

Markers of Bone Turnover in Bone Metastasis from Prostate Cancer

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Bone homeostasis is achieved through a continuous remodelling process on the bone surface of the balanced resorption of old bone by osteoclasts and the formation of new bone by osteoblasts. Local and systemic growth factors regulate the differentiation and activity of the osteoclasts and osteoblasts (and osteocytes). Maintenance and repair of normal bone result in the release of enzymes, peptides and mineral components that have been characterised as serum and urinary biochemical markers of bone remodelling [1]. High bone turnover in cancer patients is crucial for all the steps of bone metastatic disease, from the homing of circulating cancer cells into the bone (premetastatic niche) to the complication of bone metastasis (BMT) (skeletally related events [SREs]). Therefore, elevated bone turnover marker could predict bone metastasis, risk of bone progression and risk of SREs, potentially becoming a potent prognostic predictor (Fig. 2.1). For this reason, biochemical markers of bone remodelling are potentially an ideal tool for evaluating changes in bone turnover, such as those associated with malignant bone lesions and response to treatment. Osteoclast and osteoblast activity (and probably that of cancer cells) is

associated with the release of distinct biochemical markers that are amenable to non-invasive measurements of the blood or urine.

Breakdown products of type I collagen by osteolysis as cross-linked collagen peptides (the amino (N)- and carboxy (C)-terminal cross-linked telopeptide of type I collagen, NTX and CTX, respectively), and the terminal peptides that are cleaved from procollagen before its integration into new bone matrix (e.g. procollagen type I N-terminal and C-terminal peptides, or P1NP and P1CP), can provide meaningful insights into the ongoing effects of tumour growth on bone turnover (Fig. 2.2). Bone-specific alkaline phosphatase (bone ALP) concentrations in serum reflect the ongoing rate of osteogenesis [2]. The International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine recommend that a marker of bone formation (serum procollagen type I N propeptide) and a marker of bone resorption (serum C-terminal telopeptide of type I collagen) be used as reference analytes for bone turnover markers in clinical studies [2] (Fig. 2.3). Nowadays, a number of bone markers can be determined using enzyme immunological procedures (enzyme-linked immunosorbent assay) by means of a commercial kit that can be easily adapted to laboratory automated machines to achieve greater analytical reliability during determination compared with manual methods [3]. Although a great deal of the data in the literature are obtained on markers analysed

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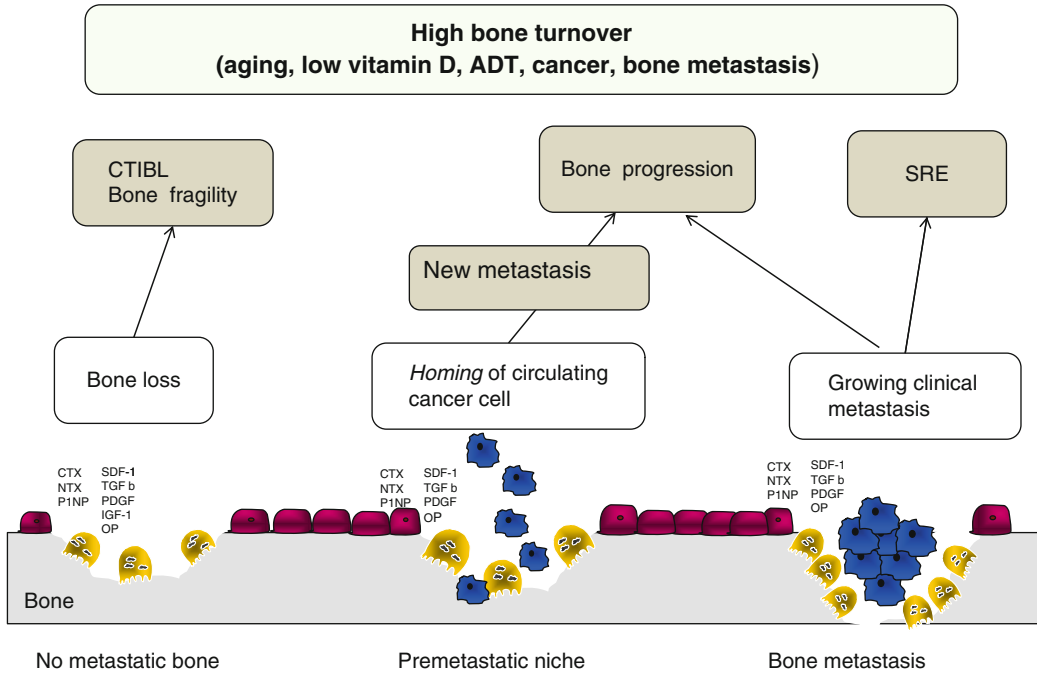


Fig. 2.1 Bone turnover is usually very high in prostate cancer (PC) patients for many reasons (aging, vitamin D deficiency, androgen deprivation therapy, or abiraterone or enzalutamide, cytokines released from primary cancer and for metastatic cancer cells activating the bone micro-environment). High bone turnover increases the rate of bone loss and impairs bone quality, increasing the risk of fragility fractures. Consensually, high bone turnover promotes the homing of circulating cancer cells and the promotion of the so-called osteoblastic premetastatic niche. A clinically evident bone metastasis (BMT) develops

and grows due to the effect of growth factors released from bone matrix breakdown. The increase in size of the BMT into a frail bone finally increases the risk of an SRE. In a patient with PC bone disease, all these steps are present at the same time as a continuum in the skeleton. ADT androgen deprivation therapy, CTIBL cancer treatment-induced bone loss, SRE skeletal related event (fracture, pain, cord compression, orthopaedic surgery, radiotherapy), yellow cell osteoclast, red cell osteoblast, blue cell PC cell

from urine samples (i.e. NTX), analysis of makers of bone turnover on serum and plasma are recommended because of lower inter- and intraindividual variability [2]. Standardised assays are available for many bone turnover markers and normal or reference ranges for several markers have been established. As the normal range changes with age and sex, selection of appropriate reference values is critical for data interpretation [2, 4]. In systemic metabolic bone diseases, such as osteoporosis, primary hyperparathyroidism and osteomalacia, biochemical markers reflect ongoing rates of bone resorption and formation in the body as a whole. Therefore, bone marker assessments in “focal” diseases, such as Paget disease or BMT, do not provide information specific to individual lesion sites. Moreover, changes in bone

marker levels are tissue specific (bone) and not disease specific and are associated with an imbalance in skeletal metabolism independently of the underlying cause [1, 5]. In cancer patients, bone turnover markers may be very high for many concomitant causes, such as age, vitamin D deficiency, adjuvant hormone therapy and BMT, but it is impossible to distinguish the contributions of the different components that elevate the marker levels in the serum and urine (Figs. 2.1 and 2.3). For example, NTX levels were similar in PC patients on androgen deprivation therapy with and without BMT. Furthermore differences between bone resorption markers and bone formation markers were not found in patients with BMT from different cancers [6, 7]. In an attempt to differentiate the source of the marker (BMT vs non-metastatic

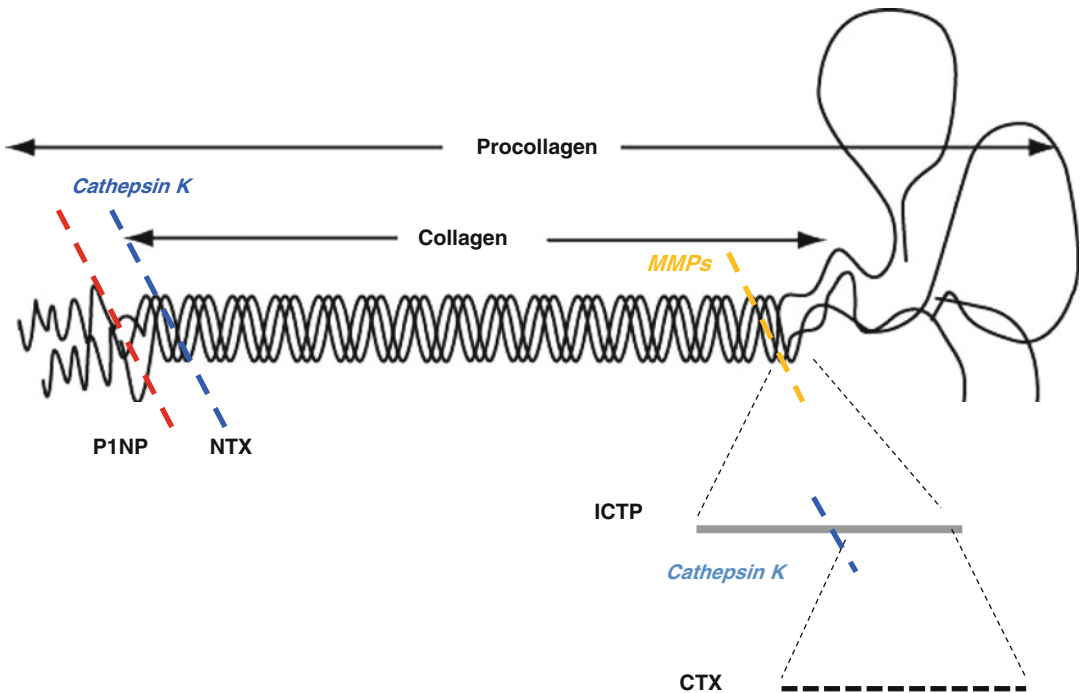


Fig. 2.2 Schematic representation of the amino-terminal propeptide procollagen type 1 (*P1NP*), N-terminal cross-linking telopeptide collagen type 1 (*NTX*), and C-terminal cross-linking telopeptide collagen type 1 (*CTX*). *P1NP* epitope is used as a marker of bone formation. *NTX*, *CTX* and *ICTP* epitopes are used as markers of bone resorption on type I collagen. *CTX* epitope is constituted by an eight-amino acid sequence on the C-telopeptide of $\alpha 1$. The

cross-linked carboxy-terminal telopeptide collagen type 1 (*ICTP*) epitope is a larger conformational epitope including at least two telopeptides and the first phenylalanine of the phenylalanine-rich region. It is a product of metalloprotease breakdown of collagen type 1. As shown in the figure, cathepsin K degrades the *ICTP* epitope whereas it generates *CTX*

skeletal), the non-isomerised form of *CTX* and type I collagen breakdown products generated by matrix metalloprotease (*ICTP*), apparently more specific for BMT breakdown, have been evaluated (Fig. 2.2) [8].

The clinical utility of bone markers as diagnostic indicators of bone metastatic disease and as prognostic indicators has been extensively examined. Several studies have revealed an association between bone turnover marker and the presence or progression of skeletal metastases from prostate cancer (PC) [9, 11, 12]. In these studies the formation marker and resorption markers are elevated in the case of typical osteoblastic osseous metastasis expressing a disrupted balance between bone formation and resorption. *P1NP*, bone sialoprotein (BSP), and osteoprotegerin (OPG) showed more signifi-

cant differences between PC patients with and without BMT. BSP is not a typical bone marker and works as a general tumour marker [13]. In addition to being elevated in PC patients with BMT, OPG correlates with the extent of osseous metastasis. Furthermore, in association with RANKL, it may predict recurrence after radical prostatectomy [14–16]. *P1NP* as bone ALP correlates with the extent of osseous changes (bone scan index). Bone ALP had the highest diagnosis accuracy (72% sensitivity, 88% specificity) and *P1NP* the greatest diagnostic specificity (92%) [11]. Recently, the elevated alkaline velocity was found to be an independent predictor of OS and BMT-free survival in patients with CRPC [17]. On the other hand, recent data do not confirm the diagnostic performance of *P1NP*. Current consensus is that

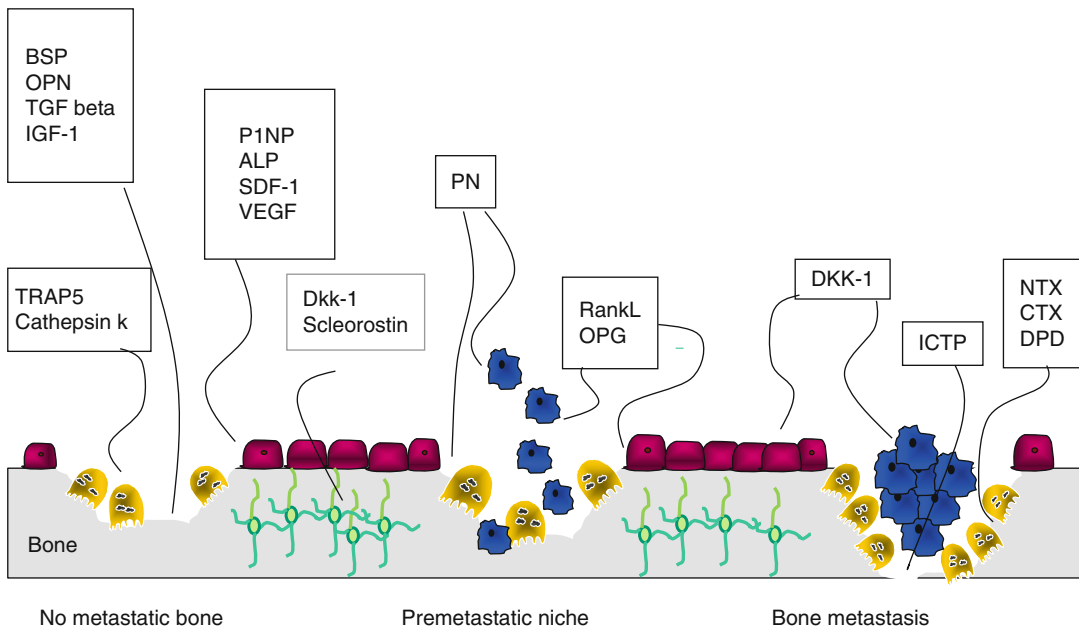


Fig. 2.3 Schematic representation of the origin of peptides used as markers of bone formation and reabsorption of bone by osteoblasts, osteoclasts, osteocytes and cancer cells. NTX and CTX derived from bone breakdown by osteoclasts through cathepsin K, ICTP mainly by cancer cell bone breakdown through metalloproteases. Cathepsin K and TRAP5 are expressed from osteoclasts during their osteolytic activity. Periostin (PN) is stored by osteoblasts during bone formation, but released during osteoclast activity. It is also expressed directly from cancer cells.

P1NP and alkaline phosphatase (ALP) expressed from osteoblasts are used as markers of bone formation. Osteoblasts also express vascular endothelial growth factor (VEGF) and chemokine (SDF-1), RANKL and osteoprotegerin (OPG). DKK-1 and sclerostin are expressed by osteocytes, osteoblasts and PC cells. Bone sialoprotein (BSP), osteopontin (OPN), transforming growth factor-1 (TGF- β) and insulin-like growth factor-1 (IGF-1) are released from bone matrix during osteoclastic (and cancer) bone reabsorption (see text for details)

the diagnostic sensitivity and/or specificity of bone markers for the presence of BMT or the prognostic role of bone lesion progression are not sufficient to utilise the results to diagnose BMT [18]. The mean values of the areas under the ROC curve from several studies were 0.81, 0.80 and 0.77 for P1NP, bone ALP and ICTP suggesting that these markers might have diagnostic values in interaction with safely defined reference thresholds or during their course [5, 10, 19]. Data on the use of bone markers as predictors for SRE and survival are quite encouraging [18, 20]. Retrospective analyses of data from phase III trials of zoledronic acid in patients with CRPC and BMT showed that both baseline and on-study elevation in bone marker levels, specifically NTX, were associated with increased risks of SRE, disease progression and death [18, 21–23]. A high baseline level of uri-

nary NTX (above 180 nmol/mmol creatinine) was associated with a more than 2.5-fold increase in the risk of death (RR 2.58, 95 % CI 1.92–3.47) compared with low baseline levels of NTX (<55 nmol/mmol creatinine) [18, 22]. Also, baseline bone ALP was associated with a 4 % increase in the risk of death and SRE per 200 IU/L increase. Elevated bone ALP levels at baseline were associated with a shorter time to the first on-study SRE and a shorter time to the first pathological fracture. The cumulative incidence of SRE over a 1-year period was nearly doubled (50.7 % vs 26.5 %) among patients with elevated versus normal baseline bone ALP [23]. Adequate suppression of NTX and bone ALP levels during treatment (zoledronic acid plus docetaxel vs docetaxel alone) was associated with longer survival time, and similar results have been confirmed by others [23, 24].

Recently, bone ALP velocity (>6.3 IU/L/year) was found to be an independent predictor of overall survival in CRPC. A fivefold increase in death was observed among CRPC patients with rapid bone ALP velocity (OR 5.11, 95 % CI 2.24–11.67) [17]. Other more recent bone markers have been found to be associated with prognosis in PC patients. P1NP and ICTP were associated with survival after 15 months of zoledronic acid therapy [25]. Baseline and 3 months after, zoledronic acid P1NP and CTX predict survival and (only P1NP) risk of SRE [26]. The association of CTX or NTX with P1NP confirmed the prognostic role of these bone markers [27].

The data summarised above suggest that bone turnover markers might be useful to optimise the use of bone-targeted therapy for metastatic bone disease. Promoting lifelong therapy contradictory with the paucity of data regarding the usefulness and the safety (osteonecrosis of jaw and atypical hip fractures) of treatment durations with bone-modifying agents beyond 2–3 years. The serial measurement of BTMs could be a strategy in tailoring the therapy regimen and could help the decision on the optimal duration of antiresorptive therapy, which could allow treatment frequency to be reduced and even theoretically removed for periods in the context of optimal bone metabolism control [28]. In summary, at present, the potential for the clinical use of markers of bone turnover for diagnosis, prognosis and monitoring therapy in cancer patients with BMT remains unfulfilled and the routine use of these markers cannot yet be recommended. As stated in consensus publications, there is a need for harmonisation, standardisation and common reference ranges [18, 29, 30] although a recent position paper solicited their introduction into a clinical setting [28].

2.1 New Bone Markers

2.1.1 ICTP

ICTP, which reflects non-osteoclastic bone resorption mediated by metalloproteases (MMPs), is liberated to the bloodstream during pathological conditions. Serum ICTP is relatively

insensitive to changes in bone remodelling mediated by normal osteoclastic activity.

In a retrospective analysis of four bone markers (NTX-I, ICTP, total ALP, and TRAP5b) in breast cancer patients with and without BMTs, only ICTP and TRAP5b were significantly higher in those patients with BMTs compared with those without (visceral metastases or no metastases). The ICTP and TRAP5b levels were also related to the number of BMTs on the other hand [31]. Furthermore in another study in breast cancer patients comparing a cohort with and without BMTs, ICTP was the marker with higher sensitivity (65 %), and it had similar specificity to bone ALP (91 vs 92 % for bone ALP) [32].

In a prospective cohort study, three bone markers (NTX-I, ICTP, and bone ALP) were tested in 123 patients with various metastatic cancers, 26 of which were extraosseous only (45 bone-only and 52 bone plus visceral). NTX-I and ICTP, but not bone ALP, were associated with bone disease progression. Moreover, NTX-I had the highest sensitivity (70 %), specificity (80 %), positive (72 %), and negative (79 %) predictive values for bone disease progression in the set of markers analysed (for an increase X30% from baseline). Curiously, when assessing ICTP, not only did it increase in the context of bone and extraskeletal progression, but it also did not decrease with bisphosphonate (BP) therapy [9]. This led the authors to speculate that ICTP could represent a bone collagen product derived from an osteoclast-independent mechanism of bone degradation (MMP-1 action on bone collagen) and therefore not influenced by BP therapy (Fig. 2.3).

2.2 Periostin

Periostin is a highly conserved matricellular protein that shares close homology with the insect cell adhesion molecule fasciclin 1. Periostin is expressed in a broad range of tissues, including the skeleton, where it serves both as a structural molecule of the bone matrix and as a signalling molecule through integrin receptors and Wnt-beta-catenin pathways, stimulating osteoblast function and bone formation. The development

of periostin-null mice has allowed the crucial role of periostin in dentinogenesis and osteogenesis to be elucidated, in addition to the skeletal response to mechanical loading and parathyroid hormone. Periostin binding to the integrins activates the Akt/PKB- and FAK-mediated signalling pathways, leading to increased cell survival, angiogenesis, invasion, metastasis, and, importantly, epithelial–mesenchymal transition of carcinoma cells [33]. In situ RNA hybridisation in biopsies of breast cancer metastases showed that the periostin gene was highly expressed in the stromal cells immediately surrounding the tumour but not within the breast cancer cells themselves [34]. Although periostin is highly expressed in various types of human cancers, its function is still unclear. In mice the administration of PN1-Ab, a neutralising antibody of periostin, significantly inhibited the growth of primary tumours and metastatic tumours, associated with the prevention of bone destruction, resulting in increased survival of mice. In addition, in vitro, PN1-Ab significantly inhibited the proliferation, migration, and invasion of 4T1 mouse breast cancer cells, which produced periostin [35]. Nude mice were inoculated with human MDA-B02 breast cancer cells. Mouse-derived periostin was markedly overexpressed (eightfold) in metastatic legs compared with non-inoculated mice. Serum periostin levels were also markedly increased in metastatic mice and correlated with in situ expression levels. Immunostaining showed that periostin is derived from the surrounding stromal cells of BMT. It was suggested that periostin might be a biochemical marker of the early stromal response associated with breast cancer BMT formation [36]. The use of circulating periostin as a potential clinical biomarker has been explored in different non-skeletal conditions. These include cancers and, more specifically in the metastasis process, respiratory diseases such as asthma, kidney failure, renal injury, and cardiac infarction. A study including breast cancer and small cell lung cancer patients showed that serum periostin levels were elevated in breast cancer patients presenting with BMTs compared with similar breast cancer patients with no evidence of BMT. No correlation was found between the serum periostin level and any other prognostic factors, such as clinical

stage and lymph node metastasis in breast cancer [37]. In postmenopausal osteoporosis, serum levels have been shown to predict the risk of fracture—more specifically non-vertebral—independently of bone mineral density. Because of its preferential localisation in cortical bone and periosteal tissue, it may be speculated that serum periostin might be a marker of cortical bone metabolism, although additional studies are clearly needed (Fig. 2.3) [36].

2.3 Bone Sialoprotein and Osteopontin

Small integrin-binding ligand N-linked glycoproteins (SIBLINGs), a family of five integrin-binding glycoprophosphoproteins, including osteopontin (OPN) and bone sialoprotein (BSP), are an emerging group of proteins used by cancer cells to facilitate expansion [38].

High levels of OPN and BSP expression could enhance the affinity of metastasis of cancer cells to the bone. However, the value of OPN and BSP in predicting BM and survival in NPC has not been elucidated. It has been suggested that OPN is overexpressed and associated with tumour progression in various cancers, including breast cancer and PC [39, 40].

SIBLING expression in different osteotropic cancers may be useful for establishing the risk of BMT in cancer patients. For example, increased expression of BSP in many osteotropic cancers, including PC, may predict BMT in this cancer [41].

Studies examining BSP levels in primary breast cancer tissue suggest that elevated levels of this SIBLING might be prognostic for shorter survival and correlate with the development of BMT [42]. Similarly, elevated levels of BSP in the blood correlate with, and may be predictive of, BMT in several osteotropic malignancies, including the breast, lung, prostate, and multiple myeloma [43].

Serum BSP levels in PC increase only in the later stages of the disease, calling into question the prognostic value of BSP in PC [13, 44]. Some authors consider BSP and OPN to be general tumour markers rather than exclusive bone markers, as serum levels also increase in localised PC,

and currently BSP and OPN are seen as bone markers with ambivalence (Fig. 2.3) [5, 44].

2.4 Sclerostin and DKK-1

Among the potential markers, dickkopf-1 (DKK-1) and sclerostin have shown interesting evidence, as they have been found to be elevated in different cancer types, including PC. Sclerostin and dickkopf-1 (DKK-1) are specific inhibitors of Wnt signalling and are also considered as bone remodelling markers. Sclerostin is produced by osteocytes, whereas DKK-1 is produced by osteoblasts and by a variety of different cells in several tissues, including cancer cells. Both sclerostin and DKK-1 are secreted into the circulation, and serum levels reflect the inhibition of bone formation. Wnt proteins physiologically induce the differentiation and maturation of osteoblasts, and the secretion of Wnt proteins was shown to increase bone formation in osteoblastic metastases [45]. DKK-1 is a negative regulator of bone formation by antagonising the Wnt pathway, and it is also involved in the proliferation of stem cells and tumorigenic processes. The expression of DKK-1 in PC samples is conflicting, because literature data report either an increase or a non-significant change in PCa samples. Sclerostin is a related cysteine-rich glycoprotein that is predominantly secreted by osteocytes. Sclerostin interaction with LRP5/LRP6 leads to complex formation with Kremen and subsequent degradation, therefore leading to inhibition of Wnt signalling. Given the central role played by Wnt proteins within bone biology, the involvement of Wnts and Wnt inhibitors in PC-induced osteoblastic metastases has been extensively investigated. Interestingly, gene and protein expression in BMT specimens from PC patients showed that sclerostin and DKK-1 were not significantly different in osteoblastic and osteolytic metastases [46]. There are conflicting results on the levels of DKK-1 in PC patients with or without BMTs [47, 48]. Cumulative data suggest that the balance between Wnt and Wnt inhibitors might determine the osteogenic nature of PCa skeletal

metastases and that DKK-1 may serve as a molecular switch between osteolytic and osteoblastic aspects of PCa BMTs. The use of DKK-1 and sclerostin as markers of bone turnover in a clinical setting seems rather premature (Fig. 2.3).

2.5 Other Emerging Markers of Bone Metastatic Disease from Prostate Cancer

New biomarkers, in combination with traditional markers of bone turnover, could help to improve the strategy for managing bone metastatic disease. Recently, xMAP multiplex technology has been developed, enabling the simultaneous measurement of large numbers of circulating biomarkers in a small sample volume.

In a recent study, nine new bone markers were tested by a commercially available multiplex Human Cancer/Metastasis Biomarker Panel [49]. Dickkopf-related protein 1 (DKK-1), growth differentiation factor 15 (GDF15), neuron-specific enolase (NSE), osteoprotegerin (OPG), osteonectin, periostin, tartrate-resistant acid phosphatase (TRAP5), tumour necrosis factor-related weak inducer of apoptosis (TWEAK), and chitinase-3-like protein 1 (YKL40) were tested in patients with BMTs from prostate, breast, lung and pancreatic cancer and compared with carboxy-terminal telopeptide (CTX) and procollagen type 1 N-terminal propeptide (PINP). Among the nine new markers of BMT, only GDF15, TRAP5, TWEAK, and YKL40 showed a promising profile.

Growth differentiation factor 15 (GDF15) is a divergent member of the transforming growth factor- β (TGF- β) superfamily, also known as macrophage inhibitory cytokine-1 (MIC-1), prostate-derived factor (PDF), placental TGF- β (PTGF- β), placental bone morphogenetic protein, and nonsteroidal anti-inflammatory drug-activated gene-1 (NAG-1). GDF15 expression level is usually low in resting cells, but may be substantially increased following a response to diverse cellular stress signals, such as hypoxia, inflammation, short-wavelength light exposure, acute tissue injury and during cancer progression. The deregulation of GDF15 expression has been associated with

diverse human disease development and cancer progression. The GDF15 level was increased in the serum of patients with various cancers, including melanoma, oral squamous cell carcinoma, and gastrointestinal, colorectal, pancreatic, prostate, breast, and cervical epithelial cancers. GDF15 resulted in higher levels in patients with BMT than in controls. GDF15 may play an anti-tumoral role during the early stages of cancer, but, conversely, it can promote invasiveness and metastatic behaviour at advanced stages, and is involved in the epithelial-mesenchymal transition in tumours [50]. The roles of GDF15 in modulating osteoclast differentiation and in therapy for BMTs from PC have recently been identified [51].

Westhlin et al. described the role of GDF15 in osteoclast differentiation and showed an association between high serum GDF15 level and bone disease in multiple myeloma [52].

A further promising marker for BMT in the multiplex panel is TRAP5. This is one of the most abundant enzymes in osteoclasts and is a well-known marker of osteoclast activity and bone resorption. Elevated TRAP levels are found in many benign metabolic bone diseases such as Paget disease, haemodialysis, primary hyperparathyroidism, and metastatic malignancies involving bone resorption, multiple myeloma and bilateral ovariectomy [53]. TRAP has been found to be elevated in patients with BMTs compared with patients with no BMTs, in patients without treatment (denosumab) compared with the control group, and in patients with extensive BMTs [54, 55]. Recently, TRACP-5b, pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP), N-terminal cross-linking telopeptides of type I collagen (NTX), and bone-specific alkaline phosphatase (BAP) were measured in breast cancer patients with BMTs treated with zoledronic acid or denosumab. Although bone-modifying agents reduced the baseline levels of TRACP-5b, NTX, and BAP significantly, the reduction patterns differed. TRACP-5b appears to affect levels most quickly and sensitively, possibly because of its direct link to the number and activity of osteoclasts [56].

Tumour necrosis factor-related weak inducer of apoptosis is a member of the TNF ligand superfamily and is also a multifunctional soluble

cytokine. TWEAK mRNA and protein have mainly been detected in endothelial cells, activated monocytes and T cells, macrophages, and dendritic cells. The multiple biological effects of TWEAK are mediated by binding to its cognate receptor Fn14 and include cell death, apoptosis, inflammation, angiogenesis, and cell proliferation. For these characteristics, TWEAK is an established key player in the pathogenesis of inflammatory diseases. Serum levels of TWEAK were found to be higher in patients with solid tumour and bone metastatic disease compared with patients without metastases in the bones. TWEAK plays a role in the progression of multiple myeloma and may facilitate bone destruction and solid tumour spread into bones [57].

Finally, higher serum levels of YKL40 (chitinase-3-like protein 1) were found in the bone metastasis groups compared with the controls. YKL40 is secreted by chondrocytes, synovial cells and macrophages and is suspected to play a role in remodelling or degradation of the extracellular matrix [58]. YKL40 has been found to be related to testosterone tissue levels in nipple aspiration fluid of patients with breast cancer and in breast cancer cell lines [59]. It plays a role in inflammation and tissue remodelling in several human diseases. YKL40 is described as being associated with a poor outcome of metastatic PC and non-small cell lung cancer (NSCLC) and a marker for early death in PC. Thus, it could serve as a new prognostic biomarker in patients [60].

Interestingly, when these new markers were compared with “classic” bone markers, such as CTX and PINP, the best marker of BMTs was PINP, whereas the five novel markers surprisingly performed better than CTX [49].

References

1. Fohr B, Dunstan CR, Seibel MJ (2003) Clinical review 165: markers of bone remodeling in metastatic bone disease. *J Clin Endocrinol Metab* 88(11):5059–5075
2. Vasikaran S, Eastell R, Bruyère O, Foldes AJ, Garnero P, Griesmacher A, McClung M, Morris HA, Silverman S, Trenti T, Wahl DA, Cooper C, Kanis JA, IOF-IFCC Bone Marker Standards Working Group (2011) Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treat-

- ment: a need for international reference standards. *Osteoporos Int* 22(2):391–420
3. Schafer AL, Vittinghoff E, Ramachandran R, Mahmoudi N, Bauer DC (2010) Laboratory reproducibility of biochemical markers of bone turnover in clinical practice. *Osteoporos Int* 21(3):439–445
 4. Coleman R, Brown J, Terpos E, Lipton A, Smith MR, Cook R, Major P (2008) Bone markers and their prognostic value in metastatic bone disease: clinical evidence and future directions. *Cancer Treat Rev* 34(7):629–639
 5. Jung K, Lein M (2014) Bone turnover markers in serum and urine as diagnostic, prognostic and monitoring biomarkers of bone metastasis. *Biochim Biophys Acta* 1846(2):425–438
 6. Michaelson MD, Marujo RM, Smith MR (2004) Contribution of androgen deprivation therapy to elevated osteoclast activity in men with metastatic prostate cancer. *Clin Cancer Res* 10(8):2705–2708
 7. Garnero P, Buchs N, Zekri J, Rizzoli R, Coleman RE, Delmas PD (2000) Markers of bone turnover for the management of patients with bone metastases from prostate cancer. *Br J Cancer* 82(4):858–864
 8. Garnero P, Ferreras M, Karsdal MA, Nicamhlaobh R, Risteli J, Borel O, Qvist P, Delmas PD, Foged NT, Delaissé JM (2003) The type I collagen fragments ICTP and CTX reveal distinct enzymatic pathways of bone collagen degradation. *J Bone Miner Res* 18(5):859–867
 9. Costa L, Demers LM, Gouveia-Oliveira A, Schaller J, Costa EB, de Moura MC, Lipton A (2002) Prospective evaluation of the peptide-bound collagen type I cross-links N-telopeptide and C-telopeptide in predicting bone metastases status. *J Clin Oncol* 20(3):850–856
 10. Koizumi M, Yonese J, Fukui I, Ogata E (2001) The serum level of the amino-terminal propeptide of type I procollagen is a sensitive marker for prostate cancer metastasis to bone. *BJU Int* 87(4):348–351
 11. Zafeirakis AG, Papatheodorou GA, Limouris GS (2010) Clinical and imaging correlations of bone turnover markers in prostate cancer patients with bone only metastases. *Nucl Med Commun* 31(3):249–253
 12. Koopmans N, de Jong IJ, Breeuwsma AJ, van der Veer E (2007) Serum bone turnover markers (PINP and ICTP) for the early detection of bone metastases in patients with prostate cancer: a longitudinal approach. *J Urol* 178(3 Pt 1):849–853
 13. Fedarko NS, Jain A, Karadag A, Van Eman MR, Fisher LW (2001) Elevated serum bone sialoprotein and osteopontin in colon, breast, prostate, and lung cancer. *Clin Cancer Res* 7(12):4060–4066
 14. Brown JM, Vessella RL, Kostenuik PJ, Dunstan CR, Lange PH, Corey E (2001) Serum osteoprotegerin levels are increased in patients with advanced prostate cancer. *Clin Cancer Res* 7(10):2977–2983
 15. Mountzios G, Terpos E, Syrigos K, Papadimitriou C, Papadopoulos G, Bamias A, Mavrikakis M, Dimopoulos MA (2010) Markers of bone remodeling and skeletal morbidity in patients with solid tumors metastatic to the skeleton receiving the bisphosphonate zoledronic acid. *Transl Res* 155(5):247–255
 16. Todenhöfer T, Hennenlotter J, Leidenberger P, Wald A, Hohneder A, Kühs U, Mischinger J, Aufderklamm S, Gakis G, Blumenstock G, Stenzl A, Schwentner C (2014) Serum receptor activator of nuclear factor κB ligand (RANKL) levels predict biochemical recurrence in patients undergoing radical prostatectomy. *BJU Int* 113(1):152–159
 17. Metwalli AR, Rosner IL, Cullen J, Chen Y, Brand T, Brassell SA, Lesperance J, Porter C, Sterbis J, McLeod DG (2014) Elevated alkaline phosphatase velocity strongly predicts overall survival and the risk of bone metastases in castrate-resistant prostate cancer. *Urol Oncol* 32(6):761–768
 18. Coleman R, Costa L, Saad F, Cook R, Hadji P, Terpos E, Garnero P, Brown J, Body JJ, Smith M, Lee KA, Major P, Dimopoulos M, Lipton A (2011) Consensus on the utility of bone markers in the malignant bone disease setting. *Crit Rev Oncol Hematol* 80(3):411–432
 19. Kamiya N, Suzuki H, Yano M, Endo T, Takano M, Komaru A, Kawamura K, Sekita N, Imamoto T, Ichikawa T (2010) Implications of serum bone turnover markers in prostate cancer patients with bone metastasis. *Urology* 75(6):1446–1451
 20. Saad F, Eastham JA, Smith MR (2012) Biochemical markers of bone turnover and clinical outcomes in men with prostate cancer. *Urol Oncol* 30(4):369–378
 21. Coleman RE, Major P, Lipton A, Brown JE, Lee KA, Smith M, Saad F, Zheng M, Hei YJ, Seaman J, Cook RJ (2005) Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. *Clin Oncol* 23(22):4925–4935
 22. Cook RJ, Coleman R, Brown J, Lipton A, Major P, Hei YJ, Saad F, Smith MR (2006) Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. *Clin Cancer Res* 12(11 Pt 1):3361–3367.99–100
 23. Smith MR, Cook RJ, Coleman R, Brown J, Lipton A, Major P, Hei YJ, Saad F (2007) Predictors of skeletal complications in men with hormone-refractory metastatic prostate cancer. *Urology* 70(2):315–319
 24. Som A, Tu SM, Liu J, Wang X, Qiao W, Logothetis C, Corn PG (2012) Response in bone turnover markers during therapy predicts overall survival in patients with metastatic prostate cancer: analysis of three clinical trials. *Br J Cancer* 107(9):1547–1553
 25. Jung K, Miller K, Wirth M, Albrecht M, Lein M (2011) Bone turnover markers as predictors of mortality risk in prostate cancer patients with bone metastases following treatment with zoledronic acid. *Eur Urol* 59(4):604–129
 26. Alcaraz A, González-López R, Morote J, de la Piedra C, Meseguer C, Esteban E, Climent M, González-Gragera B, Alvarez-Ossorio JL, Chirivella I, Mellado B, Lara PC, Vázquez F, Contreras JA, Carles J, Murias A, Calderero V, Comet-Batlle J, González-Del Alba A, León-Mateos L, Mañas A, Segarra J, Lassa A, González-Enguita C, Méndez MJ, Samper P, Unda M, Mahillo-Fernández I, Bellmunt J; TUGAMO GROUP (2013) Biochemical markers of bone turn-

- over and clinical outcome in patients with renal cell and bladder carcinoma with bone metastases following treatment with zoledronic acid: the TUGAMO study. *Br J Cancer* 109(1):121–30
27. Brasso K, Christensen JJ, Johansen JS, Teisner B, Garnerø P, Price PA, Iversen P (2006) Prognostic value of PINP, bone alkaline phosphatase, CTX-I, and YKL-40 in patients with metastatic prostate carcinoma. *Prostate* 66(5):503–513
 28. Coleman R, Body JJ, Aapro M et al (2014) Bone health in cancer patients: ESMO Clinical Practice guidelines. *Ann Oncol* 25:1–14. doi:[10.1093/annonc/mdl013](https://doi.org/10.1093/annonc/mdl013)
 29. Bauer D, Krege J, Lane N, Leary E, Libanati C, Miller P, Myers G, Silverman S, Vesper HW, Lee D, Payette M, Randall S (2012) National Bone Health Alliance Bone Turnover Marker Project: current practices and the need for US harmonization, standardization, and common reference ranges. *Osteoporos Int* 23(10):2425–2433
 30. Cavalier E, Bergmann P, Bruyère O, Delanaye P, Durnez A, Devogelaer JP, Ferrari SL, Gielen E, Goemaere S, Kaufman JM, Toukap AN, Reginster JY, Rousseau AF, Rozenberg S, Scheen AJ, Body JJ (2016) The role of biochemical of bone turnover markers in osteoporosis and metabolic bone disease: a consensus paper of the Belgian Bone Club. *Osteoporos Int* 27(7):2181–2195
 31. Wada N, Fujisaki M, Ishii S, Ikeda T, Kitajima M (2001) Evaluation of bone metabolic markers in breast cancer with bone metastasis. *Breast Cancer* 8:131–137
 32. Ulrich U, Rhiem K, Schmolling J, Flaskamp C, Paffenholz I, Salzer H et al (2001) Cross-linked type I collagen C- and N-telopeptides in women with bone metastases from breast cancer. *Arch Gynecol Obstet* 264:186–190
 33. Morra L, Moch H (2011) Periostin expression and epithelial-mesenchymal transition in cancer: a review and an update. *Virchows Arch* 459(5):465–475
 34. Sasaki H, Yu CY, Dai M, Tam C, Loda M, Auclair D, Chen LB, Elias A (2003) Elevated serum periostin levels in patients with bone metastases from breast but not lung cancer. *Breast Cancer Res Treat* 77(3):245–252
 35. Kyutoku M, Taniyama Y, Katsuragi N, Shimizu H, Kunugiza Y, Iekushi K, Koibuchi N, Sanada F, Oshita Y, Morishita R (2011) Role of periostin in cancer progression and metastasis: inhibition of breast cancer progression and metastasis by anti-periostin antibody in a murine model. *Int J Mol Med* 28(2):181–186
 36. Contié S, Voorzanger-Rousselot N, Litvin J, Clézardin P, Garnerø P (2011) Increased expression and serum levels of the stromal cell-secreted protein periostin in breast cancer bone metastases. *Int J Cancer* 128(2):352–360
 37. Bonnet N, Garnerø P, Ferrari S (2015) Periostin action in bone. *Mol Cell Endocrinol*. pii: S0303-7207(15)30170-2. doi:[10.1016/j.mce.2015.12.014](https://doi.org/10.1016/j.mce.2015.12.014)
 38. Kruger TE, Miller AH, Godwin AK, Wang J (2014) Bone sialoprotein and osteopontin in bone metastasis of osteotropic cancers. *Crit Rev Oncol Hematol* 89(2):330–341
 39. Carlinfante G, Vassiliou D, Svensson O et al (2003) Differential expression of osteopontin and bone sialoprotein in bone metastasis of breast and prostate carcinoma. *Clin Exp Metastasis* 20:437–444
 40. Khodavirdi AC, Song Z, Yang S et al (2006) Increased expression of osteopontin contributes to the progression of prostate cancer. *Cancer Res* 66:883–888
 41. Waltregny D, Bellahcene A, Van Riet I, Fisher LW, Young M, Fernandez P et al (1998) Prognostic value of bone sialoprotein expression in clinically localized human prostate cancer. *J Natl Cancer Inst* 90:1000–1008
 42. Bellahcene A, Kroll M, Liebens F, Castronovo V (1996) Bone sialoprotein expression in primary human breast is associated with bone metastases development. *J Bone Miner Res* 11:665–670
 43. Uccello M, Malaguarnera G, Vacante M, Motta M (2011) Serum bone sialoprotein levels and bone metastases. *J Cancer Res Ther* 7:115–119
 44. Jain A, McKnight DA, Fisher LW, Humphreys EB, Mangold LA, Partin AW et al (2009) Small integrin-binding proteins as serum markers for prostate cancer detection. *Clin Cancer Res* 15:5199–5207
 45. Ferreira A, Alho I, Casimiro S, Costa L (2015) Bone remodeling markers and bone metastases: from cancer research to clinical implications. *Bonekey Rep* 4:668
 46. Larson SR, Zhang X, Dumpit R, Coleman I, Lakely B, Roudier M, Higano CS, True LD, Lange PH, Montgomery B, Corey E, Nelson PS, Vessella RL, Morrissey C (2013) Characterization of osteoblastic and osteolytic proteins in prostate cancer bone metastases. *Prostate* 73(9):932–940
 47. D'Amelio P, Roato I, Oderda M, Soria F, Zitella A, Ferracini R, Mengozzi G, Gontero P, Isaia GC (2014) DKK-1 in prostate cancer diagnosis and follow up. *BMC Clin Pathol* 14(1):11
 48. Roato I, D'Amelio P, Gorassini E, Grimaldi A, Bonello L, Fiori C, Delsedime L, Tizzani A, De Libero A, Isaia G, Ferracini R (2008) Osteoclasts are active in bone forming metastases of prostate cancer patients. *PLoS One* 3(11):e3627
 49. Windrichova J, Fuchsova R, Kucera R, Topolcan O, Fiala O, Finek J, Slipkova D, Karlikova M, Svobodova J (2016) Testing of a novel cancer metastatic multiplex panel for the detection of bone-metastatic disease – a pilot study. *Anticancer Res* 36(4):1973–1978
 50. Li C, Wang J, Kong J, Tang J, Wu Y, Xu E, Zhang H, Lai M (2016) GDF15 promotes EMT and metastasis in colorectal cancer. *Oncotarget* 7(1):860–872
 51. Vanhara P, Hampl A, Kozubik A, Soucek K (2012) Growth/differentiation factor-15: prostate-cancer suppressor or promoter? *Prostate Cancer Prostatic Dis* 15:320–328

52. Westhlin M, Moen SH, Holien T, Mylin AK, Heickendorff L, Olsen OE, Sundan A, Turesson I, Gimsing P, Waage A, Standal T (2015) Growth differentiation factor 15 (GDF15) promotes osteoclast differentiation and inhibits osteoblast differentiation and high serum GDF15 levels are associated with multiple myeloma bone disease. *Haematologica* 100:e511–e514
53. Halleen JM, Tiitinen SL, Ylipahkala H, Fagerlund KM, Vaananen HK (2006) Tartrate-resistant acid phosphatase 5b (TRACP5b) as a marker of bone resorption. *Clin Lab* 52:499–509
54. Sarvari BK, Sankara Mahadev D, Rupa S, Mastan SA (2015) Detection of bone metastases in breast cancer (BC) patients by serum tartrate-resistant acid phosphatase 5b (TRACP 5b), a bone resorption marker and serum alkaline phosphatase (ALP), a bone formation marker, in lieu of whole-body skeletal scintigraphy with technetium99m MDP. *Indian J Clin Biochem* 30:66–71
55. Tang C, Liu Y, Qin H, Li X, Guo W, Li J, Wang W, Qu L, Hu H, Xu C, Zheng L, Huang Y, Liu B, Gao H, Halleen JM, Liu X (2013) Clinical significance of serum BAP, TRACP 5b and ICTP as bone metabolic markers for bone metastasis screening in lung cancer patients. *Clin Chim Acta* 426:102–107
56. Nishimukai A, Higuchi T, Ozawa H, Yanai A, Miyagawa Y, Murase K, Imamura M, Takatsuka Y, Miyoshi Y (2016) Different patterns of change in bone turnover markers during treatment with bone-modifying agents for breast cancer patients with bone metastases. *Breast Cancer*. doi:10.1007/s12282-016-0695-2
57. Mehta RS, Chong DQ, Song M, Meyerhardt JA, Ng K, Nishihara R, Qian Z, Morikawa T, Wu K, Giovannucci EL, Fuchs CS, Ogino S, Chan AT (2015) Association between plasma levels of macrophage inhibitory cytokine-1 before diagnosis of colorectal cancer and mortality. *Gastroenterology* 149:614–622
58. Volck B, Price PA, Johansen JS, Sorensen O, Benfield TL, Nielsen HJ, Calafat J, Borregaard N (1998) YKL40, a mammalian member of the chitinase family, is a matrix protein of specific granules in human neutrophils. *Proc Assoc Am Physicians* 110:351–360
59. Shidfar A, Fatokun T, Ivancic D, Chatterton RT, Khan SA, Wang J (2016) Protein biomarkers for breast cancer risk are specifically correlated with local steroid hormones in nipple aspirate fluid. *Horm Cancer* 7(4):252–259
60. Thom I, Andritzky B, Schuch G, Burkholder I, Edler L, Johansen JS, Bokemeyer C, Schumacher U, Laack E (2010) Elevated pretreatment serum concentration of YKL40 — an independent prognostic biomarker for poor survival in patients with metastatic nonsmall cell lung cancer. *Cancer* 116:4114–4121

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