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SCHOLARLY REVIEW

An Opinion on the Interpretation of Bone Turnover Markers Following Acute Exercise or Nutrition Intervention and Considerations for Applied Research

Mark J. Hutson[1] **and Ian Varley**[2]
[1]School of Sport, Faculty of Life and Health Sciences, Ulster University, Coleraine, United Kingdom; [2]School of Science and Technology, Nottingham Trent University, Nottingham, United Kingdom

It is important for athlete and public health that we continue to develop our understanding of the effects of exercise and nutrition on bone health. Bone turnover markers (BTMs) offer an opportunity to accelerate the progression of bone research by revealing a bone response to exercise and nutrition stimuli far more rapidly than current bone imaging techniques. However, the association between short-term change in the concentration of BTMs and long-term bone health remains ambiguous. Several other limitations also complicate the translation of acute BTM data to applied practice. Importantly, several incongruencies exist between the effects of exercise and nutrition stimuli on short-term change in BTM concentration compared with long-term bone structural outcomes to similar stimuli. There are many potential explanations for these inconsistencies, including that short-term study designs fail to encompass a full remodeling cycle. The current article presents the opinion that data from relatively acute studies measuring BTMs may not be able to reliably inform applied practice aiming to optimize bone health. There are important factors to consider when interpreting or translating BTM data and these are discussed.

Keywords: bone metabolism, bone health, bone remodeling

There is a growing need within sports and exercise science to improve our understanding of how exercise and nutrition influence bone health. Osteoporosis is a disease characterized by low bone mineral density (BMD) and millions suffer osteoporotic fracture each year (primarily the elderly and postmenopausal women), costing $17.9 and £4 billion to U.S. and U.K. health care systems, respectively (Clynes et al., 2020). Low BMD is also prevalent in endurance-based athletes, in 28% of adolescent female runners (Barrack et al., 2008) and 89% of male masters cyclists (Nichols & Rauh, 2011), increasing the risk of bone injury and early onset osteoporosis. For example, it has been shown that up to 21% of female distance runners experience at least one bone stress injury per year (Barrack et al., 2014; Hutson, O'Donnell, Petherick, et al., 2021; Scofield & Hecht, 2012). Exercise and nutrition are known to influence bone health; however, it takes at least several months for stimuli to result in observable change in bone mass using the gold standard method of dual-energy X-ray absorptiometry (Ahola et al., 2009). Therefore, high-quality studies measuring bone using dual-energy X-ray absorptiometry bear a high time demand, the effects of specific practices are difficult to categorically confirm, and research progression is slow. Bone turnover markers (BTMs) offer the potential to reveal bone responses immediately postexercise (acute) and within days (short term) of a given exercise or nutrition intervention in the rested state (Smith et al., 2021). For this reason, it is tempting to consider that BTMs may be used to accelerate bone research in sport and exercise science. This article provides an important opinion on the extent to which acute and short-term BTM responses to exercise and nutrition intervention may be relied upon to inform applied practice aiming to optimize bone health during developmental and older years in athletes and nonathletes.

Bone Turnover Markers

BTMs are typically products or signaling molecules released into the circulation during one or more stages of osteoblastic bone formation or osteoclastic bone resorption (Shetty et al., 2016; see Table 1 for more detail on specific markers). They are often measured in plasma, serum, or urine to determine the rate of these processes on a systemic level at the time of measurement. The fact that studies measuring BTMs can be much shorter in duration compared with studies using imaging techniques allows for tighter control of extraneous variables, reduces participant burden, and lowers the risk of participant dropout. Nevertheless, several laboratory visits are required under strict control. BTMs also provide mechanistic information regarding bone cell activity and data may be used to inform and justify larger scale long-term intervention studies. Furthermore, BTMs do not necessarily incur the same equipment purchase and maintenance costs of radiological scanning. These are some of the factors that have led to a growth in the use of BTMs in sport and exercise science; however, ambiguity remains over their association with bone mass change (Bennell et al., 1997).

A bone remodeling cycle begins with osteoclastic bone resorption lasting up to 27 days, followed by several days of reversal until coupled osteoblast activity forms new osteoid bone in the resorptive cavity, which then becomes mineralized, with the entire cycle lasting >100 days (Agerbæk et al., 1991). BTMs provide a snapshot of the rate of bone formation and resorption at the time of measurement, and typical pretest–posttest study designs are much too short in duration to capture a complete cycle at any remodeling site initiated during the intervention. Outcomes will also be

Varley https://orcid.org/0000-0002-3607-8921
Hutson (m.hutson@ulster.ac.uk) is corresponding author, https://orcid.org/0000-0003-0064-6314

influenced by remodeling cycles that were initiated prior to study entry. Detailed reviews of the many available BTMs and associated limitations exist elsewhere (Hlaing & Compston, 2014; Vasikaran et al., 2011). BTMs are measured systemically whereas bone remodeling is highly localized and site-specific, at least in response to mechanical loading (Hart et al., 2017), and some can lack specificity to either the process of formation or resorption (or even bone tissue itself; Table 1). Unlike the loss or gain of bone tissue measured via imaging techniques, there is no consensus as to what constitutes a meaningful change in any BTM in response to exercise or nutrition intervention. Several factors are known to influence the accurate measurement of BTMs, including circadian and seasonal variation, diet and exercise, disease and medication, hormonal status, intrinsic day-to-day variations, renal function, blood flow, and sampling procedures and type (blood or urine; Hlaing & Compston, 2014). A summary of BTMs most frequently used in the studies cited herein is provided in Table 1; however, for the purpose of this article, findings will mostly be described in terms of the processes of bone formation and resorption rather than the specific marker(s) measured.

Effects of Exercise on Bone

The effects of habitual exercise on bone health are well documented (Santos et al., 2017). Cross-sectional (Nilsson et al., 2009; Tenforde & Fredericson, 2011; Varley et al., 2021) and longitudinal intervention studies (Evans et al., 2012; Nilsson et al., 2012; Weidauer et al., 2012) have repeatedly shown the benefit of weight-bearing exercise (including running) on BMD and bone structure.

Table 1 A Summary of Several Bone Turnover Markers Commonly Used in Exercise and Nutrition Research

Marker (abbreviation)	Origin	Main activity	Comments
Bone formation			
Amino-terminal propeptide of Type I collagen (P1NP) Carboxy-terminal propeptide of Type 1 collagen (P1CP)	N-terminal extension peptide of Type 1 collagen precursor molecule. C-terminal extension peptide of Type 1 collagen precursor molecule.	P1NP and P1CP are both cleaved from newly synthesized Type 1 collagen following secretion into the extracellular space and released into the bloodstream.	P1NP is the international reference standard marker of bone formation and the most used marker of bone formation in the studies cited in the current article. P1NP and P1CP are formed following the synthesis of newly formed Type 1 collagen in other tissues (e.g., skin, dentin, cornea, vessels, fibrocartilage, and tendons) as well as bone.
Osteocalcin (OC)	Noncollagenous protein secreted by osteoblasts.	OC encompasses both carboxylated (cOC) and undercarboxylated (ucOC) forms. cOC binds to hydroxyapatite and increased concentrations have previously been used as a marker of increased bone formation. ucOC does not bind to hydroxyapatite. It is predominantly released into the circulation and is proposed to have various endocrine functions. It has been used as a marker of bone formation, such that increased levels reflect decreased bone formation.	cOC fragments bound to hydroxyapatite within the bone matrix are released into the circulation during bone formation. It is suggested that ucOC is involved in several processes in an endocrine manner, including glucose homeostasis. OC may be measured in its various forms, or as total OC, but it may be that none are markers of bone formation specifically, and may be influenced by bone formation, resorption, and several other metabolic processes.
Bone alkaline phosphatase (BAP)	Bone-specific isoform of a membrane-bound glycoprotein. Found on outer surface of osteoblasts.	Hydrolysis of mineralization inhibitor pyrophosphate and adenosine triphosphate, forming inorganic phosphate accumulation and promoting hydroxyapatite mineralization.	Bone alkaline phosphatase is considered a highly bone- specific marker of bone formation; however, available assays exhibit some cross-reactivity with other alkaline phosphatase isoforms (e.g., liver).
Bone resorption			
Carboxy-terminal telopeptide of Type 1 collagen, β-isomer (β-CTx) Amino-terminal telopeptide of Type 1 collagen (NTx)	Telopeptides found on the C-terminal and N-terminal of tropocollagen molecules.	Forms cross-links between peptides within or between adjacent tropocollagen molecules, and are cleaved and released into the circulation during collagen breakdown.	β-CTx is the international reference standard marker of bone resorption and the most used marker of bone resorption in the studies cited in the current article. β-CTx and NTx are involved in cross-link formation in other collagen-based structures. Other collagen telopeptide bone markers exist that reflect different types of cross-links (e.g., carboxy-terminal cross-linked telopeptide of Type 1 procollagen) and various isoforms of specific cross-links (e.g., α-CTx).
Pyridinoline (Pyd or Pyr) Deoxypyridinoline (Dpd or D-Pyr)	Pyridinium crosslink compounds formed during extracellular maturation of collagen fibrils.	Pyd and Dpd mechanically stabilize collagen by bridging collagen peptides and are released into the circulation during resorption as mature cross-linked collagens are broken down.	Pyd and Dpd are formed in various other tissues of the body that also contain collagen.

However, the BTM response to running has been shown to be variable, with both bone formation and resorption markers shown to increase (Scott et al., 2011), decrease (Zittermann et al., 2002), and remain unchanged (Nishiyama et al., 1988) in the hours following a running bout. Moreover, a recent systematic review and meta-analysis showed no change in commonly studied BTMs in response to running (Civil et al., 2023). Systematic reviews of the literature have concluded that nonweight-bearing exercise (cycling and swimming) does not benefit BMD (Gomez-Bruton et al., 2016; Nagle & Brooks, 2011; Olmedillas et al., 2012). Nonweight-bearing exercise interventions tend to result in a moderate postexercise increase in bone resorption; however, there is significant variability in this response with effect sizes indicating a very low certainty (Dolan et al., 2020). For example, bone formation has been shown to increase (Herrmann et al., 2007; Rong et al., 1997), decrease (Herrmann et al., 2007), and remain unchanged (Guillemant et al., 2004; Pomerants et al., 2008) in response to ergometer-based cycling.

Reasons for the varied response could be multifactorial and may include the following: lack of control over diet or exercise, history of physical activity, population studied, other tissues releasing studied markers, and systemic measurement of tissue which exhibits site-specific adaptations. Another reason for the inconsistency in the findings could be the time taken for bone markers to significantly increase in concentration following an exercise bout being greater than the time period of follow-up (typically a maximum of 72 hr). Alternatively, an insufficient period of preintervention standardization may have been employed, such that the increase or decrease in BTMs being captured during the measurement window could have been activated by a stimulus incurred well before the start of the study. The inability of studies to follow-up for longer than 72 hr is likely due to practical and logistical reasons. However, it could be theorized that the effects of an exercise bout are not evident until >72 hr post intervention. For example, it is unlikely that bone formation marker P1NP would increase in the 72 hr post exercise because it is a marker of Type 1 collagen deposition, which is unlikely to be formed and deposited in a short space of time (Dolan et al., 2020). The observed increase in P1NP seen in some studies could be a result of leakage from other tissues containing collagen (Civil et al., 2023), or, due to changes in plasma volume (Brahm et al., 1996) that are not typically accounted for. Therefore, literature may be making erroneous conclusions regarding the effects of acute exercise on bone health due to the methodologies employed not adequately capturing the full bone metabolic response.

Effects of Low Energy Availability and Low-Carbohydrate High-Fat Diets on Bone

Nutritional practices can also influence bone health, and the effects of various interventions on BMD and BTMs have been investigated (Palacios, 2006; Sale & Elliott-Sale, 2019). Energy and macronutrient (particularly carbohydrate) demands of athletes vary between and within days and this is a key driver of dietary intake, such that a degree of periodization in energy and carbohydrate intake is typically recommended (Stellingwerff et al., 2019). Planned and unplanned bouts of low energy availability (LEA) and low-carbohydrate diets (with or without high fat) have been observed in various groups of athletes; thus, the bone response has been of specific interest. It has been hypothesized that LEA and low carbohydrate high fat (LCHF) have detrimental effects on bone health (Garofalo et al., 2023; Hutson, O'Donnell, Brooke-Wavell, et al., 2021). This raises ethical issues (in addition to the practical difficulties) of prolonged dietary control and standardization of LEA and LCHF. Therefore, when measuring bone imaging outcomes in humans, investigations into LEA and LCHF have tended to employ observational or cross-sectional designs (Garofalo et al., 2023; Hutson, O'Donnell, Brooke-Wavell, et al., 2021). No gold standard measure exists for LEA, so surrogate markers of LEA such as menstrual function or cumulative risk score are utilized for group comparisons (Ackerman et al., 2011; Heikura et al., 2018); creating a demand for highly controlled short-term studies to support conclusions. In contrast, the effects of various nutrition interventions hypothesized to improve bone health (e.g., increased protein, vitamin D, and calcium intake) have been extensively examined in well-controlled prospective studies utilizing bone imaging techniques (Mitchell et al., 2015). Studies have begun to characterize the BTM response to <7 days of LEA or LCHF in men and women (Anton-Solanas et al., 2016; Clayton et al., 2020; Ihle & Loucks, 2004; Murphy et al., 2021; Papageorgiou et al., 2017, 2018; Zanker & Swaine, 2000) and these will be the focus of this section.

It is often described that short (decreased bone formation and, sometimes, increased bone resorption in the resting and fasted state) and longer term bone outcomes to LEA (lower BMD and differences in cortical bone geometry and trabecular microarchitecture) are both detrimental to bone health (Hutson, O'Donnell, Brooke-Wavell, et al., 2021; Murphy et al., 2021; Papageorgiou et al., 2017). However, the following evidence suggests that there is an array of confounding factors that impact this congruency. For example, men are more robust in defending against the effects of a standardized bout of short-term LEA compared with women (Papageorgiou et al., 2017). Nevertheless, similarly high rates of LEA and low BMD exist in men and women participating in sports emphasizing leanness, and there is growing evidence to support that male athletes with LEA have impaired bone health (De Souza et al., 2019; Mountjoy et al., 2023; Viner et al., 2015). Short-term LEA induced by treadmill running may not impact bone formation and resorption (Papageorgiou et al., 2018). However, a large body of evidence shows that female distance runners who exhibit symptoms of chronic LEA have impaired bone health (Hutson O'Donnell, Brooke-Wavell, et al., 2021). Carbohydrate restriction, independent of LEA, has been shown to decrease bone formation and increase bone resorption within 6 days of a LCHF diet in elite racewalkers (Fensham et al., 2022). Comparatively, a recent systematic review in overweight and obese populations found no evidence of negative effects of longer term LCHF on BMD, although existing human studies are lacking in robust design and statistical power (Garofalo et al., 2023). There are also no robust long-term data in athletic populations by which to compare. Furthermore, 4 days caloric restriction of −630 ± 50 kcal/day from estimated energy requirement reduced bone formation but had no effect on bone resorption in healthy young women (Ihle & Loucks, 2004). However, 12 months caloric restriction of −280 ± 29 kcal/day from estimated energy requirement had no effect on bone formation but increased bone resorption and caused loss of BMD in young healthy men and women, with no difference between sexes (Villareal et al., 2016). A far greater energy deficit can be accumulated over more prolonged periods of energy restriction (e.g., 12 months compared with 4 days) even if the daily deficit is less severe, and this likely contributed to the differences identified between the studies by Ihle and Loucks (2004) and Villareal et al. (2016). The comparisons presented suggest that while short-term

Table 2 Considerations Regarding the Use and Interpretation of BTMs in Applied Exercise and Nutrition Research and Practice

• Implement rigorous control measures and standardization procedures for as long as feasibly possible preceding BTM measurement, considering the potential lasting influence of prior exercise or dietary practices on bone remodeling
• There is no consensus regarding what represents a meaningful change in BTM concentrations
• Longitudinal monitoring of BTMs (with as many repeat measurements as feasibly possible) should be preferred to cross-sectional or pre–post comparisons
• Integrate BTM measurement with imaging techniques during longitudinal monitoring
• Research aiming to make inferences regarding bone health should use imaging techniques for primary outcome measures
• Avoid concluding a beneficial, detrimental, or null effect of exercise or nutrition intervention based on BTM data alone
• Avoid relying solely on BTM outcomes to inform applied exercise or nutrition practice aiming to impact bone health

Note. BTM = bone turnover marker.

studies measuring BTMs may have the potential to identify a bone response, they do not reliably predict how bone mass (or even bone metabolism) will change during a similar but more prolonged intervention and should not be used as evidence upon which to base applied practice aiming to optimize bone health.

Findings of impaired bone health in women exhibiting symptoms of severe chronic LEA are highly consistent (Ackerman et al., 2011, 2012; Hutson, O'Donnell, Brooke-Wavell, et al., 2021; Singhal et al., 2019). This does not necessarily mean that a decrease in bone formation and an increase in bone resorption in response to severe acute LEA (or LCHF) are detrimental. It is plausible that an acute and transient bout of LEA might accelerate bone adaptation by initiating greater resorptive activity which, provided adequate energetic recovery, may be followed by an equivalent increase in bone formation, as per a typical remodeling cycle. However, the typical pretest–posttest design of acute studies fails to capture a complete bone remodeling response and energy status is fixed.

A recent study has performed repeated postexercise BTM measurement for up to 3 hr (Fensham et al., 2022); however, it would be difficult to maintain appropriate standardization for the duration of an entire bone remodeling cycle. Interestingly, Fensham et al. (2022) showed elevated postexercise bone resorption for up to 3 hr following 6 days of LEA and LHFC compared with a control diet. It was suggested that these changes were unfavorable, but it is intriguing to consider the bone health result assuming an equal and opposite bone formation response in following the days, weeks, or months. In this scenario, parallels may be drawn with acute "train-low" strategies, which have been shown to augment exercise stress and specific adaptations in muscle tissue provided daily energy status is not compromised (Hansen et al., 2005). A hypothetical benefit of carbohydrate or energy periodization could help to explain why an observational study failed to show prospective losses in BMD over 12 months in women exhibiting symptoms of long-term LEA (Singhal et al., 2019). There is also little evidence that intermittent fasting protocols negatively impact bone health and, on the contrary, some might even protect against bone loss during weight loss (Clayton et al., 2023). It is not clear exactly how long or how many samples would be required to characterize a full bone remodeling response to an acute stimulus of LEA (or indeed any nutrition or exercise stimulus), but it would likely become very expensive and difficult to maintain appropriate control and standardization. Considering that months of repeat samples could be required, the time and cost benefit of measuring BTMs instead of using imaging techniques might all but disappear.

Conclusions

BTMs can be valuable tools for research and practice, particularly for monitoring an individual's ongoing bone metabolic activity throughout a prolonged and consistent exercise or nutrition intervention. However, the opinion presented herein is that pre–post change in BTM concentration immediately following exercise or following several days of exercise or nutrition intervention should not be relied upon to inform applied practice, where the goal is to optimize bone health. A summary of the factors that should be considered when using and interpreting acute BTMs is presented in Table 2. Highly controlled short-term studies may still be useful to accelerate bone research by informing longer term follow-up studies with greater efficiency. Regular measurement of BTMs in combination with imaging techniques during long-term prospective research will help to build a better understanding of how these markers relate to structural change in response to exercise and nutrition intervention.

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