral approach also called as the transgluteal approach initially described by first described by McFarland and Osborne in 1954, popularized by Hardinge in the modern age gives good exposure to the hip joint preserving most of gluteus medius minimus and vastus lateralis, and the vascularity. It exposes the femur well with good access to the joint.

Position The patient is placed and supported in the lateral decubitus position; however, the supine position with the greater trochanter lying over the edge of the table is also acceptable.

Technique The skin incision is centered over the greater trochanter and extends approximately 6–8 cm distally along the anterior aspect of the trochanter and down the anterior lateral aspect of the femoral shaft. Proximally, the skin incision extends 6–8 cm in line with the fibers of the gluteus maximus muscle. The iliotibial band is entered and split distally, and the gluteus maximus muscle is split proximally. The gluteus maximus is retracted posteriorly and the tensor fascia lata retracted anteriorly. The deep exposure begins at the anterior margin of the trochanter and extends distally to include the anterior third of the vastus lateralis muscle. Proximally, the incision extends about 4–5 cm past the trochanteric tip and splits the gluteus medius musculature in line with its fibers separating its anterior one-third from the posterior two-thirds. Splitting the gluteus medius muscle more than about 4–5 cm proximal to the tip of the trochanter should be avoided as it may injure the superior gluteal nerve. The interval is developed by subperiosteally releasing the antero-oblique fibers of the gluteus medius from the trochanter in line with the remaining anterior fibers of the more proximally fan-shaped portion of the medius musculature. The anterior third of the vastus lateralis muscle is elevated from the

trochanter and proximal femur for a distance of about 5–7 cm. The sleeve of tissue containing this portion of the abductors and the vastus lateralis is then reflected anteriorly and retracted with a narrow Hohmann retractor. This allows ready access to the anterior capsule. The gluteus minimus muscle is detached from the trochanter beginning anteriorly and separated from the capsule to the extent needed for adequate exposure. A curved Hohmann retractor placed over the femoral neck facilitates retraction of the medius and minimus musculature. The capsule is excised anteriorly, placed over the femoral neck, and further release of the lateral and inferior aspect of the capsule is performed as needed.

Internervous plane As the gluteus medius tendon and muscle fibers and the vastus lateralis muscles are split, there is no true internervous plane. However, it is important are split protect the superior gluteal nerve by making the incision distal to the point which it enters the muscle.

Dislocation The hip is dislocated by external rotation and flexion. For this exposure, the leg may be placed in a sterile pocket anteriorly to prepare the femoral canal.

Closure Gluteus minimus is reattached to its insertion. Gluteus medius is closed with a series of interrupted sutures, as is vastus lateralis. The deep fascia and the iliotibial tract are closed similarly.

Advantages This approach gives good access to the hip and yet preserves vascularity, minimizes risk of damage to sciatic nerve, and has low dislocation rates.

Disadvantages There can be damage to gluteal muscle mainly medius, which increase recovery time. Heterotopic ossification may also be a problem.

10.10 Posterior Approach (Moore)

This is the most popular approach for total hip replacement in the USA. The common feature of posterior exposures is the release of the short rotators. Variation is introduced by the manner of developing the exposure dealing with the gluteus maximus muscle and the iliotibial track. The repair of the rotators with capsule is also variably described.

Position The patient is placed and supported in the lateral decubitus position.

Technique The skin incision is along the posterior to the lateral side of the greater trochanter and carried distally about 6 cm along the femoral axis. Proximally, the incision runs slightly curved toward the posterior superior iliac spine (PSIS) to a point approximately 6 cm proximal to the greater trochanter. The fascia lata is incised, and the gluteus maximus fibers are divided by blunt dissection. Retraction of the proximal part of gluteus maximus exposes the greater trochanter, and the overlying trochanteric bursa is either incised or partially excised. Retraction of the posterior fibers of gluteus maximus posteriorly exposes the short external rotators of the hip. The short external rotators are then divided. Piriformis is cut through its tendon lateral to the stay suture. Obturator internus and the gemelli may be divided adjacent to the trochanter if the head and neck are to be sacrificed, as in hip arthroplasty. If this is not the case, divide them 1 cm from their trochanteric insertion in order to preserve the posterior circumflex artery. Internal rotation of the hip facilitates identification and division of the rotators because it stretches them. Elevation and retraction of the short external rotators expose the posterior part of the capsule and the posterior surface of the acetabulum. The posterior part of the joint capsule is incised.

Internervous plane As the gluteus maximus is split through the fibers rather than between muscle planes, it is difficult to find a true internervous plane. However, as the nerve enters, the muscle medial to the split the muscle denervation is unlikely.

Dislocation The hip is dislocated by flexion, adduction, and internal rotation.

Closure At the end of the procedure, the posterior capsular flap is sutured, and then, the external rotators tendons are reinserted to their anatomic insertion on the posterior greater trochanter. A secure repair of the tendons and

capsule decreases the risk of hip prosthesis dislocation after a posterior approach.

Advantages This approach provides excellent exposure to both acetabulum and the femoral head and neck, making it easier to surgical procedures well. The approach limits muscle cutting and separation, and the medius and minimus gluteus muscles are kept intact and patients have fast recovery after operation.

Disadvantages The main disadvantage in the past was high rate of dislocations; this problem is seen less nowadays with the use of large diameter femoral heads and with a correct positioning of the acetabular component. Other documented complications seen are damaged to sciatic nerve, which could be either stretching which recover usually, or permanent damage, which will result in a foot drop and damage to inferior gluteal vessels, branches of profunda femoris vessels and rarely femoral vessels, which can lead to blood loss.

10.11 Preoperative Imaging

Plain radiographs are the first-choice modality in the diagnosis of hip arthritis.

The radiographic exam includes an AP pelvic and a lateral view; different lateral views include cross-table lateral, a frog-leg lateral, and a false profile view.

Although in more complex cases of arthritis, secondary to dysplasia, Perthes disease, and slipped capital epiphysiolysis, where hip's anatomy is severely altered, CT and MR imaging are more sensitive imaging methods for the diagnosis of synovitis and/or joint effusion and for the detection of bone marrow edema, erosions, subchondral cysts, and cartilage destruction. Moreover, in some cases, bone scan can be used as additional tool to preoperative planning is an essential step that helps the surgeon to execute a successful operation. The correct placement of both acetabular and femoral components is critical for the optimal functioning of the bearings. For this reason, preoperative templating is an essential tool of a successful hip arthroplasty. It is performed on antero-posterior radiographs of pelvis, which should be taken with the femur rotated internally to reduce the effect of femoral anteversion.

The socket template is positioned first to establish the center of rotation of the reconstruction. For femoral templating, it should be considered both the part inside the bone (the size of the component), and both the part outside the bone, which sets limb length and biomechanical parameters such as the abductor muscle and joint reaction forces. Medializing the hip center of rotation and increasing the horizontal femoral offset can improve clinical outcomes and reduce wear. Modern modular systems allow limb length adjustment and biomechanical improvement for a range of patients.

In the last decades, computed systems have been developed to perform preoperative templating in order to provide a more accurate and easier measurements.

10.12 Imaging in the Follow-up

Despite the increasing popularity of modern imaging techniques such as ultrasound scanning (USS) and MRI, radiography remains the primary imaging method for the regular postoperative evaluation of hip arthroplasty. The zones described by Gruen et al. are among the most quoted assessment tools in conventional total hip arthroplasty (THA). However, the introduction of hip resurfacing arthroplasty (HRA) with metal-on-metal bearings requires a new radiographic evaluation protocol in order to assess the components and surrounding structures. The use of plain hip radiographs in the clinical evaluation of hip arthroplasty has been doubted by some authors due to the limitation of radiography in identifying soft tissue pathology.

However, the importance of radiography in the clinical setting is yet to be investigated.

The radiographic evaluation of the non-cemented acetabular component in HRA is similar to those described for THA. However, the femoral component requires different evaluation criteria to those used to describe a standard THA because there is no component in the femoral canal and the metallic femoral implant overlies, and hence obscures, the junctions between bone cement and cement prosthesis. Lucencies around the short metaphyseal HRA femoral stem can be described as defined by Amstutz et al. The authors divided the femoral zonal system into 3 PEG zones, which correspond to superior, tip and inferior zones around the metaphyseal femoral stem.

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Knee

11

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11.1 Introduction

Prosthetic knee surgery is one of the most common and successful procedures in orthopedic surgery. Newer prosthetic designs, standardization of surgical technique, and a correct post-operative rehabilitation have improved overtime the outcomes and reduced the rate of revision surgery. The imaging plays an essential role in the preoperative planning and follow-up of the prosthetic knee. This chapter describes the most common implants and surgical techniques used in knee replacement procedures as well as the imaging techniques widely used pre- and postoperatively.

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11.2 Type of Prosthesis and Implantation Technique

11.2.1 Total Knee Replacement

Primary total knee replacement (TKR) is a widely performed and successful procedure, improving the quality of life in more than 90 % of patients [1]. The goals of TKR are to obtain a correct knee alignment and a functional pain-free joint by using a stable implant with a correct soft tissue balance.

Modern designs include metal femoral and tibial components, a polyethylene liner, and a polyethylene patellar component, when necessary. Currently, TKRs can be (1) cruciate retaining or posterior stabilized; (2) with mobile-bearing or fixed-bearing tibial tray; and (3) cemented or cementless (press fit).

In cruciate-retaining TKRs, the posterior cruciate ligament is maintained and a more conforming tibial polyethylene component is used to provide anterior and posterior stability. Conversely in posterior-stabilized TKRs, the posterior cruciate ligament is substituted with a cam and post mechanism.

In mobile-bearing designs, the polyethylene insert articulates with a metallic femoral component and a metallic tibial tray (in order to reduce contact stresses and polyethylene wear), while in fixed-bearing TKRs, no motion is allowed between the tibial tray and the insert. Alternatively, between nonmobile-bearing

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designs, all-polyethylene tibia components are available on the market.

In addition, TKRs can be implanted either with a cement fixation or with a press-fit (cementless) technique. In a cemented TKR, components are fixed by using polymethylmethacrylate, which allows the implant to fit the irregularities of the bone with a strong primary fixation. In cementless implants, components have a roughened porous surface to allow bone ingrowth.

In some difficult cases, modular TKRs with continuum of constraint may be necessary. The indications range from higher degrees of ligamentous incompetency to severe restriction of the range of motion with substantial flexion contracture to post-traumatic arthritis and to post-osteotomy deformity of either the distal part of the femur or the proximal part of the tibia. Modularity allows intraoperative customization by using stems, wedges, and augments. Frequently, these difficult primary or revision TKRs require the use of posterior-stabilized constrained implants.

The most common surgical approach is the anterior approach to the knee with a medial parapatellar arthrotomy. Capsular incision is performed along the medial border of quadriceps tendon leaving 2–3 mm of tendon attached to the muscle. The capsular incision is extended distally to the medial border of tibial tubercle proximally to the pes anserinus insertion. Afterward, the medial joint capsule is elevated from the medial tibial flare at least to the midline of the tibia subperiosteally, externally rotating the leg for better exposure. Minimally invasive approaches (i.e., subvastus, midvastus) have been described to minimize surgical damage to the extensor mechanism of the knee [2]. The posterior half of infrapatellar fat pad and the lateral meniscus are removed to achieve a good lateral exposure. With the knee in full extension, the patella is laterally dislocated, possibly without eversion. The anterior cruciate ligament is then sectioned. In posterior-stabilized implants, also the posterior cruciate ligament is excised with the knee flexed at 90°, allowing for anterior dislocation of the tibia and a complete exposure of tibial plateau. Once the exposure of the tibial plateau is complete, meniscal remnants and osteophytes are removed. The surgical procedure includes a proximal tibial cut and 4 essential femoral cuts (distal, anterior, posterior, and oblique) for both cemented and cementless implants. An additional sixth cut for the removal of the intercondylar notch is performed in PCL sacrifice TKRs. The tibial and distal femoral osteotomy are independent of each other; therefore, there is no fixed order to perform the bone cuts. The authors usually begin with the tibial cut; nevertheless in tighter knees or in presence of important posterior osteophytes, it is preferable to start with distal femoral osteotomy to gain space, allowing a better view of tibial plateau. According to the prosthesis design chosen, trial components are placed first and stability, range of motion and patellar tracking are checked out. Afterward, the definitive prosthesis components are positioned.

11.2.2 Unicompartmental Knee Arthroplasty

Unicompartmental knee arthroplasty (UKA) is a surgical option which allows to manage degenerative changes involving either the medial or the lateral compartment of the knee. Both metal backed and all-polyethylene tibial components are available on the market, according to the implant selected.

A minimally invasive technique is used to implant UKAs [3]. A 6–10-cm medial parapatellar skin incision is performed, and a subvastus approach to the joint is commonly used. Some authors advocate an antero-lateral approach for the lateral compartment, but a slightly more extensile medial parapatellar approach may be used as well. The patella is then dislocated, and all osteophytes are removed. The tibial cut is performed first perpendicular to the tibial shaft. After tibial preparation, either a dependent or an independent femoral cut is carried out according to the surgeon's preferred technique and prosthetic design. Trial components are positioned and range of motion together with limb

alignment is controlled. Final components are then cemented and implanted.

11.2.2.1 Patellofemoral Arthroplasty

Patellofemoral arthroplasty (PFA) has recently risen in popularity for the treatment of isolated patellofemoral osteoarthritis in young patients. Many implants with different features are currently available. Those implants may be mainly divided in three categories: (1) in-lay implants in which trochlear component surface is at the same level of the surrounding articular surface; (2) on-lay implants characterized by a trochlear component surface prominent compared to the surrounding articular surface; (3) minimally invasive implants which allow a minimal cartilage/bone resection and component implantation with in-lay technique.

A midline skin incision is carried out to allow for future total knee arthroplasty, in case of subsequent degeneration to the tibiofemoral compartments. Quadriceps tendon, midvastus and subvastus approaches may be used. The patellar cut is performed first in order to allow for easier patellar dislocation during femoral preparation. All the osteophytes are removed, and the patellar cut is made to reestablish the original thickness with implant in place. Afterward, the trochlea is prepared removing synovium, osteophytes, and fat from anterior femur immediately adjacent to the most proximal extent of the trochlea, and the femoral cut is performed. Trial components are positioned, and patellar tracking, possible tilt, and stability are checked throughout the complete range of motion of the knee. Finally, definitive components are implanted.

11.3 Preoperative Imaging

Preoperative imaging assessment of the patient is mandatory for the planning of the surgical procedure. The aim of the radiologic preoperative evaluation is to determine: malalignment, localization, and the severity of the degenerative process, underlying bone stock, the surgical technique in terms of both approach and implant selection. Preoperative imaging is also used in order to template the prosthesis, to choose the appropriate type and size of the prosthesis, to determine component position and orientation, and to prevent limb length discrepancies.

11.3.1 Conventional Radiography

Conventional radiography remains the cornerstone of musculoskeletal imaging in the planning of knee prostheses. Preoperative radiographic assessment includes bilateral weight-bearing antero-posterior (AP) views in full extension as well as tunnel views at 30° of flexion or Rosenberg views at 45° of flexion. Lateral and axial (Merchant or Skyline) views and a weight-bearing hip-to-ankle AP view are also required for a complete evaluation of the extensor mechanism and the lower limb axis, respectively.

The AP view assesses the joint space and allows the evaluation of the medial and lateral compartments; furthermore, it provides a gross assessment of femoro-tibial alignment. Rosenberg and tunnel views demonstrate the posterior aspect of the intercondylar notch, the inner posterior aspects of the medial and lateral femoral condyles, and the tibial spines and plateaus, improving joint space narrowing visualization [4, 5]. Lateral radiographs are ideal to assess the tibial slope, posterior osteophytes, and bone loss. On lateral view, patellar height can be evaluated as well using the Insall-Salvati, Blackburne-Peel, or Caton-Deschamps indices [6]. Axial views provide an excellent evaluation of patellofemoral alignment, trochlear dysplasia, and patellofemoral articular surface. Weight-bearing hip-to-ankle AP radiographs show bone deformities and the mechanical axis of the lower limb, from the center of the femoral head to the center of the talus [7]. In a neutral mechanical axis, the line passes through the center of the knee joint. The angle of the tibiofemoral axis or anatomic axis is measured drawing a line through the center of tibial and femoral shafts, and it ranges from 5 to 7° of valgus. The tibial implant is typically placed perpendicular to the anatomic mechanical axis. This entails a slight

change from the anatomic 2–3° of varus alignment in the native tibiofemoral joint.

The femoral component is usually places with some degrees of valgus orientation. The authors prefer a 5° valgus femoral component positioning in varus knees and 3° of valgus in valgus knees. The prosthetic femoral component is placed in slight external rotation relative to the native femur (3 to 5°). Joint line orientation is also obtained using weight-bearing hip-to-ankle AP view of both limbs.

Conventional AP and lateral X-rays are widely used for templating. Templating is a preoperative process used by surgeons to plan the intraoperative steps, choose the appropriate type and size of the prosthesis, determine component position and orientation, and prevent limb length discrepancies [8]. Templating techniques are similar using either acetate overlays with properly magnified radiographs or a digital templating system. Digital templating has the advantage to accurately record the preoperative plan and sizing information, which assists the operating staff and implant inventory manager in having the necessary implant available.

11.3.2 Computed Tomography

Computed tomography (CT) provides detailed information in the assessment of osseous structures. CT is not routinely performed but is useful in assessing the extent of cystic disease in osteoarthritis or bone loss in primary/revision surgery. In addition, a CT could be obtained to assess severe axial or rotational deformities of the lower limb [9, 10].

11.3.2.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is not used as a routine technique for the preoperative planning in knee arthroplasty; however, it can be useful for the diagnosis and the severity assessment of osteonecrosis or soft tissue conditions.

Recently, a new technology using preoperative MRI data to manufacture custom cutting jigs specific to patient's bony anatomy has been developed. A hip-to-ankle MRI is obtained and sent to the manufacturer. Using a specific software, the preoperative planning is then sent to the surgeon for approval. Then, patient-specific cutting jigs are created in order to perfectly fit the tibial and femoral anatomy (osteophytes included) of the patient. The jigs allow for theoretically quicker and more precise tibial and femoral cuts, without the use of intra or extramedullary cutting guides [11–13]. This technology, originally designed for TKRs, is now available also for UKAs.

11.4 Imaging in the Follow-up

Post-operative imaging is mandatory to evaluate the correct positioning of the prosthetic components and to rule out complications that might occur over time. In addition to conventional radiographs, metal artifact reduction techniques allow the use of CT and MRI in the post-operative evaluation of prosthetic knees [14, 15].

The frequency of the post-operative imaging in the follow-up is dictated by surgeon's and institution's preference. Typically, immediate post-operative AP and lateral and Merchant views are obtained to evaluate gross malpositioning of the components, femoral notching, or up-/down-size of the components. Subsequently, at 3, 6, and 12 months weight-bearing AP, lateral, long leg and axial (Merchant or Skyline) views are obtained to rule out secondary displacement of the components. Normally on the AP film, the tibial tray should be perpendicular to the long axis of the tibia and should cover at least the 85 % of the tibial surface. Mechanical axis should be neutral and femoro-tibial angle should be anatomic (5 to 8° of valgus) on the long leg radiographs.

On the lateral view, the femoral component should be 90° to the femoral shaft, the condylar component should mirror the size of the native femoral condyles, and the anterior aspect should sit flush against and be parallel to the anterior cortex of the distal femur. A too large condylar component might be the reason of a limited range of motion, whereas an undersized condylar component may lead to instability and

notching of the anterior femoral cortex. Lateral view also allows for tibial slope evaluation. Excessive tibial slope can lead to anterior tibial subluxation, posterior polyethylene wear, and lack of extension. Lastly, on the lateral view, patellar height can be measured.

The patellar component should be centered in the trochlea of the femoral component without significant tilt. The thickness of the patellar polyethylene component should not exceed the total thickness of the native patella in order to avoid risk of increased wear and reduced range of motion.

11.4.1 Complications

11.4.1.1 Periprosthetic Fractures

Periprosthetic fractures may occur either during surgery or in the post-operative period with TKRs. The overall incidence is low, with supracondylar femoral fractures ranging between 0.3 and 3 %. Periprosthetic fractures of the proximal tibia are even rarer [1, 16]. However, particular attention should be paid intraoperatively in patients with poor bone quality (i.e., because of the age, rheumatoid arthritis). Fractures may also occur after the positioning of lateral and medial UKAs. Risk factors for postoperative fracture include osteopenia, femoral notching, poor flexion, focal osteolysis as well as component loosening. Conventionally radiographs are the first step in diagnosing periprosthetic fractures. Often a CT is required to rule out loosening of the components or better delineate the fracture's pattern.

11.4.1.2 Joint Instability

Ligamentous imbalance and the following varus-valgus instability accounts for the 1–2 % of primary instability in knee replacement surgery [5]. That is well evaluated by an asymmetric widening of the prosthetic joint space seen on the X-rays films, with or without mechanical malalignment on the long leg X-rays.

11.4.1.3 Prosthesis Wear

Many factors contribute to liner wear of the prosthesis, including weight and activity level of the patient, polyethylene thickness, alignment of the condylar component, relationship between the polyethylene spacer and the metal surface of the femoral and tibial components, and physical properties of the polyethylene. The wear involves shedding of metal or polyethylene, resulting in hypertrophic synovium, histiocytic response, and ultimately osteolysis. The thickness of the polyethylene liner should be at least 8 mm. Polyethylene wear is evaluated on standing AP and lateral views with the X-ray beam parallel to the tibial base plate. The distance from the femoral condyles to the tibial base plate is measured on serial radiographs. Interval narrowing of the joint space is suggestive of polyethylene wear. Eventually, wear can progress to metal-to-metal contact, erosion of the tibial metal back, and metal synovitis. Ultrasonography may be also used to evaluate accurately the polyethylene thickness. Osteolysis is occasionally noted on radiographs, although it is not visible until far along in the process. CT is more sensitive in the detection and quantification of osteolysis and synovitis and allows the assessment of components rotation at the same time [5]. MRI with metal suppression is useful to detect synovitis and occult osteolytic lesions offering more accurate extent and localization of osteolysis prior to revision surgery [17].

11.4.1.4 Prosthesis Loosening

Loosening can be seen in both the femoral and the tibial components, although it is more frequent in uncemented tibial components along the medial side, resulting in varus angulation (Figs. 11.1 and 11.2). A loose femoral component tends to shift into flexion. Development of thin radiolucent lines at the bone–cement or bone–prosthesis interface of less than 2 mm within the first 6 months in a cemented implant or during the first 1–2 years in noncemented implants without evidence of progression is

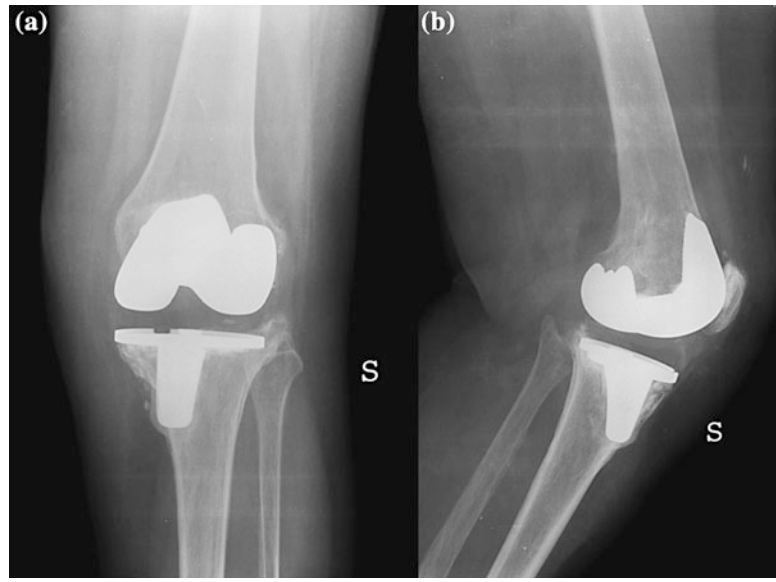

Fig. 11.1 AP and lateral views of an aseptic loosening of the tibial tray in total knee arthroplasty

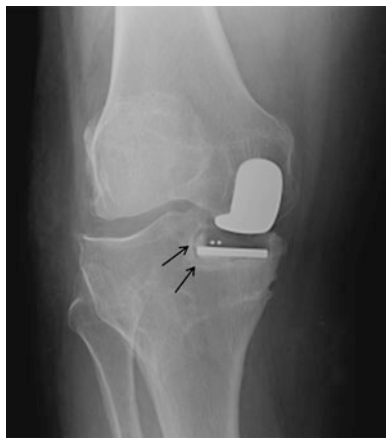

Fig. 11.2 AP view of an aseptic loosening of the tibial tray in unicompartmental knee arthroplasty

considered normal [5, 18]. Widening of greater than 2 mm at the bone–cement, metal–cement, prosthesis–bone interval, increases in the width of an existing radiolucency, cement fracture, and changes in component position suggest loosening. A bone scan may also be used to diagnose loosening. Arthrography may confirm the diagnosis showing the presence of contrast between the bone–cement and the bone–metal interface.

11.4.1.5 Metal Synovitis

Metal-induced chronic synovitis results from metal wear debris caused by abrasion of metal components that occurs after failure of the interposed polyethylene-bearing surfaces. A line of linear opacity outlining a distended knee capsule or an articular surface on radiographs (metal line sign) is secondary to the deposit of metal debris in the joint causes and is diagnostic of metal synovitis.

11.4.1.6 Patellar and Extensor Mechanism Complications

The majority of patellar complications are commonly ruled out using both lateral and axial radiographs. Instability/dislocation and loosening of patellar components as well as stress patellar fractures are the most common complications reported. Patellar instability is related to imbalance of soft tissue (tight lateral retinaculum) and malposition and malalignment of components (Fig. 11.3). Tilt and subluxation of the patella are usually recognized on the axial views, although any underlying rotatory malalignment of components is best assessed on CT. The thin polyethylene liner may wear or displace from the metal backing into the Hoffa fat pad.

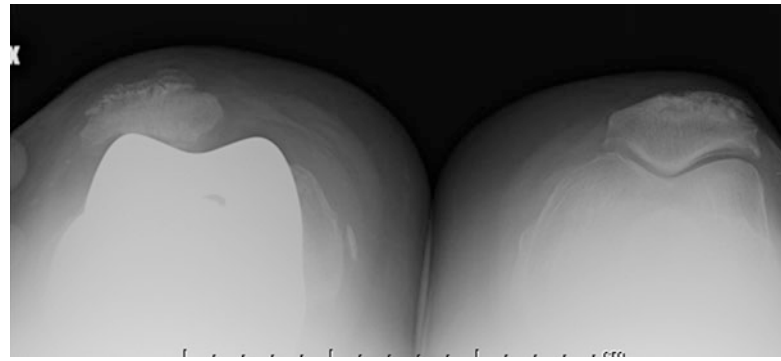

Fig. 11.3 Merchant view of patellar maltracking with lateral tilt in total knee arthroplasty

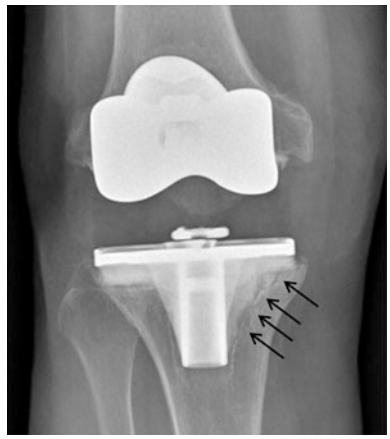

Fig. 11.4 AP view of septic loosening of a total knee replacement

Patellar fractures have been reported to be up to 21 % of cases and are commonly seen in older patients [19]. Over-resection of the patella may predispose to fractures. Radiographs can easily detect fatigue fractures, which occur frequently at the peg-plate junction of metal-backed prosthesis. Occult fractures may be ruled out by MRI study. Quadriceps tendon tear and ruptures have also been described, resulting in abnormal position of the patella observed on radiographs. Ultrasonography and MRI confirms these complications. Fibrosis and scarring of the Hoffa pad may result in a low-lying patella (patella baja) [5].

11.4.1.7 Infection

The prevalence of infections in knee arthroplasty ranges from 0.5 to 2 % [5]. Infection is typically seen within the first 2 years of surgery, although sometimes may occur later. The diagnosis of low-grade and chronic infection may be particularly difficult, and the evidence of infection is often not obvious prior revision surgery. Microorganisms, introduced at the time of surgery (usually skin bacteria) or through hematogenous spread or direct contamination from compromised adjacent tissues, adhere to the prosthesis, residing in a biofilm that limits the effects of antimicrobial agents.

Conventional radiography does not show a high sensitivity since the appearance of infection can be variable, besides radiographs are normal in most patients. Radiologic distinction between septic and aseptic loosening can be challenging (Fig. 11.4). Periosteal reaction, periprosthetic widening, osteolysis, presence of bone destruction as well as irregular periprosthetic lucency or lucency that extends completely around the prosthesis are all signs which suggest septic loosening. Soft tissue swelling is also indicative for infection.

Ultrasound is useful to detect joint effusions, soft tissue fluid collections, and in some cases, synovial hypertrophy and inflammation (aided by the use of color and power Doppler). The more advantageous use of ultrasound, however, is to guide intervention such as joint aspiration. Joint aspiration is a useful confirmatory test showing sensitivity and a specificity ranging from 67 to 82 % and from 91 to 95 %, respectively [20, 21]. In spite of the past limitation due to metal artifacts, nowadays, CT and MRI are useful tools to assess the extent of soft tissue

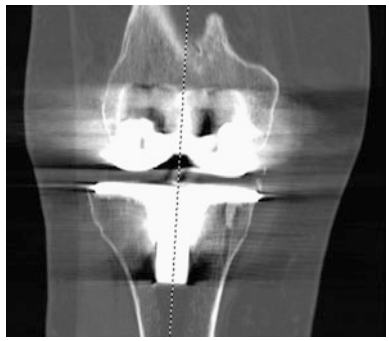

Fig. 11.5 CT scan in a correctly positioned total knee arthroplasty

infection in close proximity to the arthroplasty (Fig. 11.5).

Nuclear medicine studies are extremely useful in the evaluation prosthetic complications. Bone scan, performed with technetium-99 m (Tc-99 m)-labeled diphosphonates, is highly sensitive for detecting complications of lower extremity prosthetic joint surgery (Fig. 11.6). Both infection and aseptic loosening may show increased uptake on delayed images, but the test is not specific mostly in the early post-operative period [22]. Furthermore, even in the absence of complications, persistent periprosthetic activity has been shown to be increased for up to 2 years because of continued post-operative reparative osteoblastic activity, and performing the bone scan as a three-phase study does not improve the accuracy of the test. As a matter of fact, the blood pool images may also show increased activity in both loosening and infection. Despite the overall accuracy of bone scintigraphy in evaluation of the painful prosthetic joint is about 50–70 %, this study has a high negative predictive value and a negative bone scan excludes both loosening and infection. Therefore, it may be use as an initial screening test in conjunction with other diagnostic tests [22].

Sequential bone/gallium imaging is often performed along with a bone scan and the studies are interpreted together, but it is nonspecific and offers only a slight improvement over bone scintigraphy alone and is of limited value in differentiating prosthetic joint infection from other causes of prosthetic failure.

Labeled leukocyte [white blood cell (WBC)] imaging has been proposed as the radionuclide procedure of choice for diagnosing prosthetic infection (Fig. 11.7). Bone scan combined with Indium-111-labeled WBC has a low sensitivity and specificity, but both are increased when a Tc-99 m sulfur colloid marrow scan is done in addition offering the accuracy up to 95 % [5]. The principle of combined WBC/marrow imaging is based on the fact that WBC and marrow images both reflect radiotracer accumulation in the reticuloendothelial cells, or fixed macrophages, of the marrow. Normal individuals and in those with underlying marrow abnormalities show either a similar or spatially congruent distribution of marrow activity on WBC and marrow images. Osteomyelitis, including prosthetic joint infection, which stimulates uptake of leukocytes but suppresses uptake of sulfur colloid, results in spatially incongruent images.

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been reported to be effective for diagnosing prosthetic joint infection, since studies have shown sensitivity and specificity of 100 and 86 %, respectively, in limited numbers [5]. FDG is transported into cells via glucose transporters, but unlike glucose, it is not metabolized and remains trapped within the cell. Normal bone marrow has only a low glucose metabolism under physiologic conditions, whereas the infection shows an increased FDG uptake due to increased expression of glucose transporters in inflammatory cells and increased affinity of these glucose transporters for deoxyglucose. Degenerative bone changes usually show only faintly increased FDG uptake compared with infection. In spite of the fact FDG-PET has generated considerable interest because of its advantages, studies have concluded that PET offers no benefit over standard three-phase bone scans so far [22].

The emergence of hybrid modality imaging using integrated single photon emission computed tomography (SPECT) and PET with CT

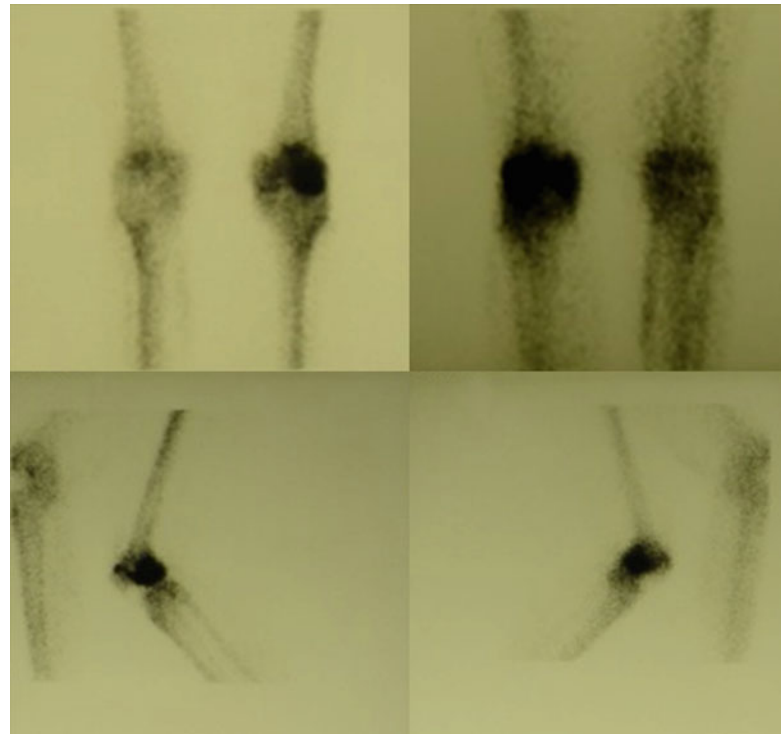

Fig. 11.6 Three-phase bone scan positive for infected TKR

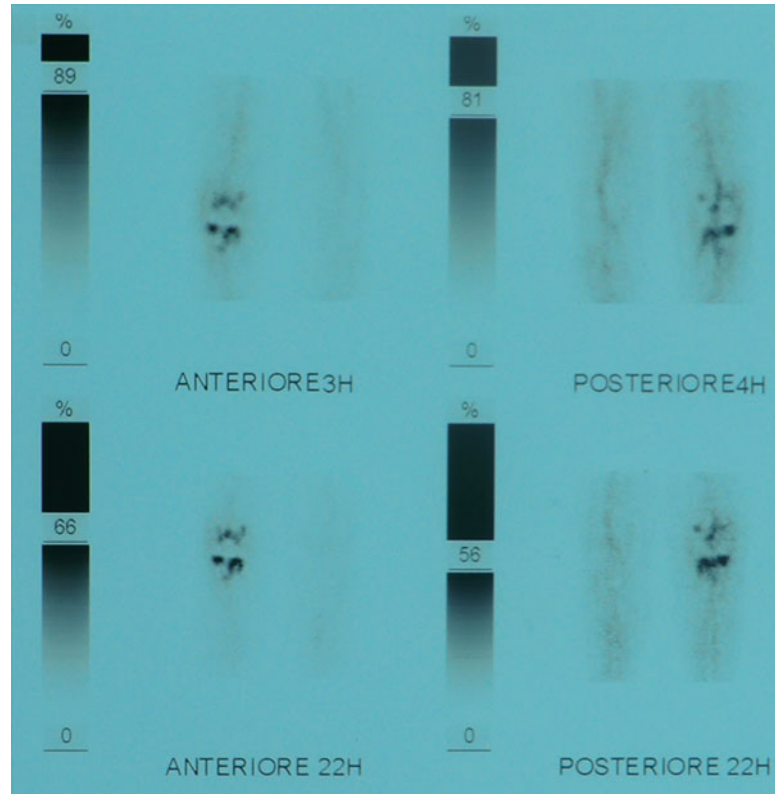

Fig. 11.7 Bone scan with Indium-111-labeled WBC. Positivity for infection in TKR

(SPECT/CT and PET/CT) may also have a contributing role for more accurate assessment of joint replacement complications, especially combined with new radiotracers [22].

11.5 Conclusions

The role of the imaging is essential in achieving the best assessment of the prosthetic knee in both preoperative and post-operative stages. Conventional radiology is still the cornerstone of both the preoperative diagnosis and planning and post-operative follow-up. In addition to radiographs, a wide number of diagnostic techniques such ultrasonography, CT, MRI, and nuclear medicine studies are available nowadays to investigate post-operative complications. However, in some cases of painful TKRs, the diagnosis is uncertain despite precise and complete imaging studies. Further studies and new technologies are necessary for a more anatomic reconstruction and to diagnose earlier complications such infections, upgrading the overall outcome of knee replacements.

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Shoulder

12

Umberto Mariotti, Pierorazio Motta and Piermario Tosco

12.1 Introduction

The history and development of shoulder arthroplasty dates back to 1892 with Pean in Paris, when he used a prosthesis in the shoulder to replace an infected tubercular joint [1]. This was the first known joint replacement with a prosthesis and preceded the first prosthetic hip joint replacement by 26 years. However, the modern era of shoulder arthroplasty began in the mid-1940s with Charles S. Neer II. The first published photograph of Neer's prosthesis appeared in an article in the *American Journal of Surgery* in 1953 [2] He then redesigned the humeral component in 1973, so as to conform to a polyethylene glenoid prosthesis [3] The biomechanical principles of medialization and lowering of the centre of rotation of reverse shoulder prostheses evidencing the importance of this new philosophy were defined by Paul Grammont in 1985 [4]. Applying these principles, he designed a successful implant and, to date, they still represent the gold standard for the treatment of degenerative arthropathy of the shoulder associated to an irreparable tear of the rotator cuff. John Fenlin introduced the first modular shoulder prosthesis in North America, in 1986, which were followed by further modular shoulder prostheses in the mid-1990s. Prominent international shoulder surgeons have now introduced numerous other prostheses, such as Drs. Cofield, Bigliani, Flatow, Dines, Walch, Boileau, Gerber, Randelli, Copeland, Wallace, Worland, Mansat, Herpel, Habermayer and Valenti worldwide, to treat proximal humeral fractures, gleno-humeral arthritis, osteonecrosis, rheumatoid arthritis, cuff tear arthropathy, pseudo-paralytic shoulders with massive irreparable cuff tears, without arthritis and proximal humeral malunion.

12.2 Type of Prosthesis

12.2.1 Fracture Prosthesis

12.2.1.1 Introduction

Shoulder fracture has increased over the last 10 years and is now the third most common fracture after the hip and the wrist [5]. Although the overall percentage is 104–105 per 100,000 persons/year, 10 % are patients over 65 [6]. These lesions have a high percentage of neurological involvement, as documented in international literature. There is a 67 % overall percentage of acute neurological injury (ANI), 58 % involve the axillary nerve and 48 % the subscapularis nerve [7]. Nowadays, the Hertel classification is used. It is divided into 12 types

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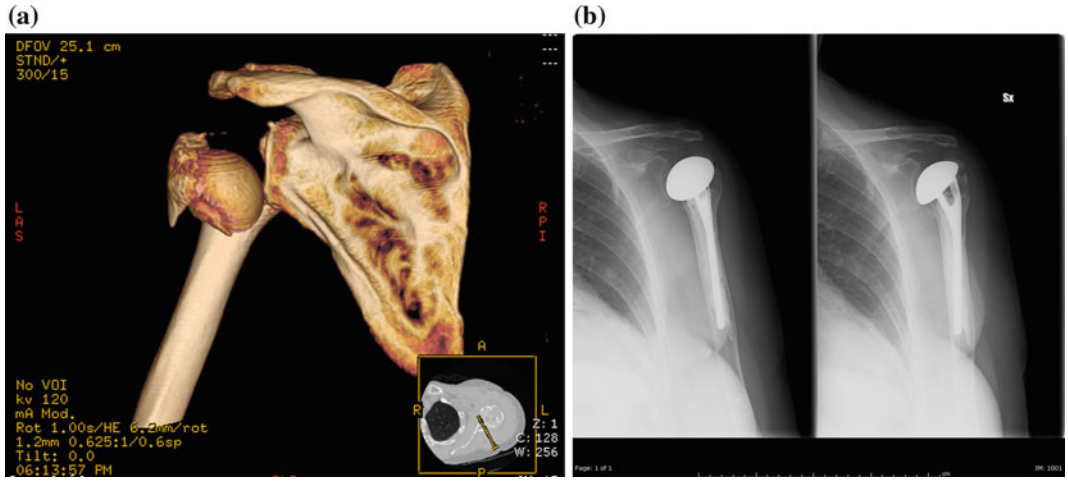

Fig. 12.1 **a** TC 3D pre-op. CT 3D Reconstruction in plurifragmented and displaced fracture of the neck and greater tuberosity of the humerus. **b** X-ray post-op. X-ray antero-posterior in extrarotation and intrarotation with prosthesis

[8] based on standard X-ray and when required, the CT scan with 3D reconstruction. Surgical treatment depends on fracture type and patient characteristics, including age, bone quality, concomitant pathologies, the vitality of the humeral head [9] and last, but not least, the time lapse between trauma and surgery with worse outcome if the time lapse exceeds 4 weeks [10].

Surgical options include percutaneous fixation with pins or screws, ORIF with plates, endomedullar nails or prosthesis. Although 93 % of patients report satisfaction and are pain free with hemiarthroplasty in fractures, there is an even higher satisfaction has been reported in patients operated on for arthritis in terms of functionality and pain [10].

12.2.1.2 Indications for Prosthesis

Proximal humerus fractures are usually the sequelae of low-energy falls in the elderly, or high-velocity trauma in the young [5]. Surgical management of these fractures depends on the fracture pattern, including number of fragments/their displacement, bone quality and the patient's functional demands. The presence of poor bone quality, which tends to increase operative difficulty, does not preclude the use of a cemented arthroplasty technique. There was a statistically significant rise in functional outcome after the advent of fracture-specific prosthetic implants [11]. When the anatomical tuberosity is re-established, it produces a "natural" external rotation. Incorrect tuberosity positioning would mean the patient would have to use 8 times the force to reach the same degree of external rotation [12]. Literature reports three negative prognostic factors: high prosthesis, excessive retroversion and a low greater tuberosity, leading to poor functionality, persistent pain and stiffness [13]. The surgical steps for the implantation of a fracture prosthesis are very similar and the prosthesis choice depends, not only on the aforementioned indications, but also on the surgeon's personal experience and preference. In my personal 25 year experience, I have used many types of prosthesis, but my preference has fallen to one in particular, the Tornier Aequalis® Fracture Shoulder Prosthesis (Fig. 12.1).

The surgical steps for this prosthesis are as follows:

1. Place the patient under anaesthesia (general or block) in the beach-chair position.
2. A classical Larghi skin incision is made to visualize the fracture in the operating field.
3. Definitive fibre wires (2 or 5) are passed around the greater tuberosity and 2 temporary ones around the lesser tuberosity (for a total of 6).

4. The head is removed and measured. Should the size fall in between sizes, then the smaller size is selected.
5. The medullary canal is prepared by hand with cylindrical reamers of increasing diameter and an Aequalis fracture stem (Tornier, St. Ismier, France) of the correct diameter is selected.
6. The correct head and stem are put together.
7. The two diaphysis holes are prepared and two other fibre wires (2 or 5) are passed through, ready for final tensioning of the tuberosity.
8. The cement is placed into the canal.
9. The stem is cemented to the predetermined depth and rotation, in slight valgus, taking care to ensure that the distance between the top of the head and the upper margin of the pectoralis major is 5.6 ± 0.5 cm [14].
10. A cancellous bone graft wedge is placed in the "window" of the fracture prosthesis, under the greater tuberosity and the medial edge of the prosthetic head.
11. The last step is to fix and tighten the tuberosity around the prosthesis with the 6 suture configuration technique, described by Boileau (Fig. 12.2 e 3)
12. The shoulder should be passed through a full range of motion to ensure that there is no micromotion of the tuberosity fragments. There should be a passive intraoperative range of motion of at least 160° of elevation, 40° of external rotation and 70° of internal rotation. With the arm in 20° to 30° of external rotation, the rotator interval or surgical rotator cuff split is closed and the biceps is tenodesed within the intertubercular groove/rotator interval to soft tissue.
13. Post-operative care requires a sling and passive motion for the first six post-operative weeks.

International literature reports that the functional results of hemiarthroplasty are unpredictable with either a very good or very bad outcome, when anterior active elevation, active external rotation, active internal rotation and pain are taken into consideration, as can be seen in adjusted constant score [15].

Therefore, as it gives more constant results and the outcome depends on the tuberosity healing, reverse shoulder arthroplasty (RSA) has been suggested as an alternative (Fig. 12.2). However, although the results of RSA are good and more predictable, they are not so good as in cuff tear arthropathy (CTA). Results with the traditional RSA were not always very encouraging [16]. Therefore, prosthesis manufactures improved on the design and surgeons worked on their techniques. Indeed, the use of the reverse shoulder prosthesis simplifies post-operative care and provides quicker recovery, more predictable results, better fixation of the greater tuberosity and better healing of acute fractures. This is particularly true in patients over 75, women with osteopenia and in cuff tears as well as poor compliance with rehabilitation. It is also very useful for greater tuberosity comminution, thin cortical bone, combined fractures of the glenoid and humerus and severe fatty infiltration of the rotator cuff muscles [17]. RSA restores active elevation despite cuff deficiency and improves shoulder function after failed HA for fracture. As aforementioned, the tuberosity healing is also important in the RSA, the technique and/or the design of the reverse prosthesis for fractures with a specific technique for tuberosity fixation has been improved, permitting the tuberosity healing and attachment, so as to restore the active external rotation (AER) [18].

12.2.2 Modular Prosthesis

The first modular shoulder prosthesis came onto the market at the end of the 1980s. An identical head and glenoid radius were no longer used, but rather the mismatched glenoid, i.e., a different radius between humerus and glenoid [19]. While the third generation imitates the 3D bony anatomical parameters of the shoulder and recreates the gleno-humeral joint according to patient anatomy [20], the system modularity free sets the basic parameters, like the humeral head diameter, retroversion angle, implant height, eccentricity and offsets (posterior and medial) of the head [21, 22] (Figs. 12.3, 12.4). These prostheses have a

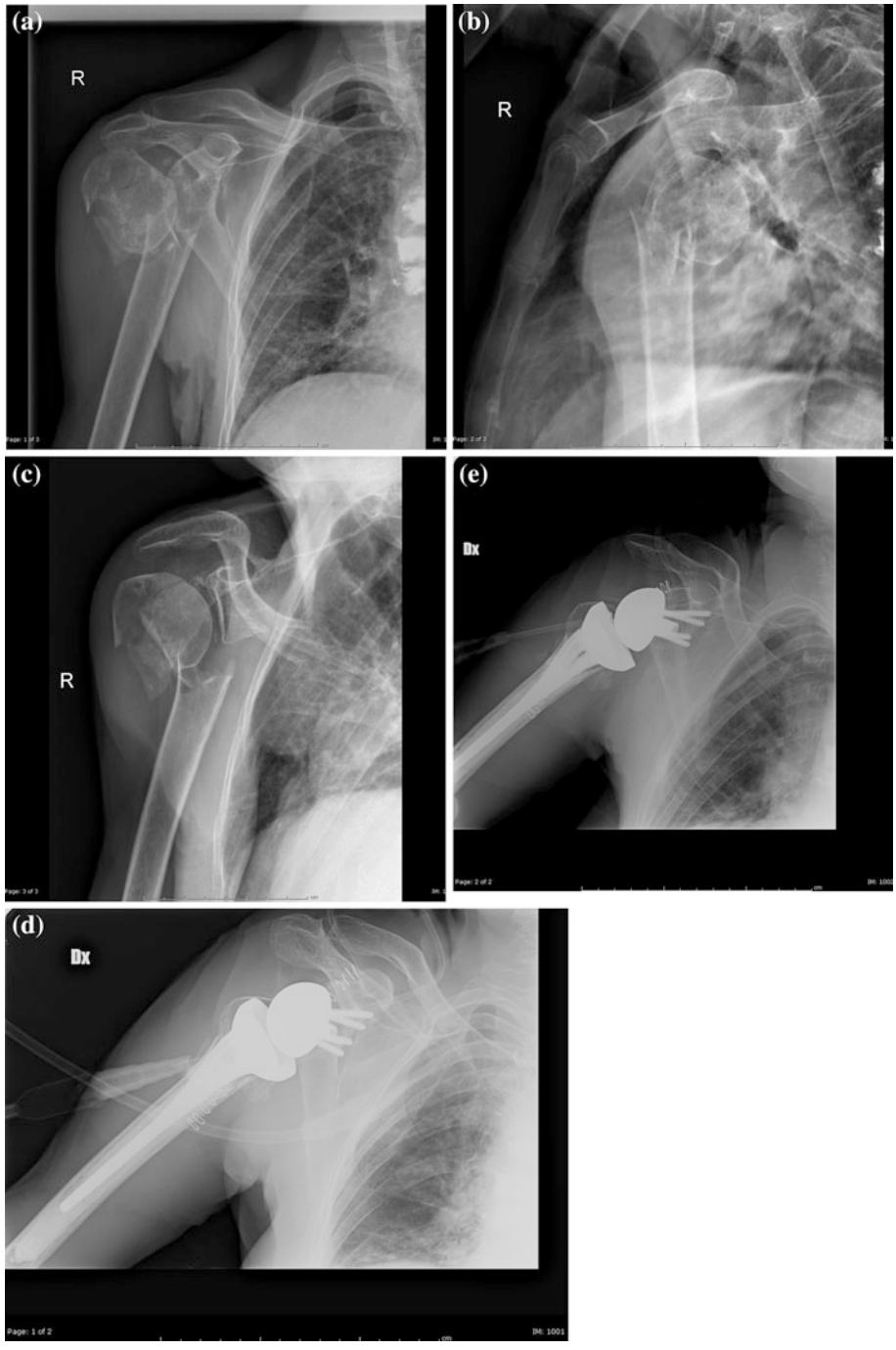

Fig. 12.2 **a** X-Ray pre-op 1. X-ray antero-posterior view in extrarotation: plurifragmented and displaced fracture of the neck of the humerus. **b** X-ray pre-op 2. X-ray transthoracic view: plurifragmented and displaced fracture of the neck of the humerus. **c** X-ray pre-op 3. X-ray antero-posterior oblique view: plurifragmented and displaced fracture of the neck of the humerus. **d** X-ray post-op 1. X-ray antero-posterior view in extrarotation treated with inverse prothesis: plurifragmented and displaced fracture of the neck of the humerus. **e** X-ray post-op 2. X-ray antero-posterior view in intrarotation treated with inverse prosthesis: plurifragmented and displaced fracture of the neck of the humerus

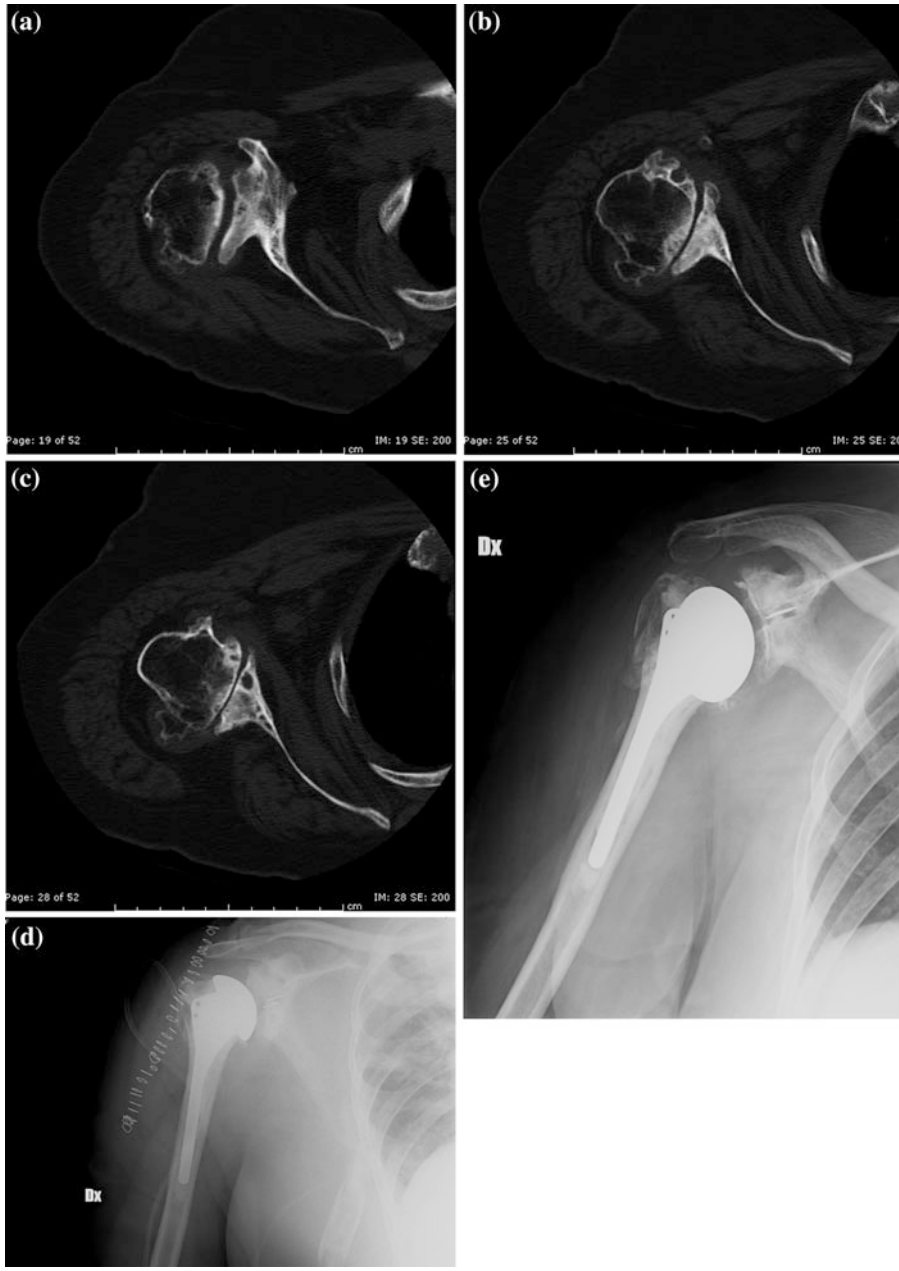

Fig. 12.3 **a** pre-op TC 1. TC axial view in severe gleno-humeral arthrosis. **b** pre-op TC 2. TC axial view in severe gleno-humeral arthrosis. **c** pre-op TC 3. TC axial view in severe gleno-humeral arthrosis. **d** PO 1. X-ray antero-posterior view in extrarotation treated with anathomic prothesis: severe gleno-humeral arthrosis**. e** PO 3. X-ray antero-posterior view in intrarotation treated with anathomic prosthesis: severe gleno-humeral arthrosis

stem, which may be cemented or uncemented (Fig. 12.5). Likewise, the glenoid component may be all in polyethylene or with a metal back. Typically, shoulder replacement with a modular prosthesis is performed in patients with advanced cartilage degeneration due to wear, disease, bone loss, osteonecrosis or trauma. Occasionally, a tumour makes a shoulder prosthesis necessary

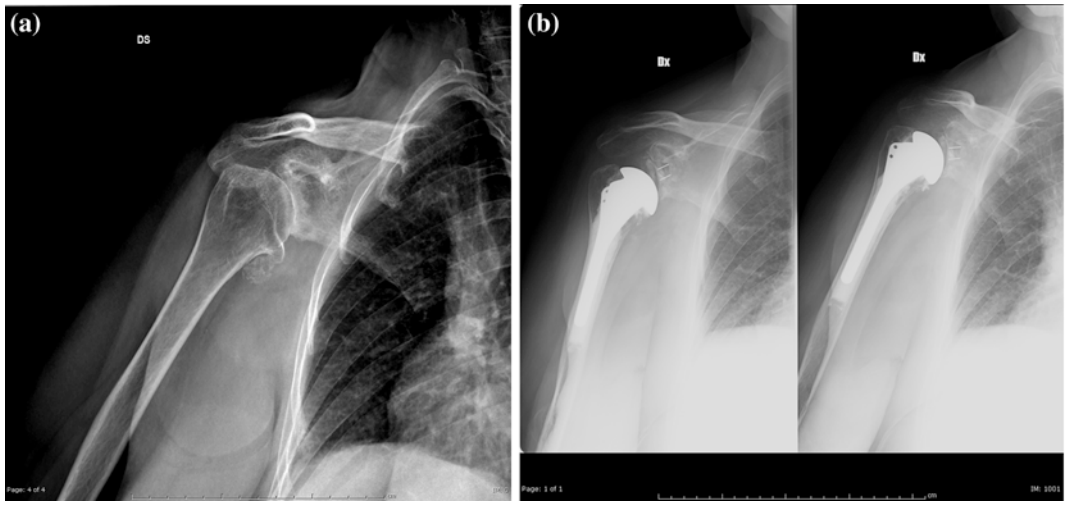

Fig. 12.4 **a** A4 pre-op. X-ray antero-posterior view in extrarotation: severe gleno-humeral arthritis**. b** A4 post-op. X-ray antero-posterior view in extrarotation and intrarotation treated with anatomical prosthesis: severe scapular-humeral arthrosis

[23]. There are various models on the market: Acumed, Biomet, Cofield (Smith and Nephew), DePuy, Encore, Exactech, Neer, Stryker Solar, Tornier, and Zimmer.

The technique of total shoulder arthroplasty foresees the following:

1. placing the patient in the beach-chair position with the torso flexed between 30° and 45° and knees flexed to 30°; the patient must have the shoulder lying far enough off the side of table so that it can be fully extended, externally rotated to avoid interference, space for some adduction should also be allowed;
2. the extended deltopectoral approach is used;
3. the arm is placed in adduction and external rotation may reduce the risk to the axillary and musculocutaneous nerves;
4. the axillary nerve is identified;
5. the subscapularis is mobilized (360° release) and detached from its insertion on the lesser tuberosity and is incised together with the underlying anterior aspect of the capsule. Alternatively, an osteotomy of the small tuberosity may be performed to restore the bone to bone relationship;
6. check for any loose bodies and remove them;
7. prepare the humerus and component insertion;
8. prepare the glenoid and component insertion:
9. wound closure: it is essential to obtain a tight closure of the subscapularis tendon, whether it be bone to bone, tendon to tendon or bone to tendon, since avulsion of the tendon at the repair site often leads to anterior instability.

12.2.3 Resurfacing Prosthesis

The resurfacing prosthesis is indicated for use as a total- or hemi-shoulder joint replacement with sufficient bone stock of the humeral head and neck, where the rotator cuff is intact or reconstructable. This implant relieves severe pain and/or any significant disability caused by degenerative pathologies, e.g., osteoarthritis, rheumatoid arthritis, post-traumatic arthritis, primary and secondary necrosis of the humeral head. We owe these prostheses to Copeland [24, 25], and the Copeland^{TM} Humeral Resurfacing Head has been implanted since 1986. The Humeral Resurfacing Head, unlike a total shoulder implant, is designed to cap only the top of the humerus (Fig. 12.6). As it requires much less bone and cartilage removal, it is more conservative than total joint implants. Both the implant design and minimally invasive approach allow patients to potentially recover more quickly and

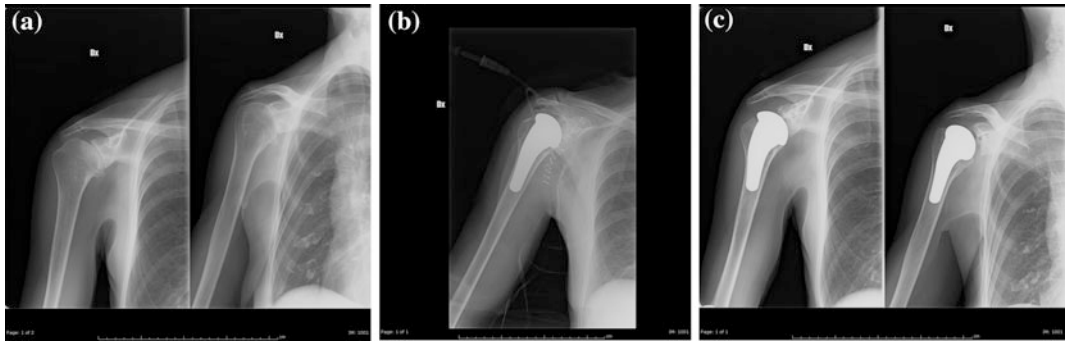

Fig. 12.5 **a** Ascend pre-op. X-ray antero-posterior in intrarotation and extratotation view: severe gleno-humeral arthritis**. b** Ascend post-op 1. X-ray antero-posterior in intrarotation view: severe gleno-humeral arthritis treated with "ascend" prosthesis**. c** Ascend post-op 2. X-ray antero-posterior in intrarotation and extrarotation view: severe gleno-humeral arthritis treated with "ascend" prosthesis

with less pain. It is also less complicated to replace should a future total shoulder replacement become necessary [26]. The most commonly used resurfacing prosthesis are Biomet Copeland Resurfacing Head, Tornier Resurfacing Head, Zimmer Durom Shoulder Cup, Biomet Copeland EAS Humeral Resurfacing Head, DePuy Global CAP, Arthrosurface HemiCAP and the Syntes Epoca Resurfacing Head.

12.2.3.1 Surgical Technique

The deltopectoral approach is the most common, with exposure of the humerus, although the superior approach is advocated by Copeland and described by Mackenzie. The anatomical neck of the humerus is to be defined, requiring complete removal of the peripheral osteophytes around the entire humeral head. A series of hemispherical sizer tools also allow for the correct positioning of the guide pin, determining the final placement of the prosthesis to maintain the original version and inclination. Preservation of the rotator cuff insertion is best achieved by selecting the proper head size, i.e., the thickness. Preservation of the dense bone of the proximal humerus and optimization of contact depend on personal clinical judgment to cease reaming. All these prostheses allow for positioning of the Glena. Glenoid exposure is more difficult with resurfacing arthroplasty than when performing a stemmed humeral component, where the humeral head is cut at the anatomical neck.

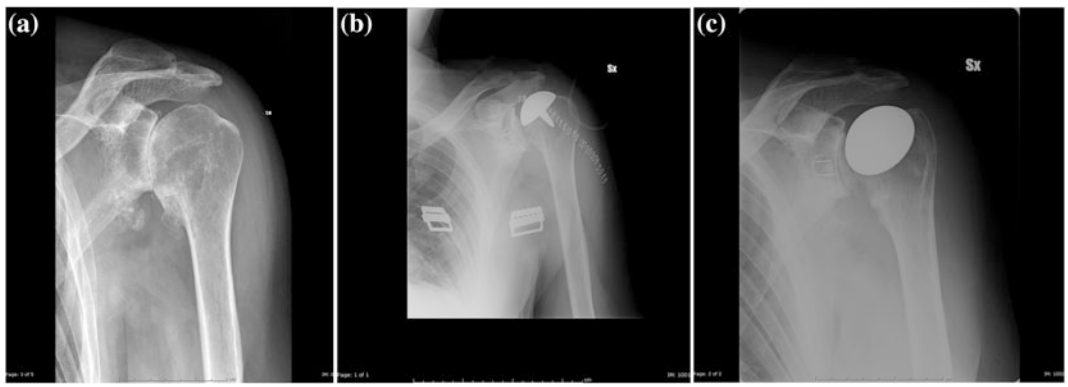

Fig. 12.6 Stemless prosthesis. **a** pre-op 1. X-ray antero-posterior in intrarotation view: severe gleno-humeral arthritis**. b** post-op 1. X-ray antero-posterior in intrarotation view: severe gleno-humeral arthritis treated with stemless prosthesis prosthesis**. c** post-op 2. X-ray antero-posterior in extrarotation view: severe gleno-humeral arthritis treated with resurfacing prosthesis

12.2.4 Stemless Prosthesis

These stemless implants have the same indications as the resurfacing implants and may be used in younger patients with a good metaphyseal bone stock, in the presence of deformities and/or osteonecrosis of the humeral head when it cannot be resurfaced (Fig. 12.7). These prostheses preserve precious bone stock for future interventions, while avoiding clinical complications associated with traditional stemmed solutions, such as peri-prosthetic fracture and humeral splitting osteotomy [27, 28] Three such examples are the Arthrex® ECLIPSE™ shoulder prosthesis [29], the T.E.S.S.® Shoulder system [30] and the Simpliciti™ Tornier.

12.2.5 Reverse Prosthesis

12.2.5.1 History and Biomechanical Principles

It soon became clear that Paul Grammont's definition of the biomechanical principles of medialization and lowering of the centre of rotation of reverse shoulder prostheses was important. He designed a successful implant on these principles, which, nowadays, is recognized as the gold standard for the treatment of degenerative arthropathy of the shoulder associated with an irreparable tear of the rotator cuff [31]. Numerous modifications and many models of reverse prostheses were then introduced. Grammont's idea was successful as his design relies on the strength of the deltoid muscle with medialization and lowering the centre of rotation. This type of design changes the mechanics of the shoulder completely and allows the artificial joint to function when the rotator cuff is either absent, or if there is significant bone loss. The reverse orientation of the prosthesis allows the resulting forces to be directed towards the centre of the gleno-sphere which, in turn, act on the neck of the scapula. His first version of this prosthesis (Delta) was brought out in 1991 and modified over time with the addition of designs by others. Indeed, the Delta III prosthesis (DePuy International Limited, Leeds, England) has been used for more than 15 years throughout the world with extensive reporting [32, 33].

12.2.5.2 Indications

This type of prosthesis is indicated in patients that have an irreparable, rotator-cuff-deficient

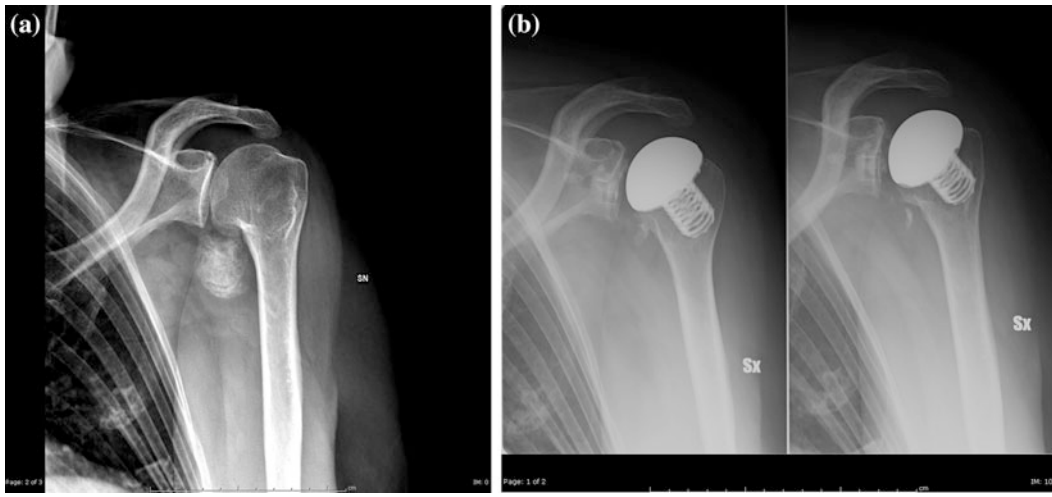

Fig. 12.7 Stemless prosthesis eclipse**. a** pre-op. X-ray antero-posterior in intrarotation view: big calcific free body in the axillar joint recess gleno-humeral**. b** post-op. X-ray antero-posterior in intrarotation and extrarotation view: Stemless prosthesis eclipse prosthesis

shoulder joint with severe arthropathy, usually with evidence of an upward displacement of the humeral head compared to the glenoid and a loss of gleno-humeral joint space (Fig. 12.8). As this limits the functional outcomes of conventional surgical methods, a reverse ball and socket design is often chosen. In difficult cases, like pseudo-paralytic shoulders with massive irreparable cuff tears and gleno-humeral arthritis, a recovery of active abduction between 120° and 130° has been reported [34], and no other technique produces equivalent functional results.

12.2.5.3 Drawbacks

The drawbacks of the reverse shoulder prostheses are now well documented [35]. Soon after surgery, there may be medial notching of the scapula due to impingement between the polyethylene cup and the axillary border of the scapula. Indeed, there is a well-known series from Nice that reported this complication in 74 % of cases (45 cases) and another from Sirveaux in 65 % (77 cases) [36]. Gerber et al. studied the passive range of motion of the prosthesis in specimens where the gleno-sphere was fixed superiorly. This confirmed that contact between the humeral cup and the pillar of the scapula is much more significant when the metaglenoid is fixed high on the glenoid [37]. Other problems include superior loosening on humeral lowering and a modified shoulder contour due to the low and medial placement of the glenoid component. Adjustment of the tension of the deltoid can be another source of complications like lengthening of the limb and neurological involvement, mostly the ulnar nerve.

12.2.5.4 Surgical Technique [38]

Grammont first described a transacromial approach for the placement of this prosthesis. However, nowadays, most surgeons use a deltopectoral, or anterosuperior approach. Our team prefers the deltopectoral approach, in as much as, not only does it spare the deltoid insertion and axillary nerve, but it is also very useful in prosthetic revision surgery.

12.2.5.5 Exposure and Humeral Preparation

In my experience with Tornier reversed 2 prosthesis the subscapularis is tenotomized 1 cm from its insertion. Release of the subscapularis continues inferiorly in selected cases, the superior 1 cm of the pectoralis insertion is also released for better exposure. The cuff is usually absent superiorly. At this point, the humerus is easily dislocated anteriorly and superiorly for humeral preparation. The highest, most lateral point on the humeral head is identified as a reference point and the head cutting guide is inserted into the humeral shaft to cut the humeral head in the correct retroversion, i.e., between 0 and 20°. Then, the metaphyseal "cheese grater" reamer is used to remove remaining cancellous bone from the proximal humerus to allow metaphyseal component placement. The surgeon may choose from 2 sizes of reamers, 36 or 42 mm. Diaphyseal reaming is then performed sequentially with reamers of 6.5, 9, 12 and 15 mm until the reamer comes into contact with diaphyseal cortical bone. A plastic cut protector is then placed into the metaphysis of the component to protect the trial component during glenoid preparation.

12.2.5.6 Glenoid Preparation

Glenoid osteophytes are removed to reveal the true glenoid anatomical shape and more correctly identify the base of glenoid bone that is most solid for baseplate (metaglene) placement. The central hole guide is assembled against the inferior most edge of the glenoid. This ensures that the metaglene is placed against the glenoid as inferior as possible, so as to have the glenosphere inferior enough and tilted inferiorly a few degrees to decrease any contact of the polyethylene insert with the scapula. This is done to prevent scapular notching. The baseplate inserter is assembled and the 8.0-mm baseplate central post is impacted into the 7.5-mm drilled hole for a press-fit into the scapula. The baseplate should be very well fixed to the bone. This requires at least 3 of the 4 screws having good purchase.

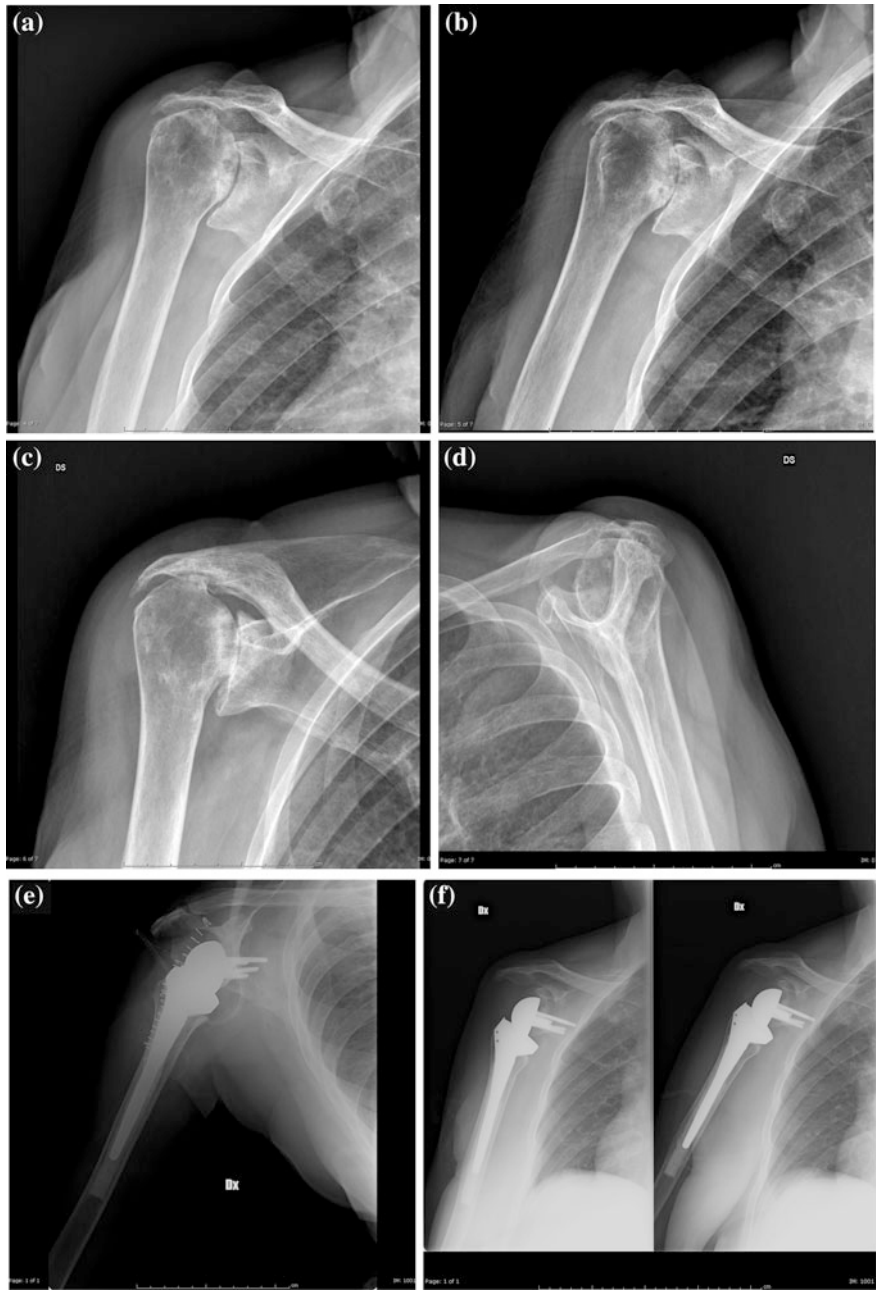

Fig. 12.8 **a** pre-op 1. X-ray antero-posterior in intrarotation view: severe gleno-humeral arthritis**. b** pre-op 2. X-ray antero-posterior in extrarotation view: severe gleno-humeral arthritis**. c** pre-op 3. X-ray antero-posterior in intrarotation view: severe gleno-humeral arthritis**. d** pre-op 4. X-ray antero-posterior in Neer's view: severe gleno-humeral arthritis**. e** post-op 1. X-ray antero-posterior in intrarotation view: severe gleno-humeral arthritis treated with inverse prosthesis**. f** post-op 2. X-ray antero-posterior in extrarotation view (abduction and adduction): severe gleno-humeral arthritis treated with inverse prosthesis

Some models use only two anchoring screws along with the baseplate central post. The gleno-sphere of choice (36 or 42 mm, in other models also 38, 40 and 44) is then guided to the metaglene. Final gleno-sphere fixation is secured by tightening the centre set screw, which threads into a mating thread on the inside of the centre peg of the metaglene. After the gleno-sphere is firmly implanted, the humerus can be re-dislocated out of the incision. A 6-mm trial humeral insert is then placed and impacted into the humeral trial metaphyseal cup. A trial reduction is performed. If the shoulder cannot be reduced with a 6-mm insert, then the trial insert is removed, adhesions lysed and additional proximal humeral bone resected if necessary. Once it has been determined that the shoulder will reduce, the proximal humeral component is cemented. After the humeral component has been well fixed with cement, the 6-mm trial insert is placed into the metaphysic and the shoulder reduced. If the tension is adequate, the shoulder is re-dislocated and the final polyethylene (6, 9 or 12 mm depending on the tension) liner impacted into the metaphyseal cup. After the shoulder has been reduced with the final implants in position, the subscapularis is repaired using 3 to 4 tendon to tendon sutures, occasionally augmenting the repair with transosseous sutures if the remaining tendon tag on the humerus does not suffice. The deltopectoral interval is closed over a drain, with a running absorbable suture. The skin is closed in the routine manner. Post-operative radiographs are taken in the operating theatre before taking the patient to the ward.

12.2.6 Post-operative Management of all Prosthesis

The shoulder is immobilized in slight abduction and in near-neutral rotation. Gentle passive motion in all planes is started immediately, taking care not to push the limit of intraoperative motion measurements [39]. Active assisted motion is started at 3 to 4 weeks post-operatively followed by active motion at approximately 6 weeks. Except in fracture prosthesis, where it is necessary to wait for 6 weeks to allow for consolidation of the tuberosity, followed by assisted active motion at 6 weeks, then active motion at 8 weeks. Pendulum exercises—with the arm down at the side, e.g., the patient swings the hand backwards and forwards gently, then from side to side and then clockwise and counterclockwise. This can usually be started the day after surgery. Along with the passive forword flexion to 90°, the external rotation, initially to the neutral position, can be gradually increased as tolerated after 6 weeks. The towel pulls start after 6 weeks and increase as tolerated as does the wall walking, for forward flexion [40].

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Elbow Arthroplasty

13

Maddalena Bertolini, Francesco Giacalone and Italo Pontini

13.1 Introduction

In orthopedic surgery practice, the use of elbow arthroplasties has become more and more common over the past decades, even if relatively few total elbow arthroplasties are still performed each year [1]. These prostheses have evolved in both component design and variety of indications. There are several types of implants that can be used to replace the radial head (capitellar arthroplasty), the capitulum humeri (capitellar resurfacing), the whole distal humerus (hemiarthroplasty), or the entire joint (total elbow arthroplasty).

Radial head replacement is most commonly performed in patients with trauma. Radial head fractures account for 33 % of all elbow fractures in adults and are often associated with ligament disruption [2–4]. In patients with a comminuted radial head fracture that cannot be treated with internal fixation with a plate and screws, radial head excision used to be the only unique solution before development of the prosthesis. This procedure though has been associated with valgus instability, chronic pain, and secondary osteoarthritis [5–7]; therefore, radial head arthroplasty is nowadays the gold standard in these cases. The goal of radial head arthroplasty is to restore or prevent loss of elbow stability, range of motion, and radius length. Specific indications for arthroplasty include comminuted Mason types III and IV radial head fracture, radial head fracture with medial or lateral ulnar collateral ligament dysfunction, Monteggia variants and olecranon fracture, coronoid process fracture, interosseous membrane disruption, and treatment of osteoarthritis [8]. Contraindications for arthroplasty include open wounds, infection, and fractures that extend beyond the radial tuberosity [9]. Disadvantages are development of secondary osteoarthritis at the elbow joint and the potential for hardware-related complications.

Capitellar resurfacing arthroplasty is mainly used in case of osteoarthritis and erosion of the capitellum, secondary to radial head trauma either left untreated or treated with radial head arthroplasty or ORIF. This can also be considered as preventive surgery: Recent studies showed that radial head arthroplasty decreases the radiocapitellar contact area by 68 %, posing a risk for osteoarthritis and capitellar osteopenia in as many as 78 % of patients [10–12].

The primary indication for total elbow arthroplasty used to be rheumatoid arthritis [13]; as a matter of fact, the elbow is involved in approximately 50 % of patients with this pathology. During the past years, the most common indication for total elbow arthroplasty changed from inflammatory arthritis to trauma:

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Prosthesis can be used to replace the joint in case of acute comminuted fractures of the elbow that cannot be repaired. Other indications include primary or post-traumatic osteoarthritis, fracture nonunion, and post-operative resection of a tumor. Its goal is to decrease pain and restore an acceptable range of motion to the elbow joint. In general, surgery is reserved for low-functioning patient with severe pain and patients who are older than 40 years, because high complication rates (18–48 %) and revision rates (22 %) [14] are reported, especially in young and active patients [15]. Contraindications for total elbow arthroplasty include infection, presence of a large open wound, and a neuropathic joint [16].

Post-operative radiological assessment of these different types of elbow reconstructions requires an understanding of their basic component design, physiologic purpose, and normal post-operative appearance, as well as the appearance of complications. Radiologists may have little training and experience with these new orthopedic devices.

13.2 Type of Prosthesis

1. **Total Elbow Arthroplasty**

There are three main designs for total elbow arthroplasty: constrained (linked), unconstrained (unlinked), and semiconstrained.

The constrained one is the first prosthesis that has been introduced. It grants a great stability, but high rates of loosening and periprosthetic fracture are reported with this hardware design, likely a result of transfer of all physiologic forces to the hardware and bone rather than sharing of the load with adjacent soft tissues. Since the 1980s, its use has been quite abandoned.

The unconstrained, or unlinked, design of total elbow arthroplasty consists of separate cemented metal humeral and ulnar components, which articulate by way of a high-density polyethylene component [17]. No pin links the two components. Because forces are transferred to the soft tissues, this design has the lowest incidence of mechanical loosening [18]. However, because there is no hinge or link, dislocation is most common complication [19, 20].

The semiconstrained, or partially hinged, design of total elbow arthroplasty is currently the most commonly used design. It consists of titanium or cobalt chromium metal stems that are linked by a pin and bushing, a circular polyethylene ring that sits between the metal components to decrease metal-on-metal friction. Current studies report that the semiconstrained design has complication rates of only 10 % compared with those of the unconstrained and constrained designs, which were 50 % in the 1980s and 1990s. The semiconstrained design also has 10-year survival rates of over 90 %. The semiconstrained design comes in both modular and nonmodular forms. The modular form is most commonly used in patients who underwent resection of a bone neoplasm or with extensive bone loss from trauma.

13.2.1 Implantation Technique

The patient may be positioned in a lateral decubitus position or a supine position based on surgeon preference. A straight incision is made approximately 15 cm in length and centered just medial to the tip of the olecranon. The ulnar nerve is mobilized, transposed anteriorly into the subcutaneous tissue, and carefully protected throughout the remainder of the procedure. The triceps is splitted. The center of the flexion–extension axis is marked on the distal humerus: It is typically at the site of attachment of the lateral ligaments to the lateral epicondyle. The key to a successful outcome is the accurate determination of the flexion–extension axis. The articular surfaces and the medullary canals of humerus, ulna, and radius are prepared using the dedicated instruments, in order to properly fit the prosthesis components. The appropriate size of each component is selected, and then, the implants are inserted.

Almost all the stems currently used need to be cemented. Depending on the prosthetic design, a small bone graft can be placed between the

Fig. 13.1 AP (**a**) and lateral (**b**) radiographs of an elbow in a 76-year-old woman with RA. *Note* the narrowing of the joint line, the articular surfaces sclerosis, and deformity, with osteophytes and osteopenia

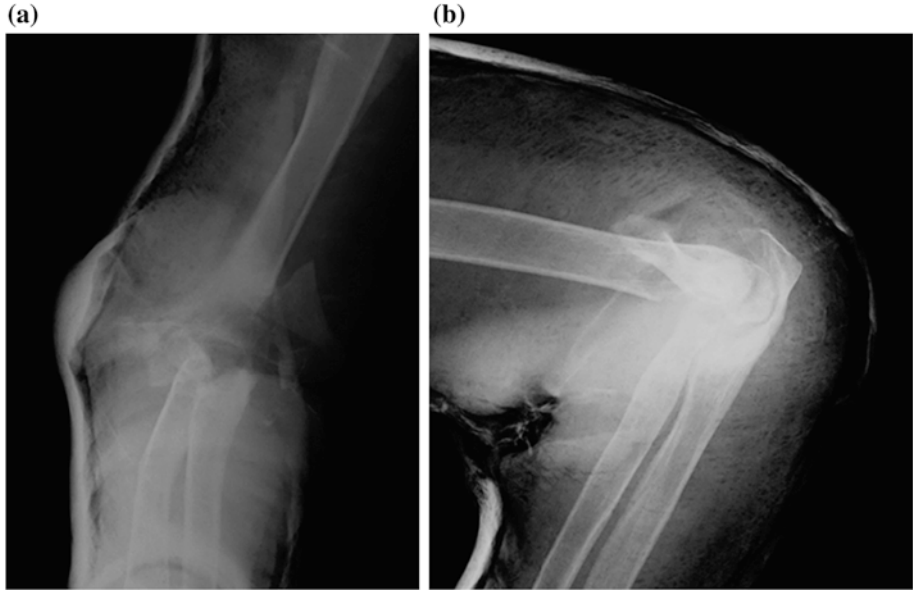

Fig. 13.2 AP (**a**) and lateral (**b**) radiographs of a 76-year-old woman with fracture-dislocation of the elbow (after reduction and cast)

humeral shaft and the anterior flange of the humeral component in order to improve the stability.

Some prostheses are designed to be only semiconstrained (e.g., the Zimmer Coonrad-Morrey), while others can be used either unconstrained or semiconstrained (e.g., the Tornier Latitude).

In some cases, a concomitant capitellar arthroplasty can be performed, and in other cases, the radial head should be excised.

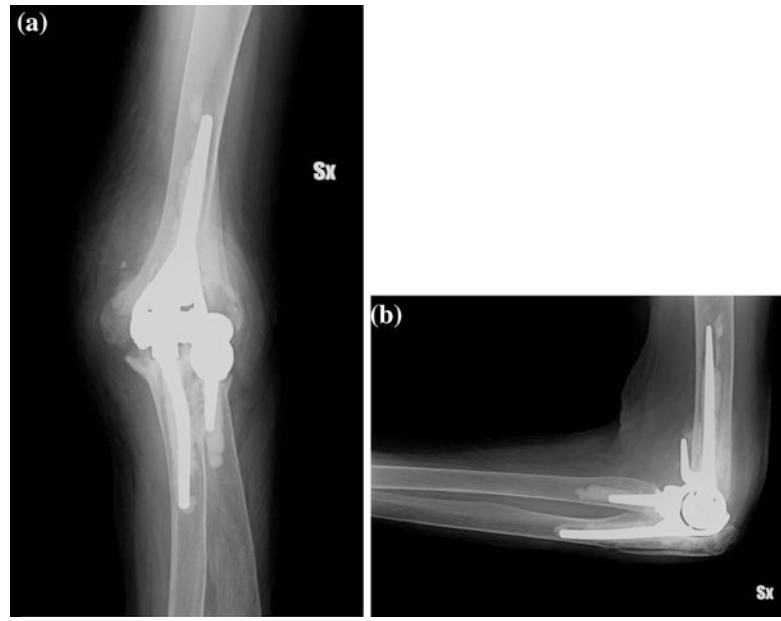

Fig. 13.3 AP (**a**) and lateral (**b**) radiographs of a semiconstrained total elbow prosthesis (Tornier Latitude) with concomitant capitellar arthroplasty, in a 76-year-old woman with RA. *Note* the cementation around the stems and the bone graft under the humeral flange

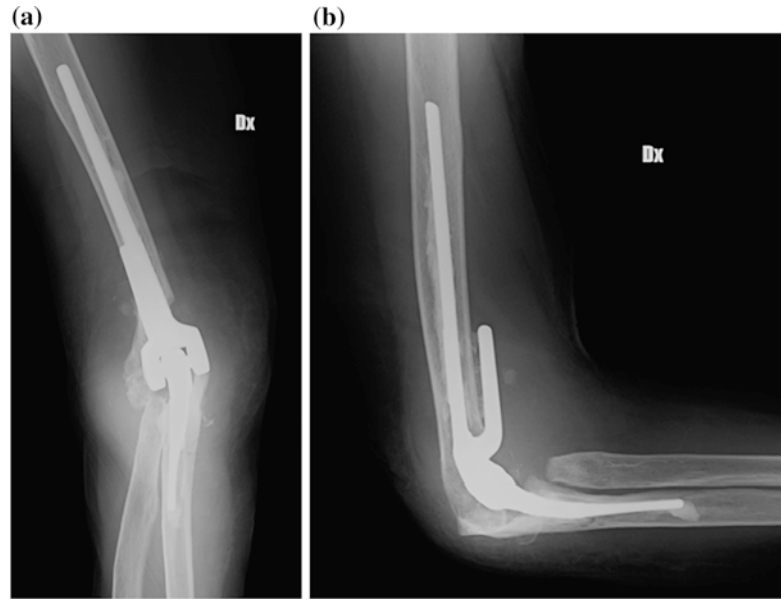

Fig. 13.4 AP (**a**) and lateral (**b**) radiographs of a semiconstrained total elbow prosthesis (Zimmer Coonrad-Morrey), in an 80-year-old woman with fracture-dislocation of the elbow. Capitellar resection has also been performed. *Note* the cementation around the stems and the bone graft under the anterior humeral flange

13.2.2 Preoperative Imaging

Standard anteroposterior and lateral radiographs with the elbow flexed at 90° are essential studies in the initial evaluation of the elbow, either arthritic (Fig. 13.1) or traumatic (Fig. 13.2). Each image is evaluated for joint space narrowing and the location and size of osteophytes and heterotopic bone. Adequacy of bone stock and quality and any deformities should be noted when joint replacement is considered.

Other studies are obtained case by case.

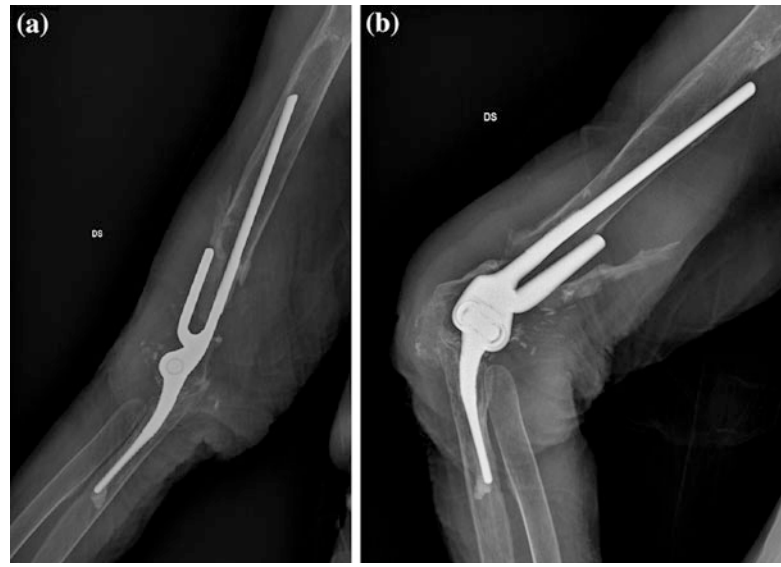

Fig. 13.5 **a** and **b** radiograms showing the aseptic mobilization of the humeral component of the prosthesis shown above (Fig. 13.4), 3 years later, with periprosthetic fracture. Note the significant osteopenia

Computed tomography (CT) can be helpful in the evaluation of comminuted fractures or in mapping the extent and location of bony involvement of a tumor. If there is a suspicion of deformity or dysplasia of humerus, ulna, or radius, a 3D reconstruction can also be performed.

Magnetic resonance (MR) imaging in conjunction with physical examination is used to evaluate ligamentous integrity, especially in cases of recurrent instability.

13.2.3 Follow-up Imaging

In the AP view, the humeral component should be centered on the humeral shaft. On the lateral view, a line drawn through the anterior humeral cortex should bisect the area between the anterior flange and the posterior humeral cortex. The ulnar stem should be centered within the medullary shaft. The proximal part of the ulnar component should be even with the tip of the olecranon and should not extend beyond or proximal to the imaginary line drawn parallel to the posterior humeral shaft (Figs. 13.3, 13.4, 13.5).

Although radiography should be the initial imaging modality used to evaluate elbow arthroplasty, CT scan can be used to identify the degree and sites of heterotopic ossification, the severity of radiocapitellar osteoarthritis, and the presence of loose intraarticular bodies and periprosthetic fractures in select cases. MR imaging may be helpful to assess soft tissue infection, ligamentous disruption, and recurrence of neoplasm. The use of CT scan and MR imaging is limited by the presence of artifacts related to the metal composition of the prosthesis.

2. **Radial Head Arthroplasty**

There are different implant designs and materials currently available in orthopedic practice for radial head arthroplasty.

Silicone hemiarthroplasty, first introduced by Swanson in 1969 [21], is rarely performed because high rates of loosening, fracture, and silicone synovitis were reported [22, 23]. Most currently used implants are composed of titanium or cobalt chromium metal (e.g., SBI-Myrmex RECON or Tornier CRF II) or, more recently, pyrocarbon (e.g., Tornier MoPyC). They can have a fixed or variable neck–head angle (unipolar or bipolar design) and can be either cemented or not (press-fit)

The unipolar, or monoblock, design consists of a radial head that does not move separately from the radial neck. The stem can either move in the radial neck and act as a spacer or may have a fixed (press-fit or cemented) design that resembles the native anatomy.

The bipolar design allows semiconstrained articulation of the radial head with the fixed metal stem and may telescope or rotate several degrees in all planes. The radial head is symmetric, composed of metal or pyrocarbon, and bridged to the radial neck by a mobile polyethylene-on-chromium bearing at the head–neck junction [24]. Physiologically, the purpose of this design is to reduce stress at the implant–bone interface and increase the contact area of the radiocapitellar joint [25] (37). However, because of this increased motion, there is greater potential for osteolysis, particle disease, and osteoarthritis at the radiocapitellar joint space.

13.2.4 Implantation Technique

The patient is supine on the operating table, and the elbow is flexed and allowed to rest on a small table. The forearm is placed and held in pronation, so that the radial nerve is medialized and the radial shaft is oriented in the axis. With the elbow flexed, an angled incision has to be centered over the tip of the epicondyle. The most popular deep approach is the lateral one, between the extensor carpi radialis brevis and the extensor digitorum communis. The other option, with the same skin incision, is to use a posterolateral approach between the anconeus, posteriorly, and the extensor carpi ulnaris, anteriorly (Kocher): This approach affords a more distal access to the radius. The annular ligament must be incised, if intact; anyway, whether it was torn or incised, it should be repaired whenever possible. Finally, the head osteotomy and the preparation of the medullary canal of the radius must be performed, with the dedicated instruments. The choice of the appropriate head size and neck length are the most critical factors in order to avoid prosthesis overstuffing and excessive ligaments stress that might cause failure of the implant. Orientation of the prosthetic neck is usually determined relative to the bistyloid plane, following the same axis. Once the trial stem has been properly seated, with cementation if necessary, the radial head can be inserted.

13.2.5 Preoperative Imaging

Preoperative assessment requires standard AP and lateral views of the head of the radius. It is important to execute also X-ray of the ipsilateral wrist, if painful, to exclude an Essex-Lopresti Syndrome.

CT scan can be helpful for a better understanding of the pattern of comminuted capitellar fractures, to decide whether to proceed with an osteosynthesis or an arthroplasty.

13.2.6 Follow-up Imaging

On both AP and lateral views, the stem of the radial head implant should be centered within the radial neck, with no tilt, and the articular surface of the radial head should be less than 1–2 mm proximal to the sigmoid notch of the ulna [26]. Transverse movement of the radial head implant, also known as translation, appears as an area of increased lucency at the tip of the stem, with the head more than 1–2 mm beyond the coronoid process on a lateral view and a narrowing of the radial–capitellar joint space.

For a correct evaluation of post-operative radiograms, it may be useful to know what kind of prosthesis has been inserted. In some implants, the stem is smooth and uncemented, and as the radial head self-centers on the capitellum during forearm rotation, it moves in the radial neck, showing a stable lucency (<2 mm) surrounding the stem on radiographs [10]. This lucency must not be confused with a sign of pathological mobilization. Otherwise, if the stem is fixed (press-fit or cemented), it should not move in the intramedullary canal; therefore, a lucency must be considered as a possible complication.

It is also important to consider if the implant is unipolar or bipolar: In the first case, the head should not move separately from the radial neck, and a variation of this angle in the different views or elbow positions may be considered pathologic. On the contrary, in the bipolar design, the head can rotate several degrees in all imaging planes (Figs. 13.6, 13.7, 13.8, 13.9).

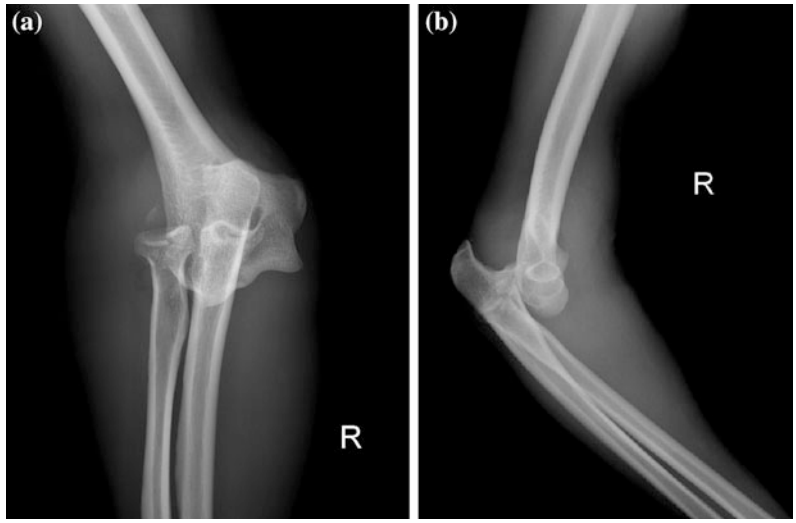

Fig. 13.6 AP (**a**) and lateral (**b**) radiographs of a 66-year-old man with fracture-dislocation of the elbow

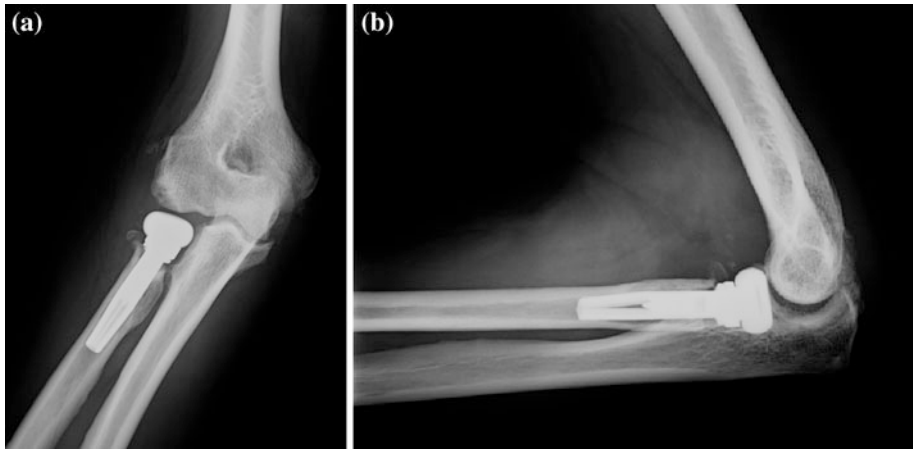

Fig. 13.7 AP (**a**) and lateral (**b**) radiographs of a 66-year-old man with a radial head arthroplasty (Tornier MoPyC, cementless, fixed pyrocarbon head)

13.3 Wrist Arthroplasty

As well as other anatomical sites, the main indications for wrist arthroplasty are pain and disfunction in patients in which medical management has failed to relieve the pain or when the deformity interferes with upper limb function.

Wrist arthroplasty is an alternative for patients with severe wrist arthritis who have specific requirements or desires to preserve motion. However, wrist replacement has its own unique risks and potential complications and is not appropriate for patients with high physical demands.

Advanced osteoarthritis of the wrist or the distal articulation of the lunate with the capitate has traditionally been treated surgically by arthrodesis. In order to maintain movement, it can be performed proximal row carpectomy with capsular interposition arthroplasty as an alternative to arthrodesis with the interposition of a pyrocarbon implant or with a total wrist arthroplasty.

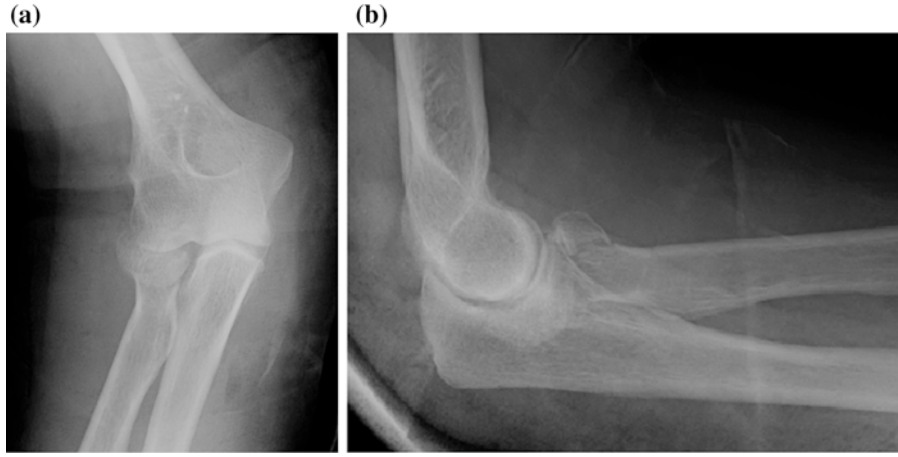

Fig. 13.8 AP (**a**) and lateral (**b**) radiographs of a 70-year-old woman with a Mason III fracture of the capitellum

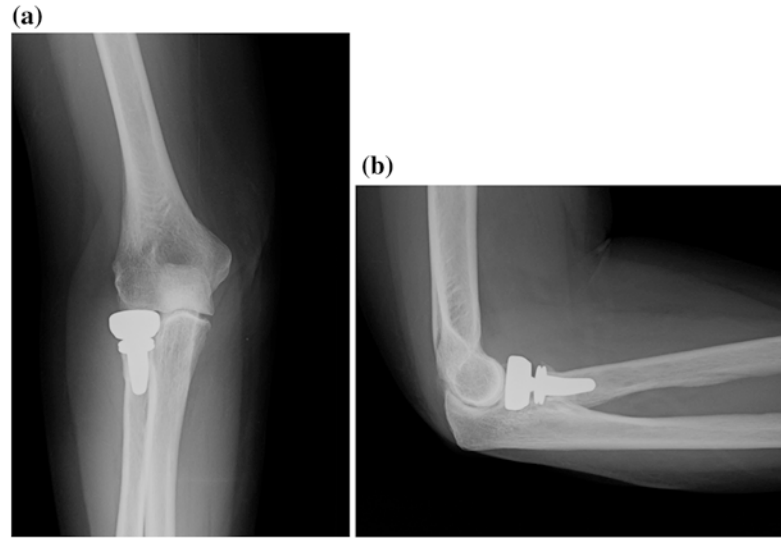

Fig. 13.9 AP (**a**) and lateral (**b**) radiographs of a 70-year-old woman with a radial head arthroplasty (SBI-Myrmex RECON, cementless, bipolar metal head). The stem of the implant is centered in the radial neck

Total wrist fusion is a palliative option that is often not well tolerated and that is not free of complications [27].

Total wrist arthroplasty gives superior functional results, but its use is limited because of the high rate of complications and failures [28, 29]. New models of prosthesis have been recently developed but still lack significant follow-up [30]. Its indication is pain and/or loss of function due to rheumatoid arthritis, SNAC or SLAC wrist, osteoarthritis, post-traumatic arthritis. The contraindications include poor bone quality (which may affect the implants stability), severe neurological or muscular deficiencies (that would compromise implant function), and infections (acute or chronic, local, or systemic). Other contraindications include disease which may compromise the function of the implant.

Recently, new types of wrist prosthesis have been developed. These implants often act as spacers, and they can partially or totally substitute carpal bones. They can be used alone in association with other procedures, such as first row carpectomy. The results of these types of implants are good, and with the proper indications, they represent a good alternative to total and partial wrist arthrodesis.

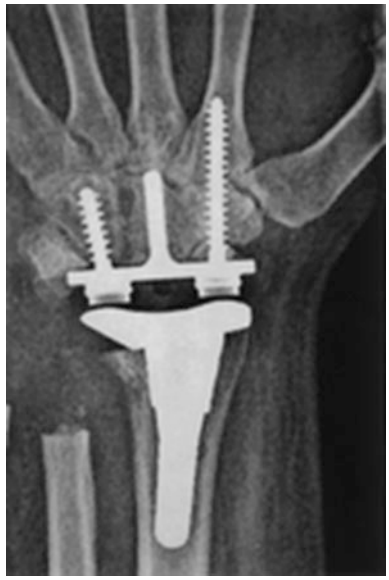

Fig. 13.10 Total wrist arthroplasty with a titanium and polyethylene implant (Re-Motion)

Total wrist arthroplasties can be done using different kind of prosthesis that can be either made of silicone (i.e., Swanson), titanium, or polyethylene (i.e., Re-Motion—Fig. 13.10) or pyrocarbon (Amandys) [31].

There are several partial wrist arthroplasties that can be performed.

Replacement of the capitate head is done with a particular type of prosthesis called Resurfacing Capitate Pyrocarbon Implant (RCPI)—Fig. 13.11) [32].

In Kienbock's disease, semilunar prosthesis can substitute the lunate, allowing a good range of motion. It can be used as an alternative for a first row carpectomy (Fig. 13.12).

For scaphoid nonunions or necrosis of the proximal pole, there are two possibilities: complete or hemi-scaphoid implants that could be either made of titanium (Fig. 13.13), pyrolytic carbon (APSI—Fig. 13.14), or PEEK [33]. The partial wrist prostheses in pyrocarbon (APSI) are dynamic spacers that restore the variable geometry of the carpus and maintain first carpal raw coherence, avoiding evolution to SLAC or SNAC wrist.

All these kind of surgical procedures represent a good alternative to total and partial wrist arthrodesis. Nevertheless, longer-term follow-up in larger series of patients is needed to assess the global survivorship of these prosthetic implants.

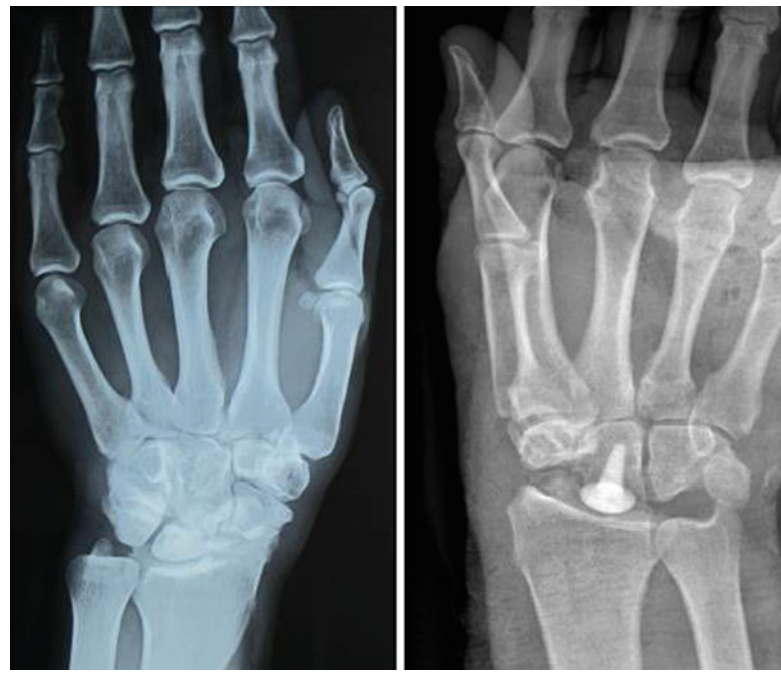

Fig. 13.11 RCPI prosthesis for the capitate proximal pole associated with a first row carpectomy (preoperative and post-operative)

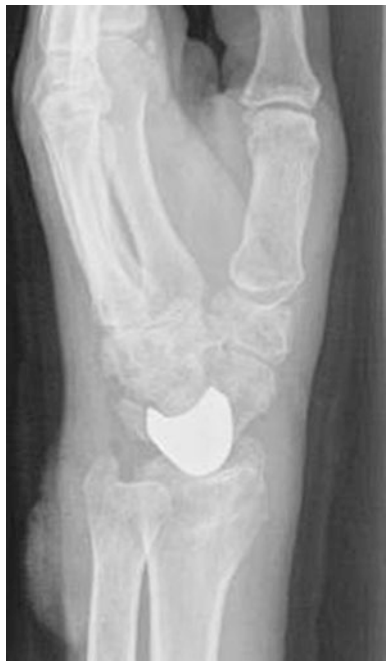

Fig. 13.12 Total semilunar prosthesis

13.4 MCP and PIP Joint Arthroplasty

The main indications of finger joint arthroplasty are pain and disfunction in patients in which medical management has failed to relieve the pain or when the deformity interferes with hand function.

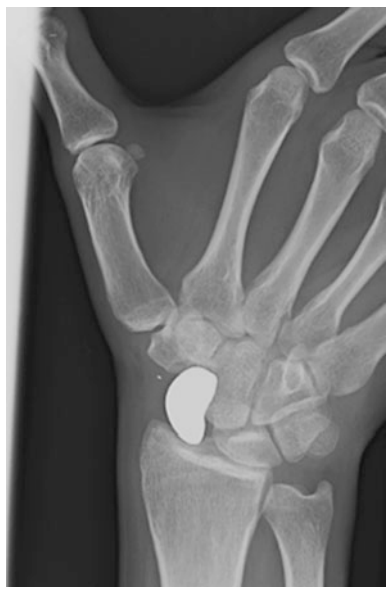

Fig. 13.13 Total and partial (APSI) scaphoid prosthesis

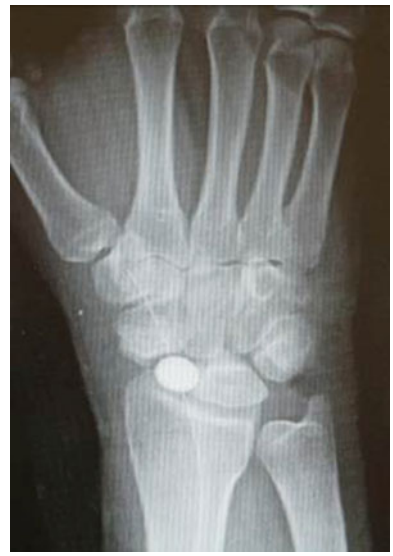

Fig. 13.14 Total and partial (APSI) scaphoid prosthesis

Many conditions lead to an articular damage: osteoarthritis, traumatic injuries, inflammatory arthritis (like rheumatoid arthritis and LES), and neoplasms.

In clinical practice, there are two main options of surgical treatment of these conditions: arthrodesis or arthroplasty. Arthrodesis leads to excellent pain relief and stability, but with sacrifice of the joint function. The MCP and PIP are hinged diarthrodial joints that can be successfully replaced in order to preserve a certain range of motion, with consequent improvement in the function and appearance of the hand.

For decades, only silastic implants were used, the most popular being the Swanson prosthesis (Fig. 13.15). These single pieces of silicone, which act as flexible spacers, are still burdened by a high complication rate, including loosening, synovitis and implant fractures and dislocations. Now, they find indication as salvage procedure in patients in which the surgical goal is to correct deformities and provide pain relief, like rheumatoid ones (Fig. 13.16). This kind of implants is then not suitable for patients who are

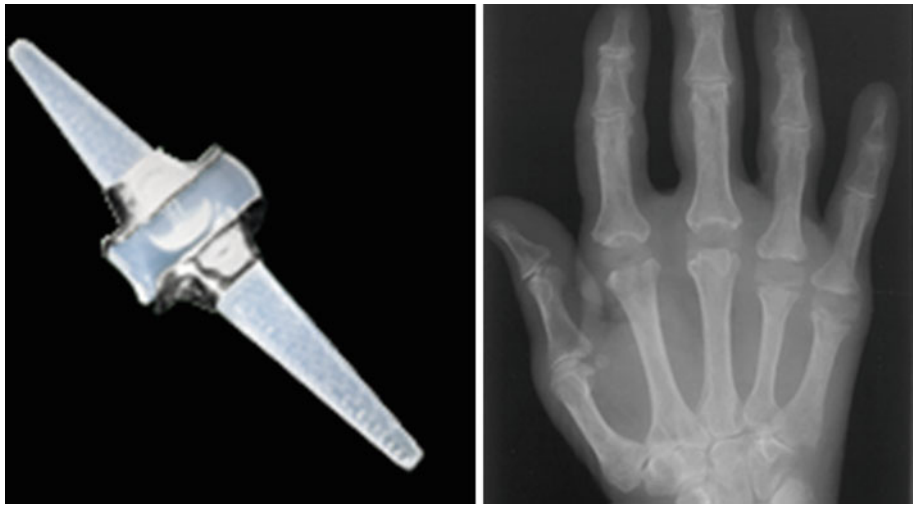

Fig. 13.15 Swanson prosthesis of the MP joints

at risk of implant fracture or dislocation, due to high demand loading conditions and frequent hand movements.

To increase implant durability, especially in younger patients, a new concept of prosthetic joint arose by the years: Resurfacing implants [34], with minimally constrained design and anatomical geometry, were created. These low-profile implants limit the amount of bone removed while preserve the integrity of the collateral ligaments [35]. They mechanically transfer loads at the PIP or MCP joints to the adjacent ligaments and tendons, distributing in this way the stress across the joint and then determining lower complication rates. Moreover, new materials were introduced, like the pyrolytic carbon, with characteristics of biocompatibility and an elastic modulus similar to cortical bone, in order to balance implant–bone stress transfer. The ideal patients for these kinds of implants are young patients with post-traumatic arthritis or osteoarthritis, with a quite high activity level, in whom soft tissues, capsule, and collateral ligaments are better preserved [36].

Common signs of prosthesis failure are the pain and loss of range of motion due to implant settling or dislocation, squeaking, and poor osteointegration (visible on X-ray as a radiolucent line at the bone–implant interface) [37].

Follow-up of prosthetic implant is usually performed by serial post-operative X-ray controls. In a recent review of 47 implants with a 10-year follow-up, a radiological analysis has been conducted. The authors investigated the eventual presence of subsidence, loosening with or without dorsal or volar tilt of the stem, subluxation, and periprosthetic fractures. The clinical outcomes chosen were pain, range of motion, stiffness, and decreased daily hand function. They found surprisingly that radiographic and clinical survival poorly correlate. They assessed that a symmetric lucency around the distal stem of 1 mm or less that stabilizes over time is normal, representing the coating layer of the pyrolytic carbon material and a thin fibrous membrane (Figs. 13.17 and 13.18). Tilt of the proximal stem and subsidence as the more common radiographic complications, when the most frequent reason of surgical revision was extensor tendon contracture or ligament laxity, as noted also in other series [38, 39]. Further studies have been conducted to determine the radiological and clinical correlation during the follow-up period, with quite similar findings. This may means that longer-term follow-up in larger series of patients is needed to assess the global survivorship of these prosthetic implants [40, 41].

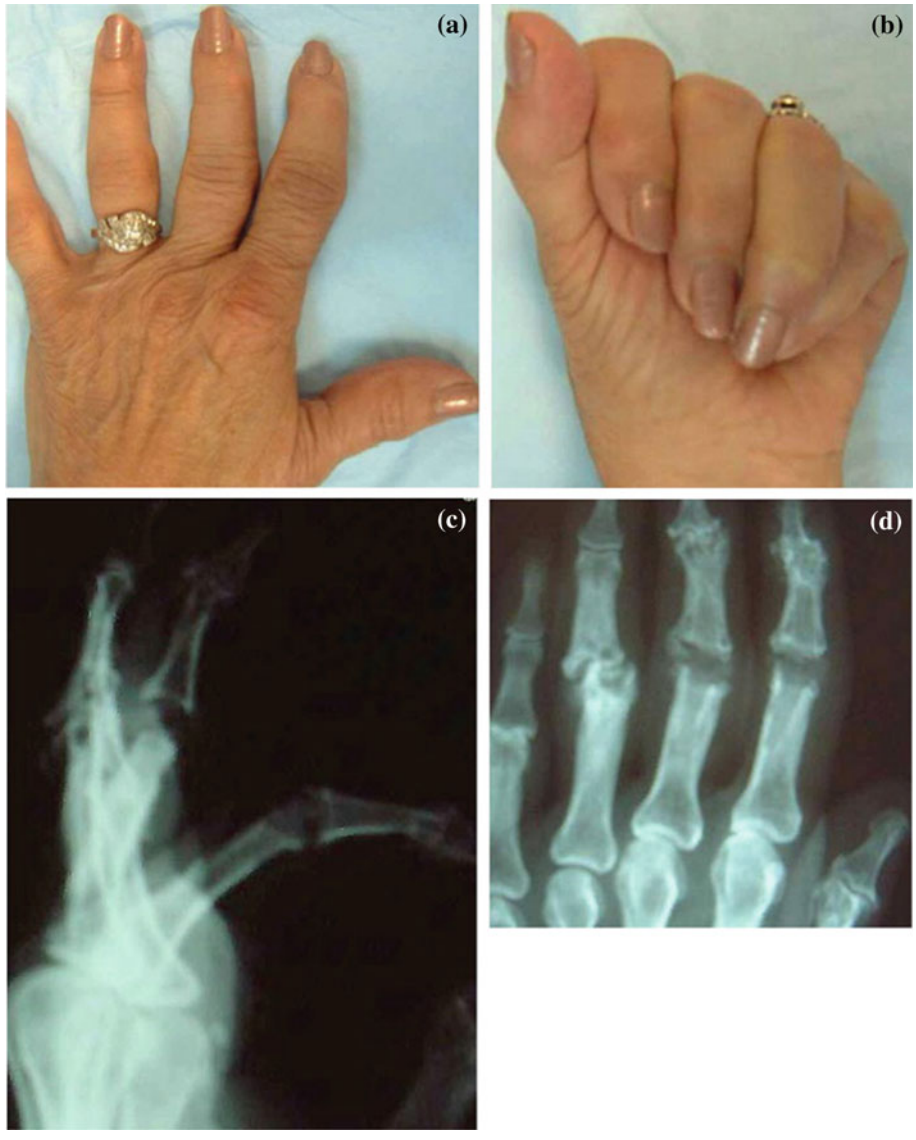

Fig. 13.16 Swanson prosthesis of IPP joints in rheumatoid patient. *Note* the radiotransparency of *P*1 and *P*2 medullary canals of II and III finger

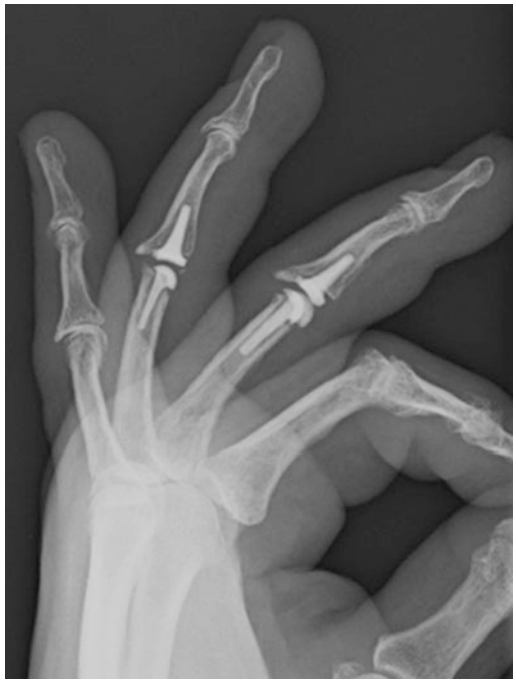

Fig. 13.17 Pyrolitic carbon prosthesis of the IPP joints. *Note* that a symmetric lucency around the distal stem of 1 mm or less that stabilizes over time is normal, representing the coating layer of the pyrolytic carbon material and a thin fibrous membrane

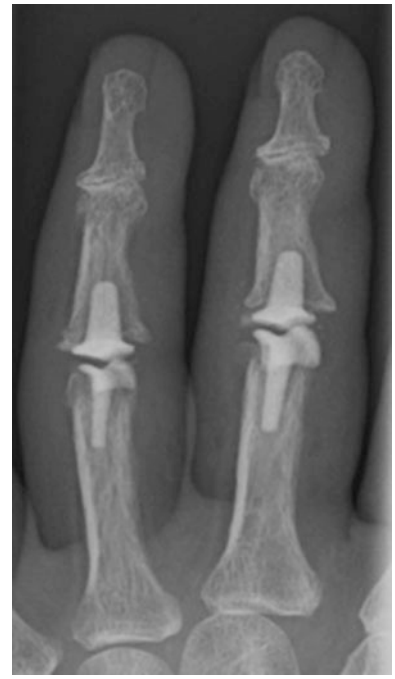

Fig. 13.18 Pyrolitic carbon prosthesis of the IPP joints. Note that a symmetric lucency around the distal stem of 1 mm or less that stabilizes over time is normal, representing the coating layer of the pyrolytic carbon material and a thin fibrous membrane

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Part IV
Drug Therapy, Bisphosphonate, Teriparatide and Parathormone, Strontium Ranelate

Drug Therapy After Implant

14

Carlina V. Albanese

14.1 Introduction

The most common cause of failure of a hip or knee prosthesis requiring revision is aseptic loosening due to periprosthetic osteolysis, which occurs if the bone supporting the implant is resorbed. Osteolysis in patients with failed orthopedic prosthesis is commonly due to multiple factors, including physical and biological components. The mechanical failure of the prosthesis–host interface arises primarily as the end result of focal periprosthetic inflammatory bone loss occurring at this interface. This proinflammatory microenvironment is driven by particulate wear debris, which is generated primarily at the articular bearing surface and at other nonarticular prosthesis or cement surfaces [1]. The local accumulation of wear particles is associated with specific serum proteins to form a particle–protein complex. This complex interacts with cell surface receptors on macrophages, activating these cells. The smaller particles are subsequently phagocytosed stimulating a cascade of events, resulting in up-regulation of proinflammatory mediators such as cytokines (Il-1, Il-6, TNF-α), activation of the RANK/RANK-L/osteoprotegerin system, and others that through complex cellular interactions are leading to the recruitment and activation of osteoclasts at the bone implant surface which begin degrading the adjacent bone [2, 3]. Stress shielding is also considered as a potent stimulator of bone resorption [4]. In general, high or unusually distributed strains stimulate increases in new bone formation, and thus a more robust structure, whereas low strains, as seen in disuse of redistributions of mechanical load relate to stem design, are associated with bone resorption and a weaker one. The high incidence of fragility fractures in postmenopausal women suggests a failure of this natural regulatory process since continued functional loading is accompanied by loss of bone tissue and an increase in bone fragility. Recently, it has been postulated that the pathogenesis of bone resorption related to stress shielding is due to the activity of osteocytes [5]. As osteocytes can neither form nor resorb bone, it has been hypothesized that they orchestrate mechanically induced bone remodeling by coordinating the actions of cells residing on the bone surface, such as osteoblasts. The recent identification of sclerostin as a molecule preferentially secreted by osteocytes that appears to be regulated by bone's mechanical environment has attracted considerable interest, particularly because this molecule stimulates osteoblasts to produce the receptor activator of nuclear factor-kB ligand (RANK-L), leading to an increase in osteoclastic activity. Therefore, blocking sclerostin action could be promising to prevent bone loss related to stress shielding phenomenon [6].

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Finally, both alteration of bone turnover and intrinsic bone tissue quality in pathologies like osteoporosis could potentially preclude an optimal bone integration [7]. Periprosthetic osteolysis is thus the result of the combined action of an increase in bone resorption, stimulated directly by the particles or through a process of inflammation, associated with reduced bone formation caused by a depression of osteoblastic activity as a result of the toxicity of the debris [8], instability, hydrostatic pressure [9], or poor bone quality [7].

In the past two decades of evolution of arthroplasty, a number of cementing techniques, as well as uncemented arthroplasties and numerous prosthetic design and material changes, have been introduced to improve prosthetic wear resistance and subsequent aseptic loosening, but to date few advances have been made in the medical management of osteolysis. Therefore, efforts to identify patients at risk of revision and develop new pharmacological treatment s to improve implant survival are urgently needed. This chapter briefly describes the major pharmacological intervention used or proposed as potential pharmacological agents, in an attempt to prevent or delay the process of aseptic loosening.

14.2 Pharmacological Agents

14.2.1 Bisphosphonates

The bisphosphonates are compound all characterized by P–C–P structure analogs of pyrophosphate that contains an oxygen atom P–O–P instead of carbon. The P–C–P structure allows a great number of possible variations, either by changing the two lateral chains of carbon atom, or by esterifying the phosphate groups. The second- and third-generation bisphosphonates: alendronate, neridronate, ibandronate, pamidronate, risedronate, and zoledronic acid have a nitrogen group and are called nitrogen-containing bisphosphonates in contrast to first-generation bisphosphonates such as etidronate, clodronate, and tiludronate, which do not. However, each compound has to be considered on its own, with respect to its use, toxicology, and its potency to inhibit bone resorption [10]. Although the detailed mechanism of action of bisphosphonates has not been elucidated, it is clear that at the tissue level, all active bisphosphonates inhibit bone resorption, bone turnover, and therefore bone loss. At the cellular level, there is a general agreement that they act directly and/or indirectly on the osteoclasts recruitment and activity [11]. Despite the myriad of data published so far, the exact mechanisms by which bisphosphonates inhibit bone resorption are still not entirely unraveled. It may be that several mechanisms are operating simultaneously [10]. With regards to wear debris and osteolysis after joint arthroplasties, these drugs seem to have a beneficial effect. It was demonstrated in a canine model that alendronate can inhibit wear debris-mediated osteolysis [12]. In a rat model incorporating a polyethylene (PE) tibial implant and repeated PE particle injections into knee, intraarticular alendronate pumped locally mitigated periprosthetic bone loss [13]. However, instability-induced bone resorption may not be responsive to alendronate [14]. Co-incubation of pamidronate with ultra-high-molecular-weight polyethylene (UHMWPE) particle induced specific macrophages apoptosis. Pre-incubation of macrophages with pamidronate prior to particle stimulation had a more potent effect in the inhibition of TNF-α release. This may suggest that the sequence of events leading to apoptotic cell death were induced by the drug in the absence of particles, thereby making the macrophages less responsive to the stimulatory effects of UHMWPE particles [15]. In a rat calvaria/macrophage co-culture model used to study the effects of various agents upon bone resorption induced by macrophage exposure to bone cement particles, pamidronate was the only agent tested which suppressed the increase in bone resorption. Non-steroidal anti-inflammatory drug, indomethacin, calcitonin, and anti-TNF antibody did not decrease bone resorption using this model [16]. There have

been recent attempts to improve implant fixation by the application of bisphosphonates both systemically [17] and locally by bonding it to hydroxyapatite-coated implants [18]. In an animal experiment, it was shown that pretreating intramedullary implants with hydroxyapatite–zoledronate composite enhances periprosthetic bone quality and bone integration [19].

Bisphosphonates are currently used for the treatment of osteoporosis and other metabolic bone disease, and their clinical effectiveness is well documented. The most extensive studies reported so far have been conducted with alendronate [20–22]. Postmenopausal women treated with alendronate gained significant increases in bone mineral density (BMD) in the spine, hip, and total body, whereas the placebo group lost about 1 % of BMD over the 3 years [20]. Also in the fracture intervention trial (FIT), osteoporotic women who received alendronate gained significantly more BMD than women of the placebo group in multiple skeletal sites [21]. Alendronate has shown its value by effectively preventing fracture [22].

To determine the current understanding of the effect of bisphosphonates on periprosthetic BMD after total joint arthroplasty, a computerized research for randomized controlled trials was conducted, evaluating the use of bisphosphonates in patients treated with primary total joint arthroplasty [17]. In this meta-analysis of six randomized, controlled trials, which included a total of 290 patients, it has been shown that significantly less periprosthetic bone loss had occurred in the treated patients than in the control patients at three months, six months, and twelve months. The larger effect on bone loss was noted following arthroplasties with cement than on bone loss following arthroplasties without cement and on bone loss following total knee arthroplasties (TKA) than on bone loss following total hip arthroplasties (THA), respectively.

In an observational study [23], bisphosphonate use was associated with significantly lower rate of revision surgery of up to about 50 % and a twofold greater median implant survival time after primary total arthroplasty of the lower limb in patients without a previous fracture. In the same study, bisphosphonate use was also associated with an almost twofold increase in implant survival time. However, a recent case–control study [24] reported an insignificant association between the long-term use of bisphosphonate and a reduced risk of revision, but an increased risk of revision due to deep infections among bisphosphonate users. Regarding the effect of bisphosphonate on periprosthetic bone loss, a recently published systematic review [25] and a meta-analysis [26] have also provided conflicting results.

14.2.2 Denosumab

The accumulation of macrophages in the prosthetic implant bed is believed to be important in aseptic periprosthetic bone loss. Many studies have shown that macrophages phagocytose the prosthetic particles, which in turn causes the release of the mediators of bone resorption [27, 28]. There is also evidence that precursors of osteoclasts reside in the granulomatous tissues adjacent to areas of periprosthetic bone loss, since cells isolated from this tissue can develop into functional osteoclasts under appropriate conditions in vitro [29]. In addition, it was found that the formation of osteoclasts from these tissues is associated with the expression of the osteoclastogenic molecules RANKL and RANK [30]. The understanding of the role of these factors in periprosthetic bone loss may help to identify targets for therapy in this pathology.

Denosumab is a novel biological agent for the treatment of osteoporosis in postmenopausal women with increased risk of fractures [31] and reduces the risk of new vertebral, nonvertebral, and hip fractures [32]. This compound is the first approved RANK ligand inhibitor and a fully human monoclonal antibody [33]. It exerts its anti-resorptive effects by inhibiting the formation, function, and survival of osteoclasts. Subcutaneous administration of denosumab once in every six months leads to a rapid and marked reduction in bone resorption. In a comparative study on murine model, it was reported that

denosumab and alendronate treatments increased strength and stiffness of the fractured bones [34]. Currently, a clinical trial using subcutaneous denosumab for nonsurgical treatment of periprosthetic bone osteolysis is ongoing, but the results are not yet available. If successful, this study will lead to further studies to develop the use of denosumab to prevent aseptic loosening.

14.2.3 Strontium Ranelate

Strontium ranelate is a pharmaceutical agent composed of an organic moiety (ranelic acid) binding two stable strontium atoms that acts via a dual mode of action with both bone-forming and bone-resorbing properties [35], leading to an improvement in bone quality, strength, and microarchitecture. Clinical trials have demonstrated the efficacy of strontium ranelate to reduce fracture risk [36]. This agent is approved for the prevention of vertebral and hip fractures in postmenopausal osteoporosis. Strontium ranelate is the only osteoporosis treatment that dissociates the processes of bone resorption and bone formation [35]. Strontium ranelate acts on osteoblast by increasing mRNA and protein levels of osteoprotegerin (OPG) and suppressing those of RANKL. Strontium ranelate also stimulates osteoblast replication and differentiation and prolongs the lifespan of osteoblasts. Knocking down calcium-sensing receptor (CaSR) suppresses strontium ranelate-induced stimulation of OPG mRNA, reductioning RANKL mRNA, and increasing replication, indicating the involvement of CaSR in these responses. These results demonstrate that osteoblasts play a key role in the mechanism of action of the anti-fracture agent, by mediating both its anabolic and anti-resorptive actions, at least in part, via activation of CaSR [37, 38]. At the same time, strontium ranelate inhibits osteoclastic activity, as shown by a reduction in expression of functional osteoclast markers and disruption of the cytoskeleton essential for resorption [39, 40]. There is also evidence of the benefits of strontium ranelate on bone microarchitecture in different animal models. The 2D and 3D histomorphometric analyses have demonstrated prevention in the deterioration of bone microarchitecture with strontium ranelate in ovariectomized rats, leading to prevention of bone strength decrease [41]. The beneficial effects of the strontium ranelate regarding the improvement of bone integration of implants have been reported in various animal models. Li et al. [42], in a study designed to evaluate the effect of systemic strontium ranelate treatment on fixation of hydroxyapatite (HA)-coated titanium screws in ovariectomized rats that received unilateral implants in the proximal tibiae, suggest that this treatment can dose-dependently improve the fixation and facilitate the stability of the implant in the osteoporotic bone. Moreover, in another rat model study, strontium ranelate was found to improve implant bone integration with a positive effect on both bone biomaterial microarchitecture and bone biomaterial properties in the vicinity of a titanium implant versus untreated animals [43]. All these data strongly suggest that strontium would have the potential to improve peri-implant bone structure. Furthermore, in a midterm evaluation of strontium-containing hydroxyapatite bone cement in a goat, revision hip hemi-arthroplasty model ranelate was superior to polymethylmethacrylate (PMMA) bone cement in terms of bone-bonding strength [44].

Another fact to consider is that the treatment with this drug is not associated with osteonecrosis of the jaw (ONJ). This represents a distinct advantage compared to bisphosphonates and denosumab as, despite the poor evidence, many dentists or oral surgeons are reluctant to administer due to the possibility of ONJ development. Lastly, it is also relevant to emphasize that BMD continues to increase after strontium saturation is reached in bone and even after stopping the drug [45]. However, these current results need to be confirmed by clinical studies and longer-term follow-up investigation to support the effect of strontium ranelate on a potential role in osteolysis.

14.2.4 Parathyroid Hormone

Bone anabolic therapy with the recombinant human parathyroid hormone (PTH) analogue, teriparatide (PTH-1-34), or full-length PTH-1-84 has been an option in the treatment of osteoporosis. Both drugs have been shown to have an anabolic effect on bone when administered intermittently. Mechanisms of action by which PTH induces bone anabolic effects include increase in osteoblast number and activity, leading to increases in trabecular bone mass and strength [46–48] and increase in cortical bone [49]. The positive effect on bone remodeling has been confirmed in human fracture prevention studies [50, 51]. However, recently, it was reported that in terms of anti-fracture efficacy, treatment with PTH is not superior to treatment with potent anti-resorptive agents. However, while the process by which osteoporosis emerges is arrested in response to anti-resorptives, PTH acts as a bone anabolic with reversal of the process. Although this mechanism of action seems favorable, the use of PTH is limited by a much higher cost than that of anti-resorptive agents. As long as a superior anti-fracture efficacy has not been proven, PTH should be confined to patients with severe spinal osteoporosis, including patients in whom treatment with an anti-resorptive has failed [52]. Some studies have investigated the effect of PTH on various types of implant fixation. These comprise rodent models with insertion in pathological bone [53–55] or transcortical implantation in normal bone [56, 57]. The general finding in these interference-fit rodent models is improved incorporation in bone. In ovariectomized rats, administering PTH [1–34] daily increased osseointegration, bone volume, stiffness, and toughness of conical titanium screws [54] that prevent resorption of newly generated trabeculae around the implant [55] and increase new bone formation on the surface of hydroxyapatite-coated implants [55]. Transcortical implantation in normal bone of rats also indicates that intermittent treatment with PTH may enhance the early fixation of orthopedic implants [56, 57]. Finally, in a canine model, intermittent treatment with PTH [1–34] improved histological bone integration of a prosthesis-inserted press-fit at surgery in cancellous bone, with no additional improvement of the initial mechanical fixation at this time point [58]. However, despite these experimental studies bring back positive results in terms of bone integration, the possible role of PTH administration in preventing osteolysis in humans after joint implants remains to be shown with controlled clinical trials and long-term evaluation of the results.

14.3 Conclusions

Different studies suggested that bisphosphonates and other pharmacological agents mainly used for the treatment of osteoporosis and prevention of fragility fractures might have a beneficial effect with regard to maintaining more periprosthetic BMD than that in controls. However, the limitations of the available studies and the lack of analyses of clinically relevant outcomes (functional outcomes, revision rates, and quality of life) necessitate the planning and conduct of a sufficiently sized, methodologically sound study with clinically relevant end points. Until this has been done, the current evidence regarding the beneficial effects of pharmaceutical compound on periprosthetic bone after total joint arthroplasty should be interpreted with caution.

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TBD: Postsurgery Rehabilitation

15

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15.1 Introduction

Rehabilitation is extremely important in the overall outcome of any joint replacement surgery. The goals of physical therapy are to prevent contractures, improve patient education, and strengthen muscles around the joint through controlled exercises.

The goals of every rehabilitative protocol in a patient that underwent a joint replacement surgery are as follows:

1. Reducing pain
2. Restoring muscular trophism and tone
3. Recovering the range of motion
4. Recovering the articular function

A critical phase, however, is the time before the surgical intervention, when the intervention is planned and not immediately necessitated by a fracture. The phase before the surgical intervention must act at the level of the musculoskeletal and at the level of the cardiovascular systems. These include exercises of controlled breathing balanced with postures for bronchial drainage. The conditions of cardiac functionality are also improved by the active mobilization of inferior and superior limbs. Presurgical reeducation also favors the recruitment of motor units and allows better healing of the articular district after the surgical intervention so that the patient can quickly regain neuromuscular coordination. Then, the protocol allows to maintain and to create general satisfactory conditions that allow the fast functional reeducation and the early and diversified load at the level of the operated limb. Also it reduces the risk of local or general complications and represents an extremely useful way to recover the range of motions and to restore the patient's activities of daily life (ADL). Occupational therapists are also part of the rehabilitation process. They educate the patients about the adaptive equipment that is available and the proper ways to do carry out ADLs [1].

During the phase of evaluation and after the surgical intervention one can carry out a computerized biomechanical analysis in a movement analysis laboratory. Several tools exist for the objective evaluation of kinetic and kinematic alteration of movements of the limbs and of deambulation. The use of a computerized laboratory for movement analysis allows to appraise objectively the joints and muscular components and to compare their alterations before and after a surgical intervention. A laboratory of movement analysis is composed of a valid computer instrumentation, dedicated software connected to an optic system of 9–12 cameras that are sensitive to infrared, and force platforms for the evaluation of

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the kinematic components of walking. Patients submitted to this type of analysis are prepared by the affixing of markers in accordance with published protocols or elaborated by the biomechanical engineer, according to the basic components of the equipment available at the facility. Below we describe an approach used at the University of Rome ''La Sapienza'' to study patients with osteoarthritis (OA) of the hip.

The aim of the study was to determine whether intra-articular injections (IA) of hyaluronic acid (HA) affect the clinical status and walking ability in hip OA patients over a 6-month period. Sixty-seven patients were evaluated, and after considering inclusion and exclusion criteria, a total of 20 subjects were enrolled [12 men, 8 women, mean age 60.5 (range 47–73)]. Prior to the commencement of treatment, each participant underwent (T0) a clinical and gait analysis evaluation. Patients were treated with 3 ultrasound-guided IA injections of 2 ml of high-molecular-weight (>1500 kDa) HA over 3 consecutive weeks, according to the manufacturer's treatment recommendations, which is considered to be a safe and effective dosage for this specific product. Clinical evaluation was performed at 1 month (T1), 3 months (T2), and 6 months (T3) after treatment ended. At T3, a gait analysis evaluation was also performed. At baseline (T0), median value (25th–75th percentiles) of visual analog scale (VAS) was 6.2 (5.7–7.2). The VAS score significantly dropped after the procedure [T1 = 5.0 (4.5–5.5); T2 = 3.0 (1.5–4.0); T3 = 3.8 (3.0–5.7); Pb0.0001]. At T3, 10 patients (50 %) were considered as VASR and 10 patients (50 %) as VASNR. Regarding WOMAC scores, a significant difference between pre- and postprocedure evaluation was found for pain [T1 = 28.3 (22.0–42.0); T2 = 17.5 (10.0–30–0); T3 = 19.1 (11.0–47.7); Pb0.001], joint stiffness [T1 = 49.0 (35.6–66.0); T2 = 24.8 (19.3–57.0); T3 = 25.7 (19.0–58.2); P = 0.005], and disability [T1 = 47.5 (30.2–50.3); T2 = 25.3 (13.4–39.0); T3 = 29.3 (20.7–51.0); P = 0.04]. With regard to the spatiotemporal parameters, patients walked at T3 with higher cadence with respect to T0 (P = 0.004) and with an improved stride length (P = 0.02). There were no significant differences in the other spatiotemporal parameters. The statistical analysis showed a significant modification at T3 with respect to baseline (P = 0.0004) for the pelvic tilt at heel contact (Fig. 15.1) and for hip flexion-extension angular impulse at loading response subphases of the gait cycle. No significant changes emerged in the other parameters. When considering the subgroup analysis, significant differences were found for stride length between VASR [0.98 (0.97–1.03)] and VASNR [1.07 (1.11–1.17)] patients at T0 (P = 0.02). Moreover, stride length significantly improved in VASR patients [1.13 (1.13–1.22)] but not in VASNR patients [1.0 (1.0–1.1)] at T3 (P = 0.008). As regards kinematic analysis, only VASNR patients showed significantly lower hip flexion–extension RoM [T0: 26.0 (22.5–38.3); T3: 21.9 (16.4–31.2), P = 0.01]. No significant changes emerged in the other parameters in the subgroup analysis. Patients in our series display a marked improvement in respect to both pain, as measured by VAS and WOMAC pain subscale, and function and disability, as measured by WOMAC joint stiffness and disability subscales, respectively. Clinical results in our series are comparable to those reported in recent literature, thereby confirming the effectiveness of IA. Interestingly, however, the best results in terms of pain reduction were noted at T2 (i.e., 3-month

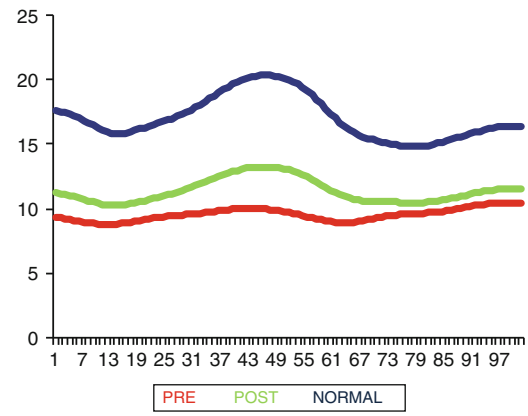

Fig. 15.1 Pelvic tilt after hip injection or hyaluronic acid

follow-up). At T3, in fact, a slight but significant increase was noted for VAS values and a trend was detected for a general worsening of all the other analyzed parameters, even if without statistical significance. Gait analysis evaluation was performed only at T3. As regards the general characteristics of gait in our sample, a significant improvement between T0 and T3 was observed in cadence and stride length, but not in mean walking speed, despite a linear relationship between these variables. This may be due to a type II error occurring because of a low study power. Hip OA patients generally display a slower walking speed as compared to normal subjects. When the effect of walking speed is removed, however, differences still exist in spatiotemporal characteristics of patients and healthy controls. Particularly, hip OA patients generally walk with shorter steps and increased cadence. Interestingly, we were able to detect an increase in stride length in our sample, even if there were no significant changes in mean walking speed after treatment. It should be noted that spatiotemporal characteristics in our sample are below those of healthy elderly people, as reported in the literature, even after therapy. Worthy of note, however, is that we could observe a significant increase in stride length, which seems to be the parameter that mostly affects the gait speed in elderly people when compared with young subjects. This suggests that changes in walking pattern happened and that these resulted in an overall change in gait performance. When gait kinematics were analyzed, in fact, a significant increase in the pelvic tilt angle at the heel contact was found between pre- and posttreatment evaluation. As also noted in the angle–angle diagram between hip flexion and pelvic tilt, this increased pelvic tilt angle was not accompanied by an increase in pelvic tilt RoM nor in hip flexion–extension RoM during the entire gait cycle. Alterations in pelvic kinematics have been extensively described in subjects with OA of the hip, in which sagittal plane alterations of pelvic mobility are generally interpreted as compensatory mechanisms to obtain better stride characteristics. We can, therefore, speculate that our patients are able to increase their stride length through an increase in pelvic tilt mobility 6 months after treatment. Interestingly, when a subgroup analysis is performed and patients are divided according to clinical response (i.e., VASR and VASNR patients), only VASR displayed a significant improvement in stride length at T3 evaluation, leading us to consider that this kinematic feature could be of importance in determining clinical results.

It is a matter of fact that pain, which represents the primary symptom of OA, is seen as entirely linked with function, with physical movements. This pain, in turn, causes limitations in physical functions. In painful OA, patients generally avoid certain movements and activities that they know will cause pain and engage in adaptive behavior to moderate the pain experience, such as organizing their homes to limit the need for movements or positions that are more likely to be painful. From this point of view, it seems that reduced walking ability before treatment may also predispose to therapeutic success considering that VASR patients have a greater stride length compared to VASNR also at T0. Improvement in hip functioning during the first part of the stance phase was also documented by changes in hip kinetics. Hip flexion–extension angular impulse at loading response subphase of the gait cycle significantly increases at T3, probably as a consequence of a change in pelvic tilt. We limited our analysis only to pelvis and hip joint, and we only analyzed those changes occurring in the sagittal plane of movement. Since kinetic and kinematic alterations are likely to occur during gait also in other planes (i.e., frontal and transversal) and in distal joints (i.e., knee and ankle), further analyses should be performed to understand whether IA injections of HA can affect also different parameters than those described in the present research.

Pain reduction after IA injection is generally considered to be the result of HA effects on osteoarthritic joints. Studies have demonstrated that injection of HA into the joint space of an osteoarthritic knee improves the quantitative and qualitative properties of endogenous HA, increasing joint lubrication in the short term. HA supplementation also provides significant

anti-inflammatory effects within the joint space, affecting leukocyte function and reducing the concentration of inflammatory mediators such as prostaglandins and fibronectin. Direct analgesic activity and chondroprotective properties of intra-articular HA injection have also been suggested by a number of recent animal studies. As regards the IA injection technique, it was performed under ultrasound guidance, which is considered more economic and faster in comparison to fluoroscopic guidance, as well as safer due to the lack of radiation or iodized contrast. The use of a guidance is otherwise advisible because the success rate of blind injections is around 50.9–65.1 % [2–6]. From this point of view, infiltrations with HA may be taken into consideration in the early stages of osteoarthritis well before any sort of prosthetic joint replacement surgery.

15.2 Rehabilitation After Hip Prosthesis

The hip is the proximal joint of the inferior limb. While being an enarthrosis from the anatomical point of view, it has three degrees of freedom:

1. Transversal–along which the movement of extension flex is effected.
2. Antero-posterior–along which the movements of abduction and adduction are effected
3. Vertical–along which the rotatory motion occurs [7].

Hip osteoarthritis is one of the most serious diseases of the motor organs, most commonly associated with aging. It leads to loss of independence and worsening of disability in elderly individuals. The disease causes pain which results in gait disorders. Hip osteoarthritis is prevalent in all races and is statistically more common in women than in men. According to latest literature reports, the overall incidence is estimated at 2–3 % of global population [8]. Total hip replacements are performed most commonly because of progressively worsening of severe arthritis in the hip joint. The most common type of arthritis leading to total hip replacement is degenerative osteoarthritis of the hip joint. This type of arthritis is generally seen with aging, congenital abnormality of the hip joint, or prior trauma to the hip joint. Other conditions leading to total hip replacement include bony fractures of the hip joint, rheumatoid arthritis, and septic necrosis, or a vascular necrosis, of the hip bone. Certainly, another frequent cause is hip fracture often due to osteoporosis. The progressively intense chronic pain together with impairment of daily function including walking, climbing stairs, and even arising from a sitting position, eventually become reasons to consider a total hip replacement. Because replaced hip joints can fail with time, whether and when to perform total hip replacement are not easy decisions, especially in younger patients. Replacement is generally considered when pain becomes so severe that it impedes normal function despite an intensive medical and rehabilitation protocol. An important way to evaluate the disability and the pain in those who undergo a surgical joint replacement is to use a validated evaluation scale. Every patient should be evaluated by the administration of these useful tools.

One of these evaluation scales is the Western Ontario and McMaster Universities Arthritis Index (WOMAC), that is widely used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip and includes the evaluation of pain, stiffness, and physical functioning of the joints. The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68). Physical functioning questions cover everyday activities such as stair use, standing up from a sitting or lying position, standing, bending, walking, getting in and out of a car, shopping, putting on or taking off socks, lying in bed, getting in or out of a bath, sitting, and heavy and light household duties [9, 10]. Another useful questionnaire is the Harris hip Score (HHS) that can be used before and after the hip joint replacement in order to evaluate the pain and the disability after the surgical intervention and after the rehabilitation program. Some studies about the utility of using

the HHS were conducted by a group of researchers from the Department of Orthopedics and Traumatology of the Medical University in Ismir, Turkey. One of these studies was conducted on a group of 60 patients subjected to total hip replacement and divided into two groups. Patients in the study group received preoperative physical therapy to improve the muscle strength in upper and lower limbs as well as the range of motion of the hip joint starting from 8 weeks before the surgery. The group also participated in rehabilitation programs regarding living with endoprosthesis. The control group received neither physical therapy nor education. The patients were evaluated in a physical assessment immediately before the procedure, at discharge, at 3 months and 2 years after the surgery. HHS, visual analog scale, and the hip abduction range of motion were evaluated. Although patients in the study group were activated earlier than the patients in the control group, there were no differences between both groups at hospital discharge. The respective p values were<0.48 for the HHS,<0.97 for the hip abduction range of motion,<0.54 for the visual analog scale, and<0.89 for the activity. As regards further follow-up, both groups showed improvement in the HHS 2 years after the surgery [11].

Another useful scale is the Short Form 36 (SF-36). The SF-36 is a 36-item questionnaire that produces scores in eight domains relating to the patient's quality of life. These are physical functioning, role limitation due to physical problems, bodily pain, general health perception, emotional vitality, social functioning, role limitation due to emotional problems, and mental health [12]. Another important evaluation scale is the FIM (functional independence measure) that analyzes the assistance and involves that the patient complete a questionnaire on the activities of daily living (ADLs) and comprises two groups of functions: cognitive (communication and relational/cognitive capacity) and motor (care of the sphincter of the person, mobility, locomotion and control) [13]. Another evaluation scale is the Barthel index. The Barthel scale or Barthel ADL index is an ordinal scale used to measure performance in ADL. Each performance item is rated on this scale with a given number of points assigned to each level or ranking. It uses ten variables describing ADL and mobility. A higher number is associated with a greater likelihood of being able to live at home with a degree of independence following discharge from hospital. The amount of time and physical assistance required to perform each item are used in determining the assigned value of each item. External factors within the environment affect the score of each item. The scale was introduced in 1965 and yielded a score of 0–20. Although this original version is still widely used, it was modified by Granger et al. in 1979, when it came to include 0–10 points for every variable, and further refinements were introduced in 1989. The Barthel index designed at the original scale was insensitive to change and had arbitrary scores. The sensitized version sharply discriminates between good and better and poor and poorer performances. The Barthel index has been shown to have portability and has been used in 16 major diagnostic conditions. It has demonstrated high interrator reliability (0.95) and test-retest reliability (0.89) as well as high correlations (0.74–0.8) with other measures of physical disability [14].

Prior to surgery, there is a general deficit in muscular strength along the affected limb as compared to the contralateral (healthy) side in patients with unilateral hip osteoarthritis (OA), and muscles such as the abductors, vastii, rectus femurs, and psoas show marked atrophy. This is evidenced by reduced cross-sectional area and infiltration of noncontractile components, i.e., an average 10 % increase in fatty infiltration of muscle (myosteatosis) in the affected limb compared to the healthy one. As well as reducing muscle strength, myosteatosis also exacerbates fall risk. This muscular dysfunction is likely to contribute to the reduced walking ability of OA patients, as loss of lower limb muscle strength has been shown to predict the onset of activities of daily living dependence in the elderly.

Consistent with the persisting functional deficits following surgery, these atrophic changes about the hip are still evident up to 2 years

following total hip replacement (THR) surgery. Frail elderly persons with sarcopenia often undergo musculoskeletal-related surgery such as THR, and the hospitalization-associated immobilization further compromises the skeletal system, with potentially grave consequences. Earlier operation may prevent the development of persistent atrophic changes that occur after THR and there is a suggestion that fatty infiltration may be reversed by intensive rehabilitation. There have been considerable technical efforts toward optimizing surgical treatment of patients with arthritis of the hip, for example with over 100 varieties of hip prostheses being available, multiple types of bearing couples and several surgical approaches. As technology and surgical techniques for THR improve, patient expectations, including for an early return to normal physical function and activities, have also increased. However, the actual health gain for many of these innovations relative to "standard" THR is small in terms of patient function and quality of life. In the past, a prolonged hospital stay after THR surgery incorporated a period of supervised rehabilitation to try to achieve restoration of physical function. However, due to the introduction of initiatives such as integrated care pathways and considerations of cost and increasing patient satisfaction, the length of hospital stay following joint replacement has been substantially reduced. Standard physiotherapy (i.e., not involving resistance training) following major surgery enables most patients to regain basal levels of function but leaves them with significant muscle wasting as it lacks the intensity of exercise required to elicit muscle hypertrophy.

The most commonly used rehabilitation regimes for elderly individuals are based on functional types of exercises without external loading. However, this type of intervention not only fails to elicit increases in muscle mass but does not prevent further muscle atrophy. In contrast, high-intensity PRT is an extremely effective and safe method for inducing muscle hypertrophy and increasing muscle strength and subsequently improving functional performance in healthy individuals, those with chronic disease, e.g., rheumatoid arthritis, and the elderly. THR surgery provides good relief for patients' pain but fails to fully restore physical function. A systematic review demonstrates that significant improvements in muscle strength and function are achievable with PRT. Regardless of the timing of the intervention, PRT appears to have a significant benefit on patient function following THR. Late PRT interventions do work and are safe, and they have been performed mainly in the home setting, but the studies done have short periods of follow-up and have a further limitation of the preexisting functional deficit due to the timing postoperatively. Early PRT regimes identified in the studies reviewed in this article have shown the need for a center-based approach, and this has demonstrable benefit, but there are issues of high costs of transport and supervision. Early home-based PRT studies that are effective and safe with adequate follow-up after THR surgery would potentially address these issues [15].

Also, the rehabilitative treatment before the surgical intervention can have utility in order to prepare the patient to the postoperational phase. It is important to educate the patient on the correct use of the aids and to precautions to be taken. Another remarkable aspect can be that of the respiratory reeducation that, besides allowing muscular relaxation, it allows to patients to work on improving their respiratory performance. It is important also to improve the ventilation of the pulmonary base functions associated with postural drainage and to apply maneuvers of vibration and of clapping. To prevent pulmonary stasis, the subject must perform exercises involving the abdominal muscle, the diaphragmatic dome, and intercostal muscles [16].

After total hip joint replacement surgery, patients must immediately start the rehabilitation program. On the first day after surgery, it is common to begin with some minor physical therapy while sitting in a chair. Initially, supportive devices such as a walker or crutches are used. Pain is monitored while exercises take place. Specific techniques of body posturing, sitting, and using an elevated toilet seat can be extremely helpful. Patients are instructed not to

cross the operated lower extremity across the midline of the body (not crossing the leg over the other leg) because of the risk of dislocating the replaced joint. They are discouraged from bending at the waist and are instructed to use a pillow between the legs when lying on the nonoperated side in order to prevent the operated lower extremity from crossing over the midline. Another important attention is to keep the operated leg always extended during the sitting position in order to limit the hip flexion. In fact, with the lower arm completely extended, it is physiologically impossible to flex the hip more than 90° [7]. The incidence of luxation decreases more than 95 % after 12 week from the surgical intervention. When the scar is completely closed, it is important to work manually on it in order to make it more elastic and less adherent to the tissues below. Patients are given home exercise programs to strengthen the muscles around the buttocks and thigh. Most patients attend outpatient physical therapy for a period of time while incorporating home exercises regularly into their daily life. Patients will continue to use supportive devices as monitored and recommended by the attending physician. Gradually, patients become more confident and less dependent on supportive devices. Patient education is important to ensure longevity of the replaced hip. Strenuous exercises such as running are discouraged. The best way to improve muscle strength and promoting mobility and endurance is to perform a period of hydrokinesitherapy. Unfortunately, it is not easy to find a place in where to perform hydrokinesitherapy, remembering that the physiotherapist needs to become further specialized in order to be able to follow the patient in water. In a second phase, when the supportive devices are dismissed, one can send the patient to a swimming pool to improve muscle strength and to promote mobility and endurance. The work in the swimming pool is important to favor a complete muscular relaxation stimulating the aerobic general capacities and to limit the risk of traumas from fall. The exercises in water allow the possibility to effect a work to variable load. The action of the water also allows a vascular exercise that normalizes the speed of the blood flux by allowing more valid metabolic exchanges. The therapeutic exercise in heated swimming pools acts across three fundamental principles: the hydrostatic effect based on the principle of Archimedes that allows floating and stimulates proprioception; the hydrodynamic effect that is represented by the resistance of the liquid and that allows the execution of exercises against resistance; and the thermal effect that induces muscular relaxation and sedative action reducing the reactions of defense [16].

The rehabilitative program can be that shown from Table 15.1[1]

15.3 Rehabilitation After Knee and Ankle Prosthesis

15.3.1 Knee Joint Prosthesis

The knee joint has three degrees of freedom. The flex extension is the principal movement; rotation and traverse movement are realizable only with flexed knees. This is important in order to guarantee the double requirement of the stability in extension to sustain the load and of the mobility in flexion to adapt the gait to irregularities of the ground [7]. Knee prostheses are now surgically applied with good results. Clinical data show that the greater the functional deterioration of the range of motion before the operation, the slower the recovery and rehabilitation after the surgical intervention. Furthermore, the patient may have activated a strategy of compensation with alterations at the level of the pelvis, trunk, and inferior limbs. The unbearable pain associated with serious

[1] Please note that the progression of rehabilitation phases and exercises must be assessed by frequent monitoring of the specialist who takes into account the appropriate timing. All types of exercise should be increasing intensity taking into account the type of surgery and any contraindications.

Table 15.1 Rehabilitative program

Days	Program
Day of the intervention	Exercises of breathing; exercises of ROM of the ankle
1st day after the surgery	Isometric exercises of the quadriceps, of the gluteal muscle (Valuate the surgical intervention), maintain the buttock in abduction, active-helped mobilization, exercises of bending of the knees
2nd, 6th day after the surgery	Weight bearing as tolerated. Deambulation with the use of a walker device or crutches
7th day—3rd month after the surgery	Progressive reinforcement and Rom of trunk, buttock, and knees (Figs. 15.2, 15.3); closed kinetic chain exercises; hydrokinesitherapy, cyclette, progressive slope of staircases [17]

functional limitations is the principal indication for surgical intervention. It is fundamental to use appropriate evaluation scales, such as:

- Rivermead Mobility Index (RMI)–a measure of disability related to bodily mobility. It demonstrates the patient's ability to move her or his own body. It does not measure the effective use of a wheelchair or the mobility when aided by someone else [18].
- Barthel index (BI)–an ordinal scale used to measure performance in activities of daily living (ADLs) as described before.

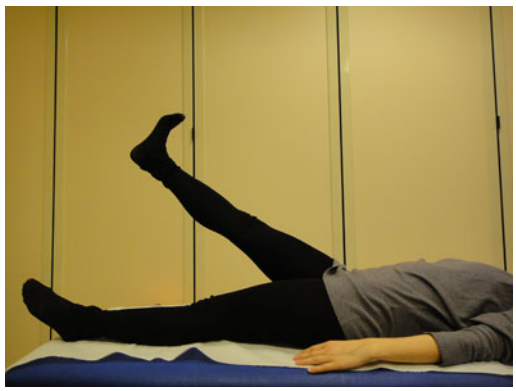

Fig. 15.2 Exercise of Leg Extention

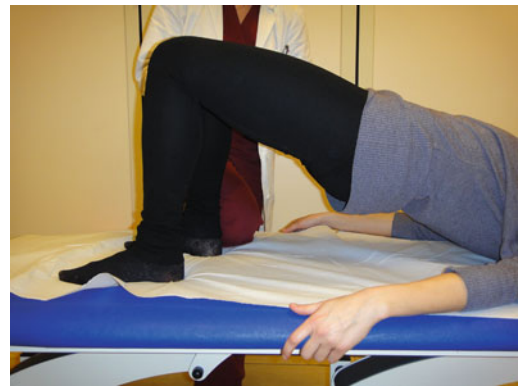

Fig. 15.3 Strengthening of the gluteal muscles

- Knee Clinical Society System rating–an easily reproducible evaluation scale that measures the capacities of the subject (deambulation, climb, descending stairs, use of aids) and also the articular function of the knees (pain, degree of movement, muscular forces, articular stability, alignment, contracture in bending, and deficit of extension) [19].
- Functional independences measure (FIM)–analyzes the assistance needed by the patient by completing a questionnaire on activities of daily living (ADLs). It considers two groups of functions: cognitive (communication and relational/cognitive capacity) and motor (care of the sphincter, mobility, locomotion, and control) [13].

Certainly, in these circumstances it is important to have prior rehabilitative preparation of the surgical intervention. The result of the surgical intervention depends on a careful clinical evaluation of the joint but also requires a change of certain unfavorable parameters: overweight, general state of the musculoskeletal and cardiovascular systems. In fact, all of these features may be provoked by the so-called hypokinetic syndrome, a condition of reduced mobility due to pain, which considerably limits their mobility. The evaluation of the range of motion and of muscle status is of paramount importance (Fig. 15.4) [20]. Also important is a program of exercises of respiratory physiotherapy to improve bronchial drainage. Before prescribing the physiotherapy, it is important to be

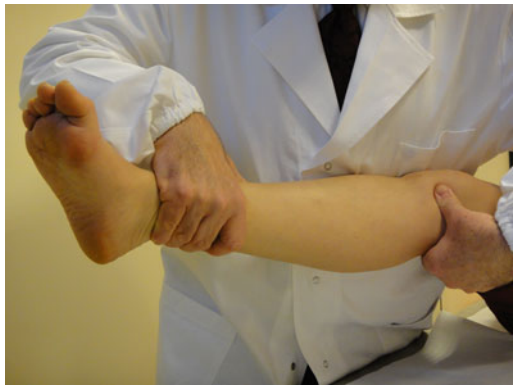

Fig. 15.4 Evaluation of the knee joint and muscle of the leg

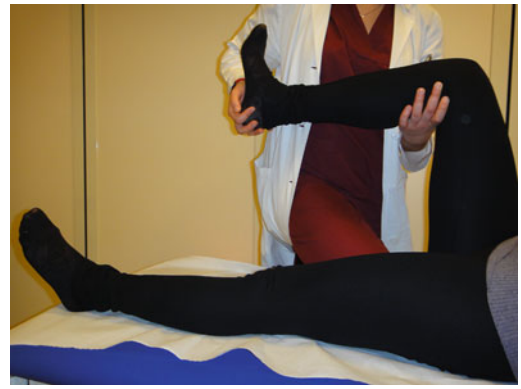

Fig. 15.5 Mobilization lower limb

informed about the sort of surgical intervention and the sort of positioned prosthesis. The motives for applying total prosthesis versus partial ones depends on various factors. The functional load is often not equally distributed and the damage may be limited to only some parts of the knee. The rehabilitative treatment must be aimed at restoring maximum safety, autonomy of walking, and best possible activities of daily life (ADL).

The objective in the first phase is to alleviate surgical stress, to fastly recover the mobility of the knees, and to control the maintenance of the normal articular mechanics. Right after the surgical intervention it is important to control the pain that causes muscular reflex inhibition. Antithrombosis elastic stockings should be worn. The external compression allows the reduction in the circumference of the limb and increases blood flux, decreasing venous stasis and the risk of the formation of thrombosis. Elastic stockings should effect decreasing compression by the ankle towards the thigh by increasing the blood flux in femoral veins. The mobilization of the operated limb must begin early on: passive continuous movement allows to recover the articular mobility and to prevent functional limitations [21]. One can make a plan of the exact parameters of time and range of passive continuous movement. The duration of the sessions must be progressively increased and must be carried several hours per day. The speed must be constant and low in order to avoid inflammatory reactions. The patient must be consciously aware of automatic movements to prevent defense reactions or unintentional movements. All this is aimed at rapidly attaining a 90-degree knee flexion. Another important issue is the mobilization of the patella, which prevents adhesion to the surrounding tissues (Fig. 15.5).

Proprioceptive excercises are also necessary for recovering coordination (Fig. 15.6). At this point, an electromyographic evaluation may be advisable to determine possible differences of force between agonists and antagonists. It may also be useful to carry out specific protocols of electromyographic biofeedback. These tools allow an early recovery of the muscle tone involving the patient directly in active and motivating excercises [22]. The role of the physiotherapist is not limited to improving the muscle tone and coordination, but also to preventing antalgic contractures that can limit rehabilitation and loosen the joint. Exercises dedicated to the hamstrings muscles are also important. The cyclette used at low resistance is an useful exercise at this stage to improve the range of motions; it must be adjusted to 'high saddle' [16]. The best way to improve muscle strength and promoting mobility and endurance is to schedule hydrokinesitherapy, as described

Fig. 15.6 Proprioceptive exercises for the lower limb

above. Also important is the correction of possible differences in length of the inferior limbs to balance and to stabilize deambulation.

15.3.2 Ankle Joint Prosthesis

Surgery of painful, end-stage ankle arthritis includes ankle arthrodesis and total ankle replacement. In the past decade, total ankle replacement has become a viable alternative to ankle arthrodesis. Modern implant designs either involve a syndesmosis fusion and resurfacing of the medial and lateral recesses of the ankle joint or the use of a three-component, mobile-bearing implant. In limited clinical series, early results of both of these prosthetic design approaches have been encouraging. In selected patients, ankle arthroplasty is an effective approach to relieving pain and improving function [23].

Ankle arthrodesis has been the treatment of choice for patients who have arthritic or degenerative ankle disease with disabling pain and loss of motion. But the results of long-term retrospective studies show that a significant percentage of arthrodeses have been unacceptable to patients and are considered to be clinically poor with many failures by the physicians. Therefore, total replacement of the ankle joint is becoming recognized as an alternative to ankle arthrodesis. This procedure eliminates pain and provides sufficient ankle motion for resumption of normal activities. Indications and contraindications for total ankle replacement are analogous to those for hip and knee joint replacement. Surgery is considered only when conservative treatment has been attempted with no improvement. Total ankle joint replacement is indicated when rheumatoid arthritis or osteoarthritis causes advanced arthritic changes with disabling pain and loss of ankle motion. Traumatic degenerative disease following ankle fracture, recurrent sprains, and injuries to the talus that could result in avascular necrosis or osteochondritis are also indications. In certain cases, total ankle joint replacement is also indicated following unsuccessful ankle arthrodesis. The rehabilitation protocols that are used actually are founded on not very recent work or are based on empirical observations.

Before surgery, the physiatrist counsels the patient regarding the procedure and explains the treatment program and goals. The patient's range of motion and muscle tone is evaluated, with special attention to the involved extremity (Fig. 15.7). The patient's ability in ADLs is assessed. The gait pattern of the patient is analyzed and gait deviations are recorded. All of the findings are documented. The patient is instructed in deep breathing and coughing exercises. Bilateral isometric contractions are taught for the gluteus maximus and quadriceps femur muscles. Isotonic ankle exercises for plantar flexion and dorsiflexion are taught for the uninvolved extremity. After surgery, the entire foot is wrapped in a bulky pressure dressing and elevated until the swelling has diminished and the joint feels comfortable to the patient. Generally, this requires three to five days [24].

Physical therapy resumes on the first day after surgery, with review of the exercises taught before surgery, along with toe flexion and extension of the involved extremity. The patient

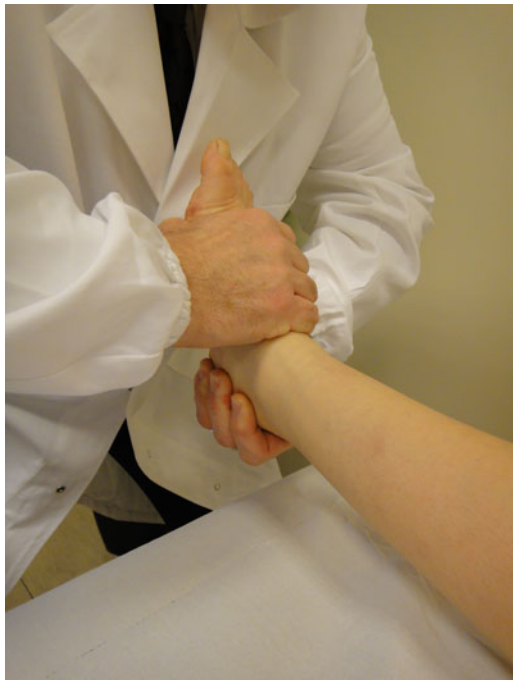

Fig. 15.7 Ankle mobilization

continues these exercises throughout the day. Transfer activities from the bed to the chair begin with the physiotherapist on the second day after surgery. The involved extremity is not allowed to bear weight or assume a dependent position. Active range-of-motion exercises in dorsiflexion and plantar flexion begin at this time if the wound has healed sufficiently. Gait training using crutches is initiated, with weight bearing to tolerance on the involved extremity. When the patient can walk independently on level surfaces, gait training progresses to elevation activities. Progression to full weight bearing using a single-point cane is determined by the patient's tolerance and the discretion of the physiatrist. The sutures are removed and the patient is discharged from the hospital 12 to 14 days after surgery. At discharge, the patient uses a single-point cane and bears weight to tolerance on the involved extremity. Normal activities are resumed three to five weeks after surgery. Six weeks after discharge, the patient has a follow-up appointment with the physician. At this time, the physiotherapist is notified if

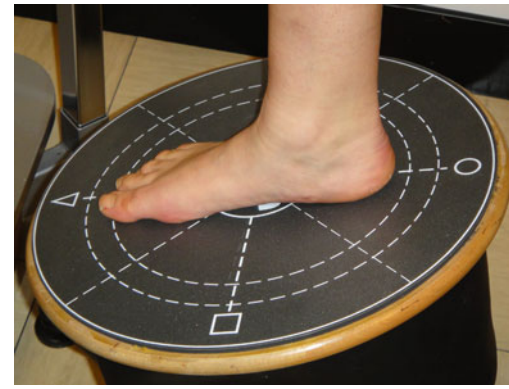

Fig. 15.8 Proprioceptive exercises for foot and ankle

additional ankle exercises or further gait training is required [25] (Fig. 15.8).

15.4 Rehabilitation After Shoulder Prosthesis

Shoulder replacement is a standard treatment intervention for patients with underlying advanced joint pathology who have persistent pain and loss of function despite conservative management. These pathologies include osteoarthritis, rheumatoid arthritis, cuff tear arthropathy, osteonecrosis, and fractures of the humeral head. Over the last 25 years, surgical techniques and prostheses have advanced greatly. However, there is still considerable variability in surgical techniques, particularly the use of cement for fixation and the type of prosthesis. Despite these significant variations, the overall reported outcomes for patients that have undergone shoulder replacement are good. Regardless of underlying pathology, operative soft tissue reconstruction is crucial for a good outcome following shoulder replacement. Soft tissue balancing at the time of surgery is the process of restoring the soft tissue anatomy to near-normal parameters, attempting to avoid either overtightened or insufficiently released structures so as to maximize joint function and stability. Subscapularis dysfunction following shoulder replacement has recently been identified as a potential postoperative

complication. Clinicians should be aware of the risk of subscapularis dysfunction following shoulder replacement. It may be the result of tendon pull-off, poor tissue quality, inappropriately progressed external rotation stretching/ROM activity, or oversized components leading to excessive tissue tension. Aggressive external rotation stretching and/or too vigorous internal rotation strengthening should be avoided. An important factor in the success of the procedure is postoperative rehabilitation. It is widely reported that postoperative rehabilitation is crucial to the overall functional outcome of individuals that have undergone a shoulder replacement [26]. It is important to evaluate the patient's condition using an adequate evaluation scale before and after the treatment, like the Simple Shoulder Test (SST), the Constant Score (CS), and the modified American shoulder and elbow surgeon's (M-ASES) questionnaire. The Constant Score was developed by Constant and Murley in 1987 and was one of the first outcome measures developed to assess shoulder function. Although it was created before the introduction of modern outcome tool development methodology, it is easy to administer with clear instructions and is therefore extensively used. It comprises both clinician-assessed physical examination findings and subjective patient-reported assessments. The Constant score is available free for use by clinicians and researchers [27, 28].

As for all the interventions of joint replacement, one must anticipate, in the according cases, a rehabilitative phase before the surgical intervention. In this phase it is also important to carry out a functional evaluation of the shoulder:

1. Scapular-thoracic joint: it is important to determine its possible limitation of movements on the chest or whether it presents instability or hypermobility as an expression of scapular dyskinesis.
2. Subacromial space: it may be reduced for damage to the headgear of the rotator cuff, they can present reactive bursitis. In this case, exercises of decoaptation and lowering of the humeral head are useful.
3. Acromion clavicular joint: its alterations can limit the recovery after surgical intervention [16].

It is also important to consider that shoulder prostheses are characterized by a certain degree of instability, because the surgical intervention eliminates certain elements of articular stabilization. First of all, the passive stabilizers are the intra-articular negative pressure and the glenohumeral ligaments. The range of motion of the replaced joint depends in particular on the characteristics of the implant; in the absence of the headgear of the rotatory, a traditional implant hardly can allow an active satisfactory motility. In using an inverse prosthesis the extension and the flexion can be improved, but the rotations could be lost, yet satisfactory results can be reached by training the patient to use the latissimus dorsi and the pectoralis major [16].

After the surgery it is essential to take into account the surgical access and the sort of intervention effected. For example, if the surgical intervention has involved the section of the acromion, with a consequent instability of the proximal insertion of the deltoid, it could be necessary to await recovery of the synthetized acromion, which requires at least 30 days of immobilization. Yet at this point the more second-hand access is the deltoid pectoral access in which the deltoid does not suffer, while the subscapularis muscle becomes sectioned and then integrated again, repair of the subscapularis muscle requires generally 20 days. It is necessary to determine the passive mobility intraoperatively because it will be the reference for rehabilitation. It is necessary to pay good attention to the integrity of the rotator cuff.

The rehabilitation programs after shoulder prosthesis involve protocols that currently represent a reference standard. The diagram below provides a rehabilitative generic program after shoulder prosthesis surgery:

Phase I: Immediate Postsurgical Phase

Goals:

- Allow healing of soft tissue
- Maintain integrity of replaced joint

- Gradually increase passive range of motion (PROM) of shoulder; restore active range of motion (AROM)of elbow/wrist/hand
- Reduce pain and inflammation
- Reduce muscular inhibition
- Independence with activities of daily living (ADL) with modifications, while maintaining the integrity of the replaced joint

Precautions:

- Sling should be worn continuously for 3–4 weeks
- Avoid shoulder AROM
- No lifting of objects
- No excessive shoulder motion behind back, especially into internal rotation (IR)
- No excessive stretching or sudden movements (particularly external rotation [ER])
- No supporting of body weight by hand on involved side
- Keep incision clean and dry (no soaking for 2 weeks)
- No driving for 3 weeks

Postoperative Day 1 (in hospital)

- Passive forward flexion in supine to tolerance
- Gentle ER in scapular plane to available PROM (as documented in operative note), usually around 30° (attention: do not produce undue stress on the anterior joint capsule, particularly with shoulder in extension)
- Passive IR to chest
- Active distal extremity exercise (elbow, wrist, and hand)
- Pendulum exercises
- Frequent cryotherapy for pain, swelling, and inflammation management
- Patient education regarding proper positioning and joint protection techniques

Early Phase I (out of hospital)

- Continue above exercises
- Begin scapula musculature isometrics/sets (primarily retraction)
- Continue active elbow ROM
- Continue cryotherapy as much as able for pain and inflammation management

Late Phase I

- Continue previous exercises
- Continue to progress PROM as motion allows
- Begin assisted flexion, abduction, ER, IR in the scapular plane
- Progress active distal extremity exercise to strengthening as appropriate

Criteria for progression to the next phase (II):

- Tolerates PROM program
- Achieves at least 90° PROM flexion
- Achieves at least 90° PROM abduction
- Achieves at least 45° PROM ER in plane of scapula
- Achieves at least 70° PROM IR in plane of scapula measured at 30° of abduction

Phase II: Early Strengthening Phase

(not to begin before 4 to 6 weeks postsurgery to allow for appropriate soft tissue healing)

Goals:

- Restore full passive ROM
- Gradually restore active motion
- Control pain and inflammation
- Allow continue healing of soft tissue
- Do not overstress healing tissue
- Reestablish dynamic shoulder stability

Precautions:

- Sling should only be used for sleeping and removed gradually over the course of the next 2 weeks, for periods throughout the day
- In the presence of poor shoulder mechanics avoid repetitive shoulder AROM exercises/ activity against gravity in standing
- No heavy lifting of objects
- No supporting of body weight by hand on involved side
- No sudden jerking motions

Early Phase II

- Continue with PROM, active-assisted range of motion (AAROM)
- Begin active flexion, IR, ER, abduction pain-free ROM
- AAROM pulleys (flexion and abduction), as long as greater than 90° of PROM
- Begin shoulder submaximal pain-free shoulder isometrics in neutral
- Scapular strengthening exercises as appropriate
- Begin assisted horizontal adduction
- Progress distal extremity exercises with light resistance as appropriate

- Gentle glenohumeral and scapulothoracic joint mobilizations as indicated
- Initiate glenohumeral and scapulothoracic rhythmic stabilization
- Continue use of cryotherapy for pain and inflammation

Late Phase II
- Progress scapular strengthening exercises.

Criteria for progression to the next phase (III):
- Tolerates PROM/AAROM, isometric program
- Achieves at least 140° PROM flexion
- Achieves at least 120° PROM abduction
- Achieves at least 60° PROM ER in plane of scapula.
- Achieves at least 70° PROM IR in plane of scapula measured at 30° of abduction
- Able to actively elevate shoulder against gravity with good mechanics to 100°

Phase III: Moderate Strengthening

(not to begin before 6 weeks postsurgery to allow for appropriate soft tissue healing and to ensure adequate ROM)

Goals:
- Gradual restoration of shoulder strength, power, and endurance
- Optimize neuromuscular control
- Gradual return to functional activities with involved upper extremity

Precautions:
- No heavy lifting of objects (no heavier than 3 kg)
- No sudden lifting or pushing activities
- No sudden jerking motions

Early Phase III
- Progress AROM exercise/activity as appropriate
- Advance PROM to stretching as appropriate
- Continue PROM as needed to maintain ROM
- Initiate assisted shoulder IR behind back stretch
- Resisted shoulder IR, ER in scapular plane
- Begin light functional activities
- Wean from sling completely
- Begin progressive supine active elevation strengthening (anterior deltoid) with light weights (0.5–1.5 kg) at variable degrees of elevation

Late Phase III
- Resisted flexion, abduction, extension (Therabands/sport cords).
- Continue progressing IR, ER strengthening.
- Progress IR stretch behind back from AAROM to AROM, as ROM allows; (pay particular attention as to avoid stress on the anterior capsule.)

Criteria for progression to the next phase (IV):
- Tolerates AAROM/AROM/strengthening
- Achieves at least 140° AROM flexion supine
- Achieves at least 120° AROM abduction supine
- Achieves at least 60° AROM ER in plane of scapula supine
- Achieves at least 70° AROM IR in plane of scapula supine in 30° of abduction
- Able to actively elevate shoulder against gravity with good mechanics to at least 120°

Note: If above ROM are not met, then patient is ready to progress when the patient's ROM is consistent with outcomes for patients with the given underlying pathology.

Phase IV: Advanced Strengthening Phase

(not to begin before 12 weeks to allow for appropriate soft tissue healing and to ensure adequate ROM, and initial strength)

Goals:
- Maintain non-painful AROM.
- Enhance functional use of upper extremity
- Improve muscular strength, power, and endurance
- Gradual return to more advanced functional activities
- Progress weight-bearing exercises as appropriate

Precautions:
- Avoid exercise and functional activities that put stress on the anterior capsule and surrounding structures (e.g., no combined ER and abduction above 80° of abduction)
- Ensure gradual progression of strengthening

Early Phase IV
- Typically patient is on a home exercise program by this point to be performed 3–4 times per week
- Gradually progress strengthening program

- Gradual return to moderately challenging functional activities

Late Phase IV (Typically 4 to 6 Months Postoperative)

- Return to recreational hobbies.

Criteria for discharge from skilled therapy:

- Patient able to maintain non-painful AROM
- Maximized functional use of upper extremity
- Maximized muscular strength, power, and endurance
- Patient has returned to advanced functional activities [26]

15.5 Rehabilitation After Elbow, Wrist, and Hand Prosthesis

15.5.1 Elbow Prosthesis

Total elbow arthroplasty is most commonly performed for rheumatoid arthritis, osteoarthritis, and fracture of the distal humerus. As a rule, both the humeral and ulnar components are cemented in, providing immediate fixation to the bone. The extensor mechanism is violated to insert the prostheses and must heal before active extension can be performed. The radial head may either be preserved or resected depending on impingement at the time of surgery. The ulnar nerve is generally transposed anteriorly to reduce the likelihood of ulnar neuropathy following the procedure.

There are some important considerations with regard to the rehabilitation process

- Hematoma formation following elbow arthroplasty can lead to pain and loss of motion in the early phases after surgery. Attempts to reduce and mobilize edema are critical in the early phases.
- Full flexion and extension can usually be obtained on the table but stiffness may ensue rapidly.Patients must be encouraged to perform daily stretching exercises to preserve motion.
- Because the extensor mechanism must heal back to the ulna, active elbow extension, such as using the arm to assist in rising from a chair, is not permitted for 8 weeks.
- Adjacent joint therapy may be particularly important for patients with rheumatoid arthritis who may have concomitant disease of the shoulder and wrist.

Elbow fractures comprise approximately 4.3 % of all fractures. These fractures typically occur in young boys ages 5–10. In contrast, total elbow arthroplasty is also considered to be a viable treatment for women over the age of 65 with distal humerus fractures.

There are three bones and four joint articulations that have a high degree of congruence in the elbow. Also, the ulnar nerve runs directly through the ulnar groove of the humerus and travels down the medial forearm. With joint replacement, careful consideration must be taken to limit ulnar nerve entrapment. The ulnar nerve is subject to transient (10 %) or, occasionally, partial dysfunction. Routine anterior translocation has been beneficial, but there is considerable variation in the technique in this regard. Triceps insufficiency can be virtually eliminated with the Kocher lateral-to-medial or the Bryan lateral-to-medial triceps-sparing approach.

Because of the difficulties that the patient and the therapist may encounter during the process of rehabilitation after elbow prosthesis, it is important to highlight the main phases of the rehabilitation program, as done previously for the shoulder.

Prerehabilitation:

- Instruct in application of ice and encourage use as much as tolerated within a 24-h period for the first week. If using ice packs, encourage to ice 20–30 min every 3–4 h while awake
- Instruct in home program of elbow flexion, extension, pronation, and supination
- Instruct in basic progression of rehabilitation program and expectations for time course to recovery

Inpatient (0–4 days):

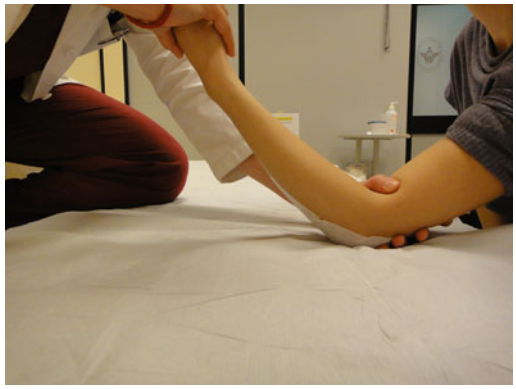

Fig. 15.9 Mobilization of the elbow (1)

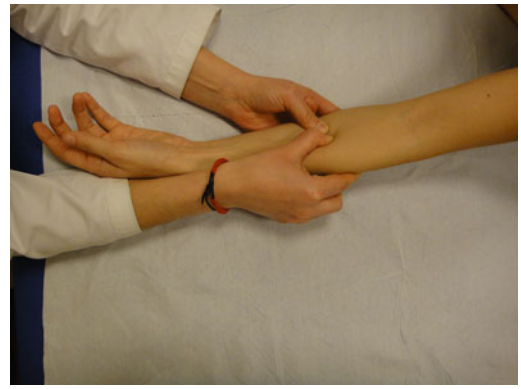

Fig. 15.11 Technical of manual fibrolysis

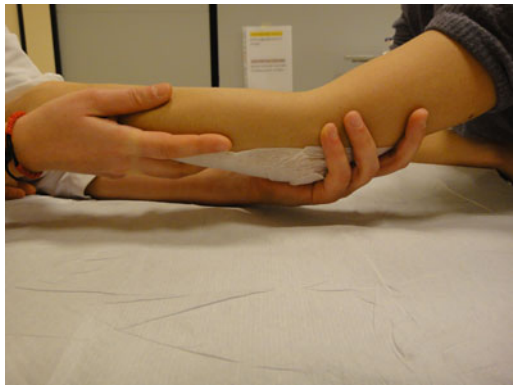

Fig. 15.10 Mobilization of the elbow (2)

- Arm is generally splinted in extension with hemo-vac drain in place for 1st 36 h to prevent swelling and reduce chance of a hematoma
- Arm is generally elevated in a sling on a pole
- Evening of the first postoperative day, the splint is removed.
- Cryotherapy
- Instruct in home program, and begin active assisted elbow and wrist flexion, extension, pronation, and supination (Figs. 15.9, 15.10, 15.11)
- Finger ROM but no aggressive grip strengthening so that muscular attachments heal

Outpatient Phase 1 (Hospital Discharge to week 4):

- Continue program active elbow and wrist flexion, pronation, and supination and active assisted elbow flexion
- Continue shoulder flexibility exercises
- Can start gentle grip strengthening but no active elbow or wrist strengthening exercises until Phase II
- Incision mobilization and desensitization
- Modalities for pain, inflammation, and edema control (no e-stim)
- Cryotherapy as needed
- Ulnar nerve desensitization

Outpatient Phase 2 (weeks 5–8):

- Continue shoulder elbow and wrist ROM
- At 6 weeks, can add active extension (antigravity only but no resistance)
- Night time extension splinting if flexion contracture developing
- May begin gentle isometric and isotonic wrist flexion/extension and elbow flexion strengthening
- Biceps strengthening should be done with elbow supported
- No elbow extension strengthening
- Sling should be fully discontinued at this point
- Continue scar massage

Outpatient Phase 3 (weeks 9–12):
ROM

- Active range of motion in all planes
- Continue nighttime extension splinting if necessary

- Continue isotonic strengthening
- May add antigravity active extension but no resistance
- May add exercises for shoulder to promote generally upper extremity conditioning

Outpatient Phase 4 (weeks 12–16):

- Continue maintenance flexibility program
- Progressive isotonic resistance including elbow extension
- Progress to functional use [29–34]

15.5.2 Considerations on Rehabilitation After Joint Replacement Surgery of the Wrist or Hand

Normal wrist motion is accomplished by a complex interaction of multiple articulations involving the radius, ulna, and carpal bones. Total wrist arthroplasty cannot duplicate this intricate system, but it can potentially produce a stable, pain-free joint with functional range of motion. Achieving a functional and durable outcome requires proper patient selection, careful preoperative planning, and accurate implantation. Because arthroplasty poses greater risks than arthrodesis, low-demand patients with special needs or desires for wrist motion are the best candidates. In particular, patients with arthritis involving multiple joints of the upper limbs often find tasks of daily living easier when some wrist motion is preserved. Other patients may choose arthroplasty over arthrodesis to better maintain their ability to perform vocational and avocational activities [35].

A total wrist replacement is generally indicated when a wrist that has sustained a traumatic injury or has been affected by a severe degenerative disease such as arthritis is unresponsive to other treatments and no longer able to function properly. In some cases, patients suffer from severe pain in the wrist and may have lost the ability to use it.

Also the metacarpal trapezium joint, the phalangeal metacarpus, and the joint between the phalanxes can be replaced by prostheses. Yet each of these prostheses has a particular limitation, and in the literature there are no good approaches with respect to the postsurgical rehabilitation.

The principal contraindications to prosthesis of hand and wrist are as follows:

1. marked osteoporosis
2. intractable tendinous and muscular alterations
3. infections
4. presences of cartilages of accretion

For evaluation one can use the DASH wrist (Disability Arm of Shoulder and Hand) score that includes 30 items related to activities of daily living (ADLs). The patient is asked to attribute a score of 1–5 on all 30 items. Scores rise with increasing disability. There is also an optional section that contains 4 items relating to disability in athletes and musicians. The raw score obtained is converted into a 0–100 scale. The DASH has been extensively investigated with respect to its reliability, repeatability, internal consistency, validity as well as its degree of acceptance in clinical practice [36]. With regard to the hand, one instead can use a dynamometer, asking the patient to tighten at maximum force a device connected to a terminal. The main measures after replacement arthroplasty of wrist or hand shall be as follows: protection of the biological recovery of the operated segment, pain control, prevention of secondary deformity, restoration of the functional range of motion and of the correct muscle-tendinous balancing. Essentially, the rehabilitation program performed consists of functional reeducation, massotherapy, and ungluing of the surgical scar. The use of splint could be important to maintain the postsurgical alignment [16].

15.6 Physical Therapies

Physical therapy is fundamental in rehabilitative programs for patients who underwent a surgical operation with joint prosthesis. These therapies can help reduce pain, recover the range of motion, and restore the muscles tone and their action.

Among the most common physical therapies which are widely used in the postoperative phase, more or less early, there are laser therapy, transcutaneous electrical neural stimulation (TENS), ultrasound therapy, muscular electrostimulation, and vibration therapy. Absolute contraindications to the use of physical therapies are: the presence of neoplasms, pregnancy, pacemakers, and active bleeding. There are also specific contraindications relative to each type of physical therapy or to the treated site.

15.6.1 Laser Therapy

The use of low levels of visible or near-infrared light for reducing pain, inflammation, and edema, promoting healing of wounds, deeper tissues, and nerves, and preventing tissue damage has been known for almost forty years since the invention of lasers. The biochemical mechanisms underlying the positive effects are incompletely understood. Furthermore, the complexity of rationally choosing among a large number of illumination parameters such as wavelength, fluence, power density, pulse structure, and treatment timing has led to the publication of a number of negative studies as well as many positive ones.

The cellular responses observed in vitro after low-level laser therapy (LLLT) can be broadly understood in terms of increases in metabolism, migration, proliferation, and increases in synthesis and secretion of various proteins. Many studies report effects on more than one of these parameters. Yu et al. reported keratinocytes and fibroblasts that were irradiated with 0.5–1.5 J/cm^2 HeNe laser. They found a significant increase in basic fibroblast growth factor (bFGF) released from both keratinocytes and fibroblasts and a significant increase in nerve growth factor release from keratinocytes. Medium from HeNe-laser-irradiated keratinocytes stimulated [^{3}H]thymidine uptake and proliferation of cultured melanocytes. Furthermore, melanocyte migration was enhanced either directly by HeNe laser or indirectly by the medium derived from HeNe-laser-treated keratinocytes. The presence of cellular responses to LLLT at the molecular level was also demonstrated. Normal human fibroblasts were exposed for 3 days to 0.88 J/cm^2 of 628-nm light from a light-emitting diode. Gene expression profiles upon irradiation were examined using a cDNA microarray containing 9,982 human genes. 111 genes were found to be affected by light. All genes from the antioxidant-related category and genes related to energy metabolism and respiratory chain were upregulated. Most of the genes related to cell proliferation were upregulated, too. Among genes related to apoptosis and stress response, some genes such as JAK-binding protein were upregulated, others such as HSP701A, caspase 6, and stress-induced phosphoprotein were downregulated. It was suggested that LLLT stimulates cell growth directly by regulating the expression of specific genes, as well as indirectly by regulating the expression of the genes related to DNA synthesis and repair, and cell metabolism.

Low-power laser therapy is used by physical therapists to treat a wide variety of acute and chronic musculoskeletal aches and pains, by dentists to treat inflamed oral tissues and to heal diverse ulcerations, by dermatologists to treat edema, nonhealing ulcers, burns, and dermatitis, by physiatrists and orthopedists to relieve pain and treat chronic inflammations and autoimmune diseases, and by other specialists, as well as general practitioners. Laser therapy is also used with good results in sports-medicine and rehabilitation clinics (to reduce swelling and hematoma, relieve pain, improve mobility, and treat acute soft-tissue injuries). Lasers and LEDs are applied directly to the respective areas (e.g., wounds, sites of injuries) or to various points on the body (acupuncture points, muscle-trigger points). Clinical applications of low-power laser therapy are diverse. In recent years, longer wavelengths ($\sim$800 to 900 nm) and higher output powers (to 100 mW) have been preferred in therapeutic devices especially to allow deeper tissue penetration. Several controlled trials reported significant improvement in pain and some improvement in objective outcome measures. Since then, several light sources have been approved as equivalent to an infrared

heating lamp for treating a wide range of musculoskeletal disorders with no supporting clinical studies [37, 38].

Numerous clinical and basic research studies have demonstrated the physiological effects and medical applicability of LLLT. Its application was initiated based on previous work that demonstrated properties of low-level laser that exert a positive influence on fibroblast and osteoblast proliferation, collagen synthesis, and bone regeneration. In vivo examinations have also shown that LLLT significantly stimulates the activity of alkaline phosphatase and calcium accumulation. In addition to cartilage damage and bone metabolism, pathological alterations are also known to exhibit reduced circulation in the vessels of the joint parallel to the degenerative changes. Numerous authors have reported increased microvascularization as a histological effect of the laser beam [39]. Low-power laser therapy has been used to control pain in different musculoskeletal conditions. Despite its widespread use, the results of the experimental and clinical studies are conflicting (see Fig. 13.12).

Fig. 15.12 Device for laser therapy

15.6.2 Transcutaneous Electrical Nerve Stimulation

Acute postoperative pain is a challenge to clinicians for postoperative care, especially in elderly patients with comorbidities such as coronary heart disease. Elderly patients undergoing total hip arthroplasty (THA) frequently experience high levels of postoperative pain [40]. Transcutaneous electrical nerve stimulation is an important alternative postoperative pain relief strategy for elderly patients. It has been reported to significantly decrease opioid requirements within 24 h postoperatively, although it can be ineffective in the treatment of postoperative acute pain in certain cases, including total knee arthroplasty. Moreover, TENS treatment on acupoints has good pain relief efficacy and can reduce the incidence of postoperative nausea and vomiting. The precise analgesic mechanism of TENS remains largely unclear. However, according to the gate theory, TENS can suppress pain transmission mediated via sensory A-d and C fibers. A published review in 2008 has examined the effectiveness of conservative treatments for the subacute lumbago. Thirteen randomized controlled studies have shown how TENS reduce the duration of the algic seizure. Another study has determined the effect of TENS in the management of chronic lumbago. Authors conclude that in the management of chronic lumbago, high-frequency TENS has a moderately meaningful effectiveness in pain reduction [42, 43] (see Fig. 15.13).

15.6.3 Ultrasound Therapy

Nonpharmacological methods including a variety of physical agents are the cornerstone of the management of chronic and acute pain. Therapeutic ultrasound (US) is among the commonly used physical modalities for treating soft tissue injuries. Therapeutic US is delivered in two modes: (1) Continuous mode, in which the delivery of US is nonstop throughout the treatment period; (2) Pulsed mode, in which the delivery of US is intermittently interrupted.

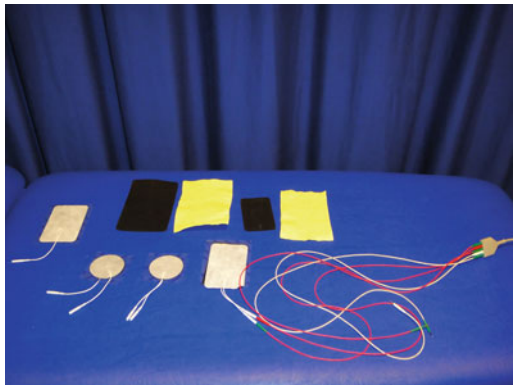

Fig. 15.13 Accessories for analgesic electrotherapy

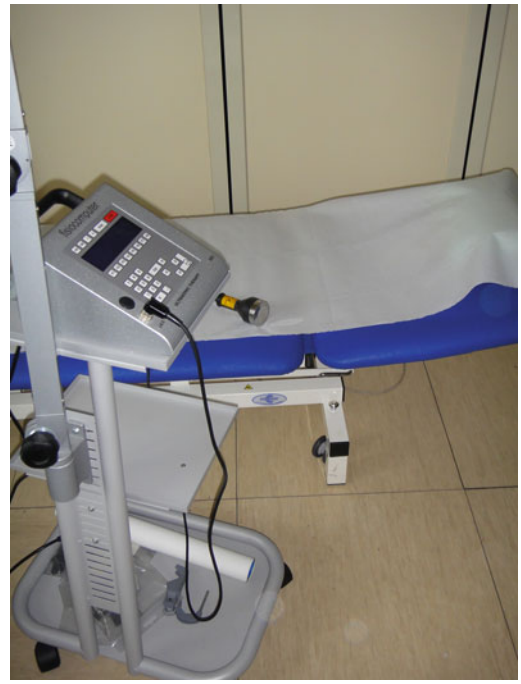

Fig. 15.14 Device for ultrasound therapy

Fig. 15.15 Handpiece for ultrasound therapy

Therapeutic effects of US are classified as thermal and nonthermal. Ultrasonic energy causes soft tissue molecules to vibrate from exposure to the acoustic wave. This increased molecular motion generates frictional heat and consequently increases tissue temperature. This increased temperature, named thermal effects, is thought to cause changes in nerve conduction velocity, increase in enzymatic activity, changes in contractile activity of skeletal muscles, increase in collagen tissue extensibility, increase in local blood flow, increase in pain threshold, and reducing muscle spasm. Acoustic waves cause the normally present minute gas pockets in the tissue to develop into microscopic bubbles or cavities. With therapeutic US, stable acoustic cavitation results, whereby the microbubbles pulsate without imploding. This pulsation leads to microstreaming of fluid around the pulsating bubbles. When occurring around cells, this process, referred to as nonthermal effects, is reported to alter cell membrane activity, vascular wall permeability, and facilitate soft tissue healing. Traditionally, continuous US is used for its thermal effects. Pulsing the US is thought to minimize its thermal effects. In fact, it is not possible to truly isolate the thermal and nonthermal effects as both effects occur with US application. Recently published randomized controlled trials, which have reported significant benefits of therapeutic US over placebo US, have used intensities of 1–1.5 W/cm^2. Mild heating in the chronic phase of injury is known to reduce pain and muscle spasm and to promote the healing process. More chronic lesions are treated with continuous US. US frequency of 1 MHz is preferable when treating large and deep soft tissue volumes. Intensities between 0.8 and 3 W/cm^2 are suggested for chronic lesions [44] (Figs. 15.14, 15.15). US can be used with excellent results in pain management before surgery. After the prosthesis implantation the ultrasound should not be used at the level of the prosthetic implant, but they can be used with

success in the management of overload pathologies of the muscles and tendons at the level of the adjacent joints.

15.6.4 Vibration Therapy

Vibration therapy is divided into general (whole body vibration, WBV) and segmental (segmental muscle vibration, SMV). SMV applies frequencies above 30 Hz with a zone of propagation confined to the area of contact producing localized effects. In essence, it is a technique that applies low-amplitude/high-frequency vibratory stimuli to a specific muscle via a mechanical device. The principal effects of the vibratory energy include:

- muscle hypertrophy
- pain control
- equilibrium improvement
- proprioception improvement
- reduction of spasticity
- reduction in bone reabsorption

SMV induces the generation of Ia inputs by activating muscle spindle primary endings. The activated Ia inputs can alter the excitability of the corticospinal pathway by modulating intracortical inhibitory and facilitator inputs to the primary motor cortex. It is widely known that a vibratory stimulus applied directly to a muscle induces presynaptic inhibition of Ia afferents, likely reducing transmitter release from the latter which will lead to a decrease of the monosynaptic reflex excitability. Vibration also reduces the stretch-related afferent input through a 'busy line' phenomenon, whereby the Ia discharge is locked to vibration and is consequently unable to faithfully transmit the stretch-induced volley owing to the high vibration frequency (>90 Hz) and the entrained action potentials in the Ia fibers. Indeed, the application of a 91-Hz vibratory stimulus to the spastic upper limb muscles of post-stroke patients results in a significant and persistent (up to 30 min) reduction in muscle tone, accompanied by a reduction in F-wave amplitude and F/M ratio, both of which point to a reduction in motor-neuronal excitability. Moreover, vibration also reduces the H reflex, probably through mechanisms of post-activation depression and dendritic depolarization [45]. It is also known that vibration applied to muscles and tendons can act on proprioception [46]. Muscle tendon vibration has also been shown to elicit motor cortex activation. A recent study with TMS has demonstrated its direct modulating effect on M1 excitability with a vibration intervention below the sensory illusion threshold [47]. A comparative analysis of brain activity with positron emission tomography (PET) showed that both the loci and levels of activation during tendon vibration did not match to those obtained during passive movement [48]. The vibration therapy should not be applied near the implantation of the prosthesis, but far from the surgical area on the muscle groups that are involved in joint stability and its control. In this respect, SMV can be used in order to improve muscle strength and proprioception, so it may be applied in the late phases of rehabilitation.

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