

# Bone Histology in Chronic Kidney Disease-related Mineral and Bone Disorder

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**Abstract:** A quantitative histological analysis of biopsied bone samples is currently regarded as the gold standard for a diagnosing procedure for bone diseases associated with chronic kidney disease-related mineral and bone disorder. Conventionally, “bone cell activities” and “bone mineralization” are applied as two independent assessment axes, and the histology results are classified into five categories according to these axes. Recently, a new bone histology classification system called the Turnover-Mineralization-

Volume system, which applied “cancellous bone volume” as another major assessing axis, was advocated; however, both classification systems have many unsolved problems. Clinicians must realize the limitations in evaluating bone metabolism by bone histology. We will need to establish a new classification method for renal bone diseases independent of histological findings. **Key Words:** Bone cell activities, Bone histology, Bone mineralization, Chronic kidney disease-related mineral and bone disorder.

Abnormality in bone metabolism is one of the three components that make up chronic kidney disease-related mineral and bone disorders (CKD-MBD) (1). A quantitative histological analysis of biopsied bone samples (2) is regarded as the gold standard for a diagnostic procedure for renal bone diseases (3,4). On the other hand, the potential problems associated with bone histological diagnosis have not yet been fully elucidated.

## CLASSIFICATION OF BONE METABOLISM IN CKD-MBD BY HISTOLOGY FINDINGS

“Bone cell activities” and “bone mineralization” are the two most evident findings that show wide spectra in patients with CKD-MBD. It is *via* the histological analysis of biopsied bone samples that clinicians can evaluate these two factors most precisely and quantitatively (5).

Figure 1 demonstrates the principle idea of the conventional histological classification of renal bone diseases. In this classification system, “bone cell activities” and “bone mineralization” are applied as two independent assessment axes. The histological results are classified into  $2 \times 3 = 6$  categories according to these axes; however, since “bone mineralization” cannot be assessed when “bone cell activity” is low, “low bone cell activities with normal bone mineralization” and “low bone cell activities with disturbed bone mineralization” are combined into one category.

Although the principle of this conventional classification appears to be easy to understand, there are many problems in the parameters that were used to perform the classification. In many of cases, “fibrous tissue volume (Fb.V/TV)” and “bone formation rate (BFR/BV or BFR/BS)” are applied as the bone histomorphometric parameters that represent bone cell activities. Fb.V/TV is usually adequate for screening those cases with extremely activated bone cells, such as those with osteitis fibrosa; however, it is of absolutely no use for screening those cases with abnormally low bone cell activities, such as those with adynamic bone. On the other hand, BFR shows low amounts in patients with low bone cell activity, but it is not a pure marker of bone cell activity because it is dependent on the mineral apposition rate. Thus, no

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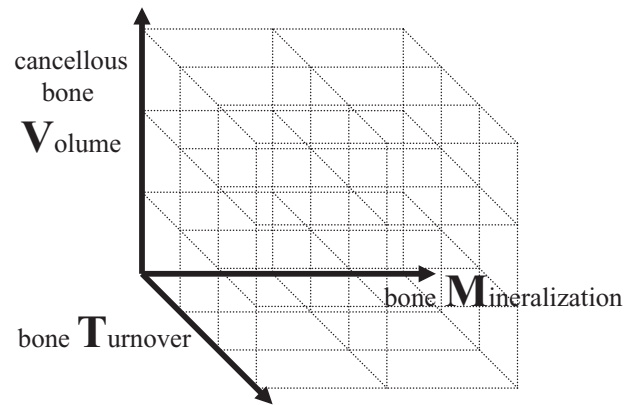
histomorphometric parameters satisfactorily represent “bone cell activities” presently.

Osteoid volume (OV/BV) is generally applied as the marker parameter of bone mineralization; however, mineralization speed is not the only factor—the speed of osteoid production seems to be a stronger factor affecting OV/BV in many cases. In fact, we often encounter those cases diagnosed as a mineralizing defect because of excess OV/BV values, which also demonstrate an excess mineral apposition rate.

As shown by these details, although the principle of conventional bone histology classification is clear, there are many unsolved problems associated with the parameters for evaluating bone histology.

Recently, Kidney Disease: Improving Global Outcomes (KDIGO) advocated a new bone histology classification system called the Turnover–Mineralization–Volume (TMV) system (Fig. 2) (1,6,7). In the TMV system, “cancellous bone volume (BV/TV)” was newly applied in addition to “bone turnover” and “bone mineralization” as another assessing axis.

In the TMV system, however, the problems displayed by the conventional classification system described above have not been solved. Moreover, one of the assessing axes was clearly designated as “bone turnover”, but not “bone cell activity”. Although “bone turnover” is a difficult concept to define in a strict sense, this term is generally used to refer to the frequency of the bone remodeling cycle; however, bone remodeling contains the bone mineralization step in its cycle. Therefore, “bone turnover” and “bone mineralization” cannot stand as assessing



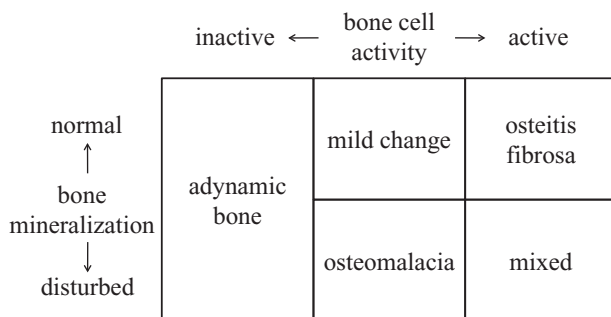
**FIG. 2.** The principle idea of the Turnover–Mineralization–Volume classification system, a newly advocated classification system for bone histology in CKD patients, which applies “bone turnover”, “bone mineralization”, and “cancellous bone volume” as three assessing axes. Unfortunately, many problems associated with the conventional system have not been solved by this new system.

axes that are independent of one another. Finally, the explanation of why BV/TV was added to the assessing axes seems unsatisfactory to us. KDIGO regards the parameter as the marker for “the balance between bone formation and bone resorption”. This assumption has never been proved by scientific studies, and moreover it seems quite unlikely that cancellous bone volume that occupies less than a quarter of the whole bone volume can possibly represent the balance between bone formation and bone resorption. Since BV/TV significantly correlates with cancellous bone connectivity (8), which is one of the determinants of bone strength (9), applying BV/TV as another assessing axis may help in evaluating bone quality from a more general perspective. Nevertheless, since the question of whether the changes in cancellous bone connectivity are specific in uremia remains unknown today, it does not seem appropriate to add the parameter to the assessing axes of CKD–MBD.

**THE SIGNIFICANCE OF BONE HISTOLOGY IN ASSESSING CKD–MBD**

“Bone cell activity” and “bone mineralization” are indeed two evident aspects that display quite wide spectra in CKD–MBD. Therefore, the principle of conventional bone histology classification that applied these two factors as the assessing axes (Fig. 1) is reasonable.

However, “bone cell activities” and “bone mineralization” are not the only factors that affect bone metabolism in CKD–MBD. Many known and probably yet unknown factors would also play roles in it.



**FIG. 1.** The principle idea of conventional classification of renal bone diseases. At first, bone histology is divided into six categories with two assessing axes, “bone cell activities” and “bone mineralization”. However, since it is technically impossible to discriminate “low bone cell activities and disturbed bone mineralization” from “low bone cell activities and normal bone mineralization”, these two categories are combined into one category. These five categories represent “bone metabolic conditions”, but not “independent bone diseases”. This misunderstanding sometimes leads users to being too dependent on this classification.

Some of those factors might be specific in CKD. We cannot assume that all of those factors must be dependent on histological findings; therefore, each category determined by histology finding is likely to originate from heterogeneous bone metabolic conditions.

KDIGO had noticed the risk described above, and therefore increased the number of assessing axes in the TMV system to make classification more precise. However, regardless of the adequacy of BV/TV, adding only one assessing axis could not possibly solve the problem of heterogeneity in the histological category. Bone histological classification is nothing but a classification dependent on the designated assessing axes rather than the absolute criteria that indicate whole bone metabolism in CKD–MBD. Clinicians must realize this limitation in evaluating bone metabolism by bone histology, even though bone histology findings do offer important information to users.

### CONCLUSION

The critical reason why histological analyses have been regarded as the gold standard for diagnosing renal bone diseases is that the condition is presently classified based on morphological concept. However, it seems quite unlikely that all the bone changes associated with CKD can be reflected by morphological findings. Thus, we will need to establish a new classification system for this disease condition,

and then bone histology will cease to be the gold standard.

**Conflict of interests:** The authors have no conflict of interests.

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