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Guidelines for the correct use of the nomenclature of biochemical indices of bone status: a position statement of the IFCC Committee on Bone Metabolism and the Joint IOF Working Group and IFCC Committee on Bone Metabolism

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Abstract

The presented guidelines are an update of the position paper, endorsed by the International Osteoporosis Foundation (IOF), on nomenclature of bone markers published over 2 decades ago. Novel insight into bone biology and pathophysiology of bone disorders has highlighted the increasing relevance of new and known mediators implicated in various aspects of bone metabolism. This updated guideline proposes the nomenclature Bone Status Indices (BSI) as the comprehensive classification rather than bone turnover markers, bone markers or metabolic markers of bone turnover, that are currently in use for the implicated molecules. On behalf of the IFCC Committee on Bone Metabolism and the Joint IOF Working Group and IFCC Committee on Bone Metabolism, the authors propose standardized nomenclature, abbreviations and measurement units for the bone status indices.

Keywords

Bone status indices, standardization, nomenclature

Introduction

In 2000, Pierre D. Delmas, during his term in office as the President of the International Osteoporosis Foundation (IOF), together with a group of other experts, authored an IOF endorsed position paper proposing the standardisation of the nomenclature of bone markers [1]. The main aim of the paper, also published in Clinical Chemistry, was "*to avoid confusion in the literature, given the growing number of various assays, especially for measurement of bone resorption*" [2,3]. Until today, the objective of consistency and uniformity in the use of the nomenclature proposed by Delmas has not been realized. Laboratories continue to use the terms and abbreviations at their own discretion without consistency or uniformity. Furthermore, there is a lack of standardisation in naming of new markers, especially several regulatory molecules, for which various terms have been used in studies to name the same markers. An example is given by osteocalcin, that is also called bone gla-protein, and is abbreviated as OC, OCN, BGLAP [4]. This inconsistency, along with the rejection, in practice, by some journals, to use the proposed nomenclature, has compelled authors to report the various aliases pertaining to the marker studied. In the era of big data sharing, it is inconceivable that either a molecule can be called differently, or different molecules share the same name. Again, the example comes from osteocalcin: it can exist in different forms with a different degrees of carboxylation, from zero to three, however these forms are overall called osteocalcin or, sometimes, uncarboxylated or undercarboxylated osteocalcin [4]. Further, the abbreviation CTX-I (carboxyterminal collagen type I crosslinks) often is used indiscriminately to indicate α-CTX-I, β-CTX-I and the CTX generated by matrix metalloproteinases activity [5]. The need for uniformity in nomenclature is driven by the need for comparability of the results among studies. These and other factors justify the need for an update and revision of the previous position paper.

The first step in standardising nomenclature is the provision of a collective names for these indices. A considerable body of literature refers to these markers as "bone turnover markers", "bone markers" or "metabolic markers of bone turnover". Each idiom contemplates specific, but not comprehensive, aspects of the functions of the molecules involved. Indeed, the term "turnover", indeed, specifically identifies a process of replacement of "old", functionally impaired (or less efficient) components by newly synthesised molecules and is mainly associated with structural elements [6]. On the other hand, the term "metabolic" refers to the anabolic-versus-catabolic activity of bone cells. Even in this case it refers to the structural and enzymological aspects, completely excluding any regulatory, hormonal, and elemental mediators [6]. Finally, these terms include only bone-derived molecules disregarding indices or mediators originating from other tissues and yet importantly affecting bone cell metabolism and bone matrix turnover are considered.

Based on these considerations we propose the alternative term Bone Status Indices (BSIs) to better embrace the entire set of molecules, including structural components, side products of either anabolic and catabolic activities, regulatory molecules, enzymatic activities, and hormones that altogether contribute to defining the status of the skeleton.

The current advances in automation and the inflexibility of laboratory software in usable characters for acronyms are other aspects to be considered. As these acronyms will be

included in laboratory reports, uniformity will help readers, patients and physicians by simplifying the retrieval of related information from specialised sources and avoid potential misunderstanding and erroneous interpretations.

The updated guidelines thus take into consideration all those additional indices that are related to bone status but do not originate from the bone.

Finally, the issue of measurement units, although not directly related to the nomenclature is associated to the need of standardisation of laboratory reports. As for indices' names, the units frequently used mostly reflect habits, often at the national level, and very often do not adhere to the standards of the International System of Units (SI).

The aim of this report, written on behalf of the International Federation of Clinical Chemistry (IFCC) Committee on Bone Metabolism and the International Osteoporosis Foundation (IOF)-IFCC Working Group on Standardisation of Bone Marker Assays, is to propose a comprehensively revised nomenclature of the BSIs with appropriate abbreviations as well as the correct measurement unit, based on the indication of the SI. As described above, the field of bone-related markers has been enlarged, in the last years, to newly discovered molecules and also to already known mediators with newly discovered roles in bone structure and metabolism. Most of these are currently used in diagnostics while others have a diagnostic potential that might justify their clinical implementation in the future. Therefore, since the variety of roles and origin of the components which measurements are useful in determining the bone status, nomenclature and related issues will be treated separately for two main groups of markers: i.e., i) bone turnover markers, and ii) regulatory molecules.

Recommended nomenclature for Bone Status Indices (BSIs)

Bone status indices (BSIs) have been categorised based on the general process they belong to: i) bone turnover markers, or ii) regulatory molecules.

Table 1 reports the main information related to grouping, nomenclature and recommended units of measurement.

Table 1. Recommended nomenclature (and related acronyms), grouping and measurement unit for BSIs

Category	Group/Family	Recommended name [UniProt/Expasy recommended name, UniProt/Expasy/PubChem ID]*	Used acronyms (acronyms marked with ** are explained in the footnote)	Recommended acronym	Recommended unit
Bone turnover markers	Type I collagen propeptides	Procollagen type I N-propeptide	PINP, P1NP	PINP	µg/L
		Intact procollagen type I N-propeptide (trimer)	intact PINP, intact P1NP, iPINP, iP1NP	iPINP	µg/L
		Procollagen type I N-propeptide (trimer + monomer)	total PINP, total P1NP, tPICP, tP1CP	tPINP	µg/L
		Procollagen type I C-propeptide	PICP, P1CP	PICP	µg/L
	Type I collagen cross-linked telopeptides	N-terminal telopeptide of type I collagen	NTX-I, NTX-1, NTx-I, NTx-1	NTX-I	µg/L
		α-isomerized C-terminal telopeptide of type I collagen	α-CTX-I, α-CTx-I, α-CTX-1, α-CTx-1, αCTX-I, αCTx-I, αCTX-1, αCTx-1, alphaCTX-I, alphaCTx-I, alphaCTX-1, alphaCTx-1	α-CTX-I (a-CTX-1)*****	µg/L
		β-isomerized C-terminal telopeptide of type I collagen	β-CTX-I, β-CTx-I, β-CTX-1, β-CTx-1, βCTX-I, βCTx-I, βCTX-1, βCTx-1, betaCTX-I, betaCTx-I, betaCTX-1, betaCTx-1, crosslaps, beta crosslaps	β-CTX-I (b-CTX-1)*****	ng/L
		C-terminal cross-linking telopeptide of type I collagen generated by MMPs (matrix metalloproteinases)	CTX-MMP, ICTP	CTX-MMP	µg/L
Regulatory molecules	Alkaline Phosphatase	(total tissue non-specific) alkaline phosphatase [UniProt: Alkaline phosphatase, tissue-nonspecific isozyme-P05186]	ALP, tnsALP, AP, TNAP	ALP	U/L
		Bone-specific alkaline phosphatase (mass concentration)	BALP, bone ALP, BAP, BSAP	BALP	µg/L
		Bone-specific alkaline phosphatase (catalytic activity)			U/L
	Acid Phosphatase	Acid phosphatase [UniProt: Tartrate-resistant acid phosphatase type 5-P13686]	ACP	ACP	U/L
		Tartrate-resistant acid phosphatase isoform 5b	TRACP5b, TRAP5b	TRACP5b	U/L

	[UniProt: Tartrate-resistant acid phosphatase type 5-P13686]			
Osteocalcin forms***	Osteocalcin (total)	OC, OCN, BGLAP, B-GLAP, bone-Gla-protein	OC	µg/L
	Intact osteocalcin [UniProt: Osteocalcin-P02818]	iOC, intact OC	iOC	µg/L
	N-mid fragment of osteocalcin	NmidOC, Nmid-OC, N-ter–mid OC	NmidOC	µg/L
	Fully carboxylated osteocalcin	/	γ_3OC (g_3OC)*****	µg/L
	Undercarboxylated osteocalcin	/	γ_2OC (g_2OC)***** γ_1OC (g_1OC)*****	µg/L
	Uncarboxylated osteocalcin	/	uγOC (g_0OC)*****	µg/L
Vitamin D metabolites	Vitamin D (total) vitamin D_2 (ergocalciferol, PubChem CID: 5280793) vitamin D_3 (cholecalciferol, PubChem CID: 5280795)	vitD $vitD_2$ $vitD_3$	vitD $vitD_2$ $vitD_3$	nmol/L, µg/L
	Calcidiol 25-(OH) vitamin D (total) 25-(OH) vitamin D_2 (25-hydroxyergocalciferol, PubChem CID: 5710148) 25-(OH) vitamin D_3 (25-hydroxycholecalciferol, PubChem CID: 5283731)	25-(OH)D 25-(OH)D_2 25-(OH)D_3	25-(OH)D 25-(OH)D_2 25-(OH)D_3	nmol/L, µg/L
	Free calcidiol Free 25-(OH) vitamin D (total) free 25-(OH) vitamin D_2 (free 25-hydroxyergocalciferol, PubChem CID: 5710148) free 25-(OH) vitamin D_3 (free 25-hydroxycholecalciferol, PubChem CID: 5283731)	f25-(OH)D f25-(OH)D_2 f25-(OH)D_3	f25-(OH)D f25-(OH)D_2 f25-(OH)D_3	pmol/L, ng/L
	Calcitriol 1,25-$(OH)_2$ vitamin D (total) 1,25-$(OH)_2$ vitamin D_2 (1,25-dihydroxyergocalciferol, PubChem CID: 129846083) 1,25-$(OH)_2$ vitamin D_3 (1,25-dihydroxycholecalciferol, PubChem CID: 5280453)	1,25-$(OH)_2$D 1,25-$(OH)_2D_2$ 1,25-$(OH)_2D_3$	1,25-$(OH)_2$D 1,25-$(OH)_2D_2$ 1,25-$(OH)_2D_3$	pmol/L, ng/L
	Free calcitriol	f1,25-$(OH)_2$D	f1,25-$(OH)_2$D	pmol/L, ng/L

	Free 1,25-$(OH)_2$ vitamin D (total) free 1,25-$(OH)_2$ vitamin D_2 (free 1,25-dihydroxyergocalciferol, PubChem CID: 129846083) free 1,25-$(OH)_2$ vitamin D_3 (free 1,25-dihydroxycholecalciferol, PubChem CID: 5280453)	f1,25-$(OH)_2D_2$ f1,25-$(OH)_2D_3$	f1,25-$(OH)_2D_2$ f1,25-$(OH)_2D_3$	
	24,25-$(OH)_2$ vitamin D (total) 24,25-$(OH)_2$ vitamin D_2 ((24R)-dihydroxyergocalciferol, PubChem CID: 6438393) 24,25-$(OH)_2$ vitamin D_3 ((24R)-dihydroxycholecalciferol, (24R)-hydroxycalcidiol, PubChem CID: 6434253)	24,25-$(OH)_2$D 24,25-$(OH)_2D_2$ 24,25-$(OH)_2D_3$	24,25-$(OH)_2$D 24,25-$(OH)_2D_2$ 24,25-$(OH)_2D_3$	nmol/L, µg/L
	3-epi-25-(OH) vitamin D (total) 3-epi-25-(OH) vitamin D_2 (3-epi-25-hydroxyergocalciferol, PubChem CID: 585790) 3-epi-25-(OH) vitamin D_3 (3-epi-25-hydroxycholecalciferol, PubChem CID: 13080214)	3-epi-25-(OH)D 3-epi-25-(OH)D_2 3-epi-25-(OH)D_3	3-epi-25-(OH)D 3-epi-25-(OH)D_2 3-epi-25-(OH)D_3	nmol/L, µg/L
	1,24,25-$(OH)_3$ vitamin D (total) 1,24,25-$(OH)_3$ vitamin D_2 (1,24,25-trihydroxyergocalciferol, PubChem CID: 9547253) 1,24,25-$(OH)_3$ vitamin D_3 (1,24,25-trihydroxycholecalciferol, PubChem CID: 6439591)	1,24,25-$(OH)_3$D 1,24,25-$(OH)_3D_2$ 1,24,25-$(OH)_3D_3$	1,24,25-$(OH)_3$D 1,24,25-$(OH)_3D_2$ 1,24,25-$(OH)_3D_3$	pmol/L, ng/L
	25-(OH) vitamin D-26,23-lactone (total) 25-(OH) vitamin D_2-26,23-lactone 25-(OH) vitamin D_3-26,23-lactone	25-(OH)D-26,23-lactone 25-(OH)D_2-26,23-lactone 25-(OH)D_3-26,23-lactone	25-(OH)D-26,23-lactone 25-(OH)D_2-26,23-lactone 25-(OH)D_3-26,23-lactone	nmol/L, µg/L
	Vitamin D-binding protein [UniProt: Vitamin D-binding protein-P02774]	VDBP, VBP, VitD-BP, DBP, VDB	VDBP	µmol/L
Parathyroid hormone	Parathyroid hormone (previously intact PTH) [UniProt: Parathyroid hormone-P01270]	PTH, intact PTH, iPTH	PTH	pmol/L
	1-84 Parathyroid hormone	1-84PTH, PTH1-84, PTH(1-84)	1-84PTH	pmol/L
Fibroblast growth factor 23	Intact Fibroblast Growth Factor 23 [UniProt: Fibroblast growth factor 23-Q9GZV9]	iFGF23, intact FGF23	iFGF23	ng/L
	C-terminal FGF23	cFGF23, C-terminal FGF23, C-ter FGF23	cFGF23	RU/L****
Wnt signalling pathway inhibitors	Sclerostin [UniProt: Sclerostin-Q9BQB4]	sclerostin, SOST	Sclerostin	ng/L

		Dickkopf-related protein 1 [UniProt: Dickkopf-related protein 1-O94907]	Dkk-1, Dkk1, DKK-1, DKK1	DKK-1	ng/L
	Tumour necrosis factor superfamily	Receptor activator of nuclear factor κB ligand [UniProt: Tumor necrosis factor ligand superfamily member 11-O14788]	RANKL, TNFSF11**, TRANCE**, OPGL**, ODF**	RANKL	ng/L
		Receptor activator of nuclear factor κB [UniProt: Tumor necrosis factor receptor superfamily member 11A-Q9Y6Q6]	RANK, TNFRSF11A**, TRANCE receptor	RANK	µg/L
		Osteoprotegerin [UniProt: Tumor necrosis factor receptor superfamily member 11B-O00300]	OPG, TNFRSF11B**, OCIF*	OPG	ng/L
	Factors involved in cell migration and adhesion	Secreted protein acidic and rich in cysteine [UniProt: SPARC-P09486]	SPARC, osteonectin, ON**, BM-40**	SPARC	ng/L
		Osteopontin [UniProt: Osteopontin-P10451]	OPN, BSP-1**, BNSP**, ETA-1**, SPP1**, Ric**	OPN	ng/L
		Periostin [UniProt: Periostin-Q15063]	PSTN, POSTN, PN, OSF-2**	PSTN	ng/L
		Periostin fragment generated by cathepsin K	kPSTN, kPOSTN	kPSTN	µg/L
	Osteoclast enzymes	Cathepsin K [UniProt: Cathepsin K-P43235]	CTSK	CTSK	µg/L

**If available

**TNFSF11: tumour necrosis factor ligand superfamily member 11; TRANCE: TNF-related activation-induced cytokine; OPGL: osteoprotegerin ligand; ODF: osteoclast differentiation factor; TNFRSF11A: tumour necrosis factor receptor superfamily member 11A; TNFRSF11B: tumour necrosis factor receptor superfamily member 11B; OCIF: osteoclastogenesis inhibitory factor; ON: osteonectin; BM-40: basement-membrane protein 40; BSP-1: bone sialoprotein 1; BNSP: bone sialoprotein; ETA-1: early T-lymphocyte activation 1; SPP1: secreted phosphoprotein 1; Ric: Rickettsia resistance; OSF-2: osteoblast-specific factor 2.

*** nomenclature is referred to the commercially available assays

**** this is a procedure-defined unit

***** in case the IT system does not allow to use the Greek letters, it possible to substitute them with the Latin counterpart

Comments to the Table

Here are some considerations that should be taken into account for a correct contextualization of the information reported in Table 1.

- CTX-I corresponds to the C-terminal octapeptide sequence of α1 chain of type I collagen (EKAHDGGR) [7]. β-CTX-I (EKAHD-β-GGR) results from the β-isomerization of αCTX-I, i.e., transfer of the peptide bound between aspartic acid (D) residues and the adjacent amino acid from the α-carboxyl group to the β-carboxyl group. The ratio between native (αCTX-I) and isomerized β-CTX-I estimates the extent of type I collagen isomerization in bone. Due to high turnover, in growing subjects, the equilibrium of isomerization cannot be achieved, resulting in a relatively higher α/β-CTX-1; once reached the peak bone mass (>20 years of age) since the rate of bone remodeling is slower than isomerization, the equilibrium is achieved, resulting in a fairly constant α/β CTX ratio [8]. aCTX-I and bCTX-I can be used in case the IT system does not allow to use the Greek letters
- The term CTX-I-MMP is recommended instead of C-terminal telopeptide of type 1 collagen (ICTP).
- The CTX-I-MMP epitope (GPPSAGFDFSFLPQPPQEKAHDGGR) is a larger conformational epitope, than CTX-I, including at least two telopeptides and the first phenylalanine (F) of the phenylalanine rich region; cathepsin K degrades CTX-I-MMP to generate CTX-I [9].
- BALP as an enzyme, the activity should be measured. However, due to the heterogeneity of the commercially available assay kits, measurement in terms of mass concentration are acceptable. Based on UK-NEQAS results, U/L can be converted into µg/L, and *vice versa*, according to the following equations [10]:
  µg/L= U/L*0.504
  U/L= µg/L*1.984
- Osteocalcin exists in the circulation in different forms, associated with a different degree of carboxylation and/or resulting from proteolytic cleavage that can be assessed by different assays [4]. Therefore, the term osteocalcin (OC) refers to the total amount of OC, i.e., the sum of intact and fragmented OC fractions regardless of their degree of carboxylation. The terms iOC and NmidOC refers only to the intact and the N-terminal plus the mid-fragment (the most abundant circulating fragment), respectively. Regarding the carboxylation in position γ ("g" can be used in case the IT system does not allow to use the Greek letters) of the glutamic acid residues (19, 21 and 24), the two limit forms should be named γ_3OC (g_3OC), the fully carboxylated one, and uγOC (g_0OC), the fully uncarboxylated one. Finally, the intermediate forms of carboxylation, i.e., those bearing either 1 or 2 carboxylic groups, should be named γ_1OC (g_1OC) and γ_2OC (g_2OC), respectively, regardless of the position of the glutamic acid residue(s) within the protein sequence.
- Vitamin D metabolites mass concentration must be expressed as nmol/L or µg/L and pmol/L or ng/L, according to [11]. Traditional units, such as ng/mL or pg/mL should be avoided however, it should be kept in mind that ng/mL= µg/L and pg/mL= ng/L. Vitamin D metabolites ratios (VMRs) are calculated parameters. It is recommended to measure both analytes simultaneously in one sample using the same analytical

technique, preferably LC-MS/MS [12]. To unify VMRs' results expression we recommend expression % for the following VMRs, although recently often used ratios are opposite to and in absolute values [13]. The term VMR is often used for 24,25-$(OH)_2$D/25-(OH)D ratio but due to possible confusion with others VMRs, the metabolite type should be always mentioned e.g. VMR(24,25/25) [14,15].
Use mass concentration units for VMR calculations.
VMR(24,25/25)= 24,25-$(OH)_2$D/25-(OH)D*100 (in %)
VMR(1,25/25)= 1,25-$(OH)_2$D/25-(OH)D*100 (in %)
VMR(1,25/24,25)= 1,25-$(OH)_2$D/24,25-$(OH)_2$D*100 (in %)

Analyte	**MW**	**To convert from µg/L (ng/mL) to nmol/L or from ng/L (pg/mL) to pmol/L multiply by factor below**
vitamin D_2 (ergocalciferol)	396.60	2.52
vitamin D_3 (cholecalciferol)	384.60	2.60
25-(OH) vitamin D_2	412.60	2.42
25-(OH) vitamin D_3	400.64	2.50
free 25-(OH) vitamin D_2	412.60	2.42
free 25-(OH) vitamin D_3	400.64	2.50
1,25-$(OH)_2$ vitamin D_2	428.60	2.33
1,25-$(OH)_2$ vitamin D_3	416.60	2.40
free 1,25-$(OH)_2$ vitamin D_2	428.60	2.33
free 1,25-$(OH)_2$ vitamin D_3	416.60	2.40
24,25-$(OH)_2$ vitamin D_2	429.00	2.33
24,25-$(OH)_2$ vitamin D_3	416.63	2.40
3-epi-25-(OH) vitamin D_2	412.65	2.42
3-epi-25-(OH) vitamin D_3	400.64	2.50
1,24,25-$(OH)_3$ vitamin D_2	444.64	2.25
1,24,25-$(OH)_3$ vitamin D_3	432.60	2.31
25-(OH) vitamin D_2-26,23-lactone	440.60	2.27
25-(OH) vitamin D_3-26,23-lactone	428.60	2.25

- Intact PTH is a misleading term now and should no longer be used. Parathyroid hormone (PTH) term includes 2nd generation PTH assays (intact PTH) that use detection antibodies against N-terminus (amino acids 12–24 or 26–32). For immunoassays, the term 1-84PTH is reserved for 3rd generation PTH assays (bioactive PTH or whole PTH) that use detection antibodies against N-terminus (amino acids 1–4). These assays also cross-react with amino-PTH. PTH and 1-84 PTH assays results differ significantly, at least in standards used and therefore we recommend to use terms PTH for 2nd generation PTH assays and 1-84 PTH for 3rd generation PTH assays. For fragments measured by LC-MS/MS or HRMS, the measured fragments should be stated in brackets e.g. (x-y)PTH. Use following PTH conversion factors:
  pmol/L= pg/mL*0.106045 and pg/mL= pmol/L*9.43
- nM BCE stays for nmoL of Bone Collagen Equivalents

Conclusions

In this paper, we propose a revised guideline for the nomenclature of circulating markers useful to monitor both the metabolic activity of bone cells and the regulatory mediators that intervene in different aspects of bone cell biology, from differentiation, to migration, mechanosensing, mineral metabolism, and extracellular matrix dynamics.

Considering the diverse role of these compounds, the general terms bone turnover markers and metabolic markers of bone turnover no longer fully cover their biological roles. Therefore, the term Bone Status Indices (BSIs) is proposed as a more comprehensive terminology.

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