RESEARCH PAPER

Advanced Diagnostic Approaches for Osteoporosis: Imaging, Biomarkers, and Risk Assessment

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ABSTRACT

Osteoporosis is a progressive disorder of the bone characterized by a decrease in bone mass and changes in its microarchitecture. The Present article focuses on the latest developments in the diagnosis of osteoporosis. Conventional techniques such as Dual-Energy X-ray Absorptiometry (DXA) have been used as a gold standard to measure bone density. However, latest advances in imaging techniques such as High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT), Quantitative Computed Tomography (QCT), and MRI have been used to evaluate the microarchitecture of the bone. Biochemical bone turnover markers and circulating microRNAs play a key role as molecular biomarkers in the monitoring of bone remodeling. Moreover, fracture risk prediction tools like FRAX, Garvan, and Q Fracture have provided a better approach to the management of osteoporosis.

Keywords: Osteoporosis, Bone mineral Density (BMD); Bone microarchitecture; micro RNAs, Bio marker.

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INTRODUCTION:

Osteoporosis is defined as a chronic and progressive bone disease that is associated with decreased bone mass and changes in the bone microarchitecture, which results in bone weakness and thereby increases the chances of bone fractures. Osteoporosis is a condition in which the bones become weaker and more susceptible to fractures due to minor injuries or falls. Osteoporosis is commonly found in postmenopausal and elder female, as associated with decreased estrogen level which is vital in maintaining the bone density and its remodeling. (Kanis et al., 2008, Khosla et al., 2012). Osteoporosis is often termed a "silent disease" due to the fact that the bone loss is gradual and not associated with any symptoms; in most cases, the disease is diagnosed when the patient is already experiencing a fracture. The most commonly fractured bones due to osteoporosis are the hips, vertebrae or the spine, and the wrist, which may result in significant pain and mortality in the elderly (Compston et al., 2019). Traditionally, the diagnosis of osteoporosis has been done using the measurement of Bone Mineral Density (BMD), and has done by using various forms of image analysis such as Dual-Energy X-ray Absorptiometry (DXA), which has been considered as gold standard imaging modality for evaluating bone density as it provides quantitative assessment of bone strength. The World Health Organization defines a T-score of -2.5 or less as a measure of osteoporosis (WHO, 2004). Nevertheless, BMD measurement is not a comprehensive measure of bone quality as it is also influenced by other factors like bone microarchitecture, bone turnover, and bone mineralization (Adams 2009; Boutroy et al 2005, Compston et al., 2019, Eastell et al., 2016). Recent advances in osteoporotic diagnostic techniques have enabled better evaluation of osteoporotic risk by using imaging techniques, biochemical markers, and fracture risk assessment tools. For instance, Quantitative Computed Tomography (QCT), High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT) and Trabecular Bone Score imaging techniques provide detailed information on bone microarchitecture and bone density, which can lead to early detection of

changes in bone structure (Boutroy et al., 2005). Moreover, biochemical markers such as osteocalcin, bone-specific alkaline phosphatase, C-terminal telopeptide, N-terminal telopeptide, among others, also have an essential role to play in assessing bone metabolism (Biver et al., 2012). Moreover, fracture risk assessment tools such as the Fracture Risk Assessment Tool (FRAX) can predict the 10-year probability of fracture occurrence due to osteoporosis based on various clinical risk factors with or without BMD. These modern diagnostic techniques give a comprehensive overview of the state of the bones and enable the early detection of osteoporotic disease to allow for effective intervention (Cheung et al., 2018, Kanis et al., 2008).

Emerging Diagnostic Tools for Evaluating Bone Microarchitecture and Fracture Risk:

Morden methods of detecting osteoporosis and new imaging technologies have greatly enhanced the early detection and assessment of the condition. The conventional methods of detecting osteoporosis have relied on the measurement of the density of the bones, although the new methods can measure the microarchitecture, strength, and risk of fracture. Osteoporosis is usually diagnosed using the Dual-Energy X-ray Absorptiometry method, which is used to measure the density of the bones in the spine, hip, and femur. The method is clinically significant as it reliably measures the density of bone and classify the severity of osteoporosis using T-score system. However, the method can only measure quantity of the bone and but not at all the quality and microstructure, which is essential in the determination of the fracture risk. With the advent of advanced imaging techniques, it has now become possible for clinicians to evaluate the quality of bones, microarchitecture, and biomechanical strength of the bones. This cannot be achieved with the use of traditional BMD (Bone Mineral Density) techniques. The limitations of the conventional methods can be overcome by the use of advanced imaging technologies which provides more accurate and detailed assessments of the bone structure and strength in the early detection and management of the condition. One of the technologies is the "High-Resolution Peripheral Quantitative Computed Tomography" technology (HR-pQCT) enables the imaging of three-dimensional trabecular and cortical bone microarchitecture within the human body at very high spatial resolution (Krug et al., 2010). It also enables the measurement of parameters such as trabecular thickness, cortical porosity, and bone volume fraction. All the above parameters are strongly correlated with bone strength and fracture risk. However, this technology is restricted to the imaging of the periphery. Similarly, Quantitative Computed Tomography (QCT) is another technology being use for CT imaging in combination with calibration standards to measure volumetric BMD (Guerri, et al. 2017). This technique also facilitates separate evaluation of trabecular and cortical bone however, it also provides in-depth imaging of the lumbar spine and hip, which show promising results for detecting early bone loss in a better manner than other technologies (Harvey et .,al 2015, Leslie et al, 2013, Link et.,ai 2020). In addition, Magnetic Resonance Imaging (MRI) has also gained more importance in the diagnosis of osteoporosis. High-resolution imaging is possible in the diagnosis of osteoporosis using MRI. Moreover, the recent advancements in the field of imaging and the use of technologies such as radiomics and artificial intelligence in the analysis of imaging data are more advantageous in the early detection and diagnosis of the condition. Furthermore, the recent advancements in the field of imaging and the use of technologies such as quantitative ultrasound and radiofrequency echographic multi-spectrometry (REMS) are more advantageous in the early detection and diagnosis of the condition. The recent advancements in the field of imaging and the use of technologies such as quantitative ultrasound and radiofrequency echographic multi-spectrometry (REMS) are more advantageous in the early detection and diagnosis of the condition (Adami et al., 2019). Thus, the emerging diagnostic technologies involving advanced imaging technologies and computational analysis, and the integration of various data modalities, are revolutionizing the field of osteoporosis diagnosis. It is allowing for a more detailed analysis of the bone density and microarchitecture and the biomechanical strength. Apart from the above, biomarkers can be used with advanced imaging modalities like Dual-Energy X-ray Absorptiometry (DXA), Quantitative Computed Tomography (QCT), High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT), and Magnetic Resonance Imaging (MRI) to arrive at a comprehensive picture, which has been summarized in Figure 1.The imaging techniques measure bone density and structure, while biomarkers measure the biological activity of bone remodeling (Boutroy et al., 2013, Tse et al.,2021).

Figure: 1. Comprehensive approaches for Osteoporosis Diagnosis and Fracture Risk Assessment.

- **Biochemical and Molecular based Biomarkers for Monitoring Bone Remodeling in Osteoporsis**

  A In recent times, scientific research has emphasized the significance of molecular and biochemical biomarkers as potential tools for the early detection and monitoring of osteoporosis. These biochemical markers are measurable substances found in blood or urine that are indicative of the dynamic process of bone remodeling, which includes bone formation and resorption as mentioned in Figure 2. Unlike other traditional methods of diagnosing the condition, biochemical markers offer additional information regarding the metabolic activities occurring in the bone. For example, bone formation biochemical markers include osteocalcin, bone-specific alkaline phosphatase, and procollagen type I N-terminal propeptide, while bone resorption biochemical markers include C-terminal telopeptide and N-terminal telopeptide (Vasikaran and Chubb 2016, Vasikaran et al., 2011).

- **Bone Turnover Markers in the Evaluation of Bone Remodeling Activity**

  A Bone turnover markers are biochemical markers used for evaluating bone formation rates and bone resorption rates. Bone Turnover Markers (BTMs) are biochemical markers used in the monitoring of bone remodeling activity, is a process in which bone formation occur by osteoblasts and bone resorption by osteoclasts in a balanced manner. While imaging studies mainly assess bone mineral density (BMD), bone turnover markers assess the metabolic activity in bone tissue. Hence, bone turnover markers are used in clinical research and practice for evaluating bone turnover rates in osteoporosis and for monitoring disease progression or response to therapy in osteoporosis (Vasikaran et al., 2011). They are commonly used for monitoring osteoporosis progression and for evaluating the efficacy of osteoporosis therapy. The bone turnover markers are categorized into two groups, that are bone formation markers and bone resorption markers, as indicated in Table 1.

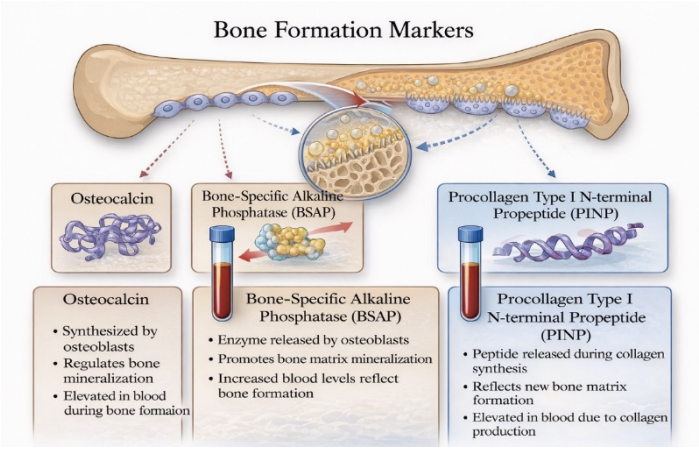

Figure 2: Key Biochemical Marker for Bone formation and remodeling

Bone formation markers are biochemical markers released during the synthesis of new bones by cells known as osteoblasts. They are effective in the assessment and evaluation of the rate of bone formation in the body. The bone formation markers are described as (a) Procollagen Type I N-terminal Propeptide (P1NP); (b) Bone-specific Alkaline Phosphatase (BALP), and (c) Osteocalcin. High concentrations of the bone formation markers are effective in the assessment and evaluation of the rate of bone formation in the body. The measurement and assessment of bone formation markers are effective in the evaluation and monitoring of bone diseases such as Osteoporosis. Osteocalcin is a non-collagenous bone matrix protein secreted by osteoblasts during bone formation. Osteocalcin is important for the process of bone mineralization and regulation of calcium ions in human body. An increase in the concentration of osteocalcin is an indication of active bone formation. Likewise, the Bone-specific alkaline phosphatase (BALP) is an

important isozyme of alkaline phosphate is secreted by osteoblasts during bone mineralization. BALP is act as a genuine biochemical marker for the differentiation of osteoblasts in the process of bone formation. Similarly, Procollagen Type I N-Terminal Pro peptide (PINP) is a marker for bone formation which released during the synthesis of type I collage is an important component of bone matrix. It is used for monitoring bone formation in during the treatment of osteoporosis, a list of this has been elucidated in Table 1.

Table: 1 Biomarkers from blood and urine sample for bone formation and resorption

Category	Biomarker	Sample type	Normal range	Observed range	Reference
BFM	Osteocalcin	Serum	11-43ng/mL	26-38 ng/mL	Osteoblastic with bone formation
BFM	BALP	Serum	10-22 U/L	20-27 U/L	Osteoblastic with bone mineralization
BFM	PINP	Serum	20-76 µg/L	55-73 µg/L	New collagen synthesis
BRM	CTX	Serum	0.1-0.6 ng/mL	0.67-0.89 ng/mL	Increased osteoclastic bone reabsorption
BRM	NTX	Urine	9-55nM/mmol	58-78nM/mmol	Degradation of type I collagen

NB: BFM: Bone Formation Marker; BRM: Bone Reabsorption Marker

The major bone turnover markers—osteocalcin, bone-specific alkaline phosphatase (BALP), procollagen type I N-terminal pro-peptide (PINP), C-terminal telopeptide (CTX), and N-terminal telopeptide (NTX)—and their comparative assessment are shown in Figure 3. Osteocalcin, BALP, and PINP represent bone formation markers, while CTX and NTX represent bone resorption markers. These levels of bone turnover markers indicate that there is active bone remodeling occurring in the body. An elevated level of CTX and NTX is associated with increased bone resorption by osteoclasts, while elevated levels of osteocalcin, BALP, and PINP are associated with bone formation activity by osteoblasts and represent potential markers for monitoring the progression of osteoporosis.

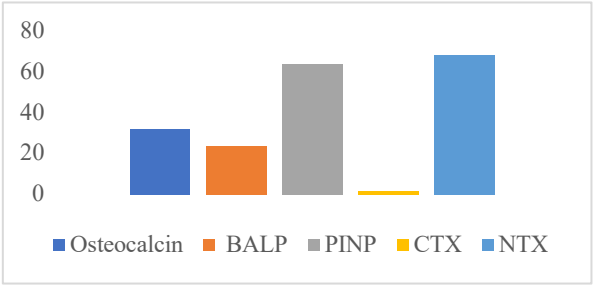

Figure: 3. Comparison of Bone Formation and Bone Resorption Biomarker in Osteoporosis

Similarly, bone resorption markers are biochemical markers released into the blood or urine as a result of the breakdown of bone tissue through the action of osteoclasts. These markers are a measure the rate of bone resorption in the process of bone remodeling. Markers of bone resorption include C-terminal telopeptides, N-terminal telopeptides, and tartrate-resistant acid phosphatase. An elevated level of resorption markers is a measure of increased resorption of bone tissue and is observed in Osteoporosis. Bone resorption markers are used as a diagnostic tool in the management of osteoporosis through the evaluation of the effectiveness of anti-resorption therapy in the management of the condition.

RESULTS

Circulating microRNAs (miRNAs) are short non-coding RNA sequences, generally consisting of 18-25 nucleotides, which regulate the gene expression through the binding to messenger RNA (mRNA) and the inhibition of its translation and/or degradation. In the last few years, circulating miRNAs have gained significant importance as

molecular biomarkers in the clinical diagnosis and monitoring of osteoporosis, as they are implicated in the regulation of the process of bone remodeling. This remodeling process is characterized by the balance between the events of osteoblasts and osteoclasts, are responsible for the formation and resorption of the bone tissue respectively.

Case no	mi R 21	miR 133a	miR 422a	Interpretation
1.	1.8	1.5	1.6	Increased bone resorption
2.	2.2	1.9	2.0	High osteoclast activity
3.	1.6	1.4	1.5	Moderate metabolic alteration
4.	2.4	2.1	2.2	Severe bone metabolism imbalance
5.	2.0	1.7	1.9	Increased bone turnover
6.	2.1	1.8	2.0	Active bone degradation
7.	2.5	2.2	2.3	Severe osteoporosis marker expression
8.	2.6	2.3	2.4	Very high bone turnover
9.	1.7	1.5	1.6	Early metabolic change
10	2.0	1.7	1.8	Elevated bone remodeling

Table: 2 microRNAs (miRNAs) used in clinical diagnosis and monitoring of osteoporosis.

The unbalance in the expression of some specific circulating miRNAs can cause the disruption in the balance between these two types of cells and can lead to the development of osteoporosis. The most studied miRNAs related to the process of bone remodeling are miR-21, miR-133a, and miR-422a. miR-21 has been recognized to perform significant character in encouraging the differentiation of osteoclasts, thereby increasing bone resorption as mentioned in Table 2 and Figure 4. An increase in the levels of miR-21 has been found to be positively correlated with enhanced osteoclast activities and reduced bone density. miR-133a is known to regulate the differentiation of osteoblasts by targeting genes that are involved in bone formation. Overexpression of miR-133a is found to inhibit the activities of osteoblasts, thereby inhibiting bone formation. miR-422a is known to be positively correlated with enhanced activities of osteoclasts (Weilner et al., 2015). These miRNAs extracted in the blood by using molecular techniques such as qRT-PCR. Circulating miRNAs are found to be stable in the blood and are strongly correlated with bone metabolism, making them promising non-invasive markers for early diagnosis of osteoporosis (Zhao et al., 2014).

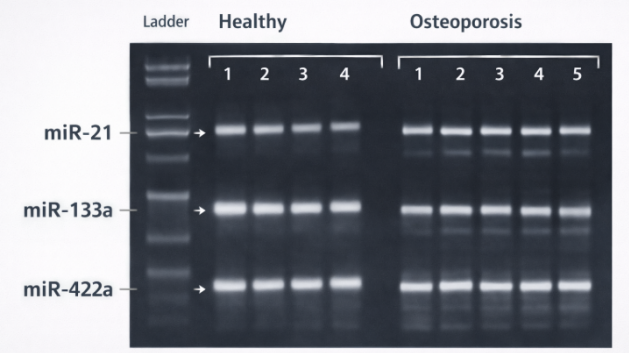

Figure: 4 Gel Electrophoresis profile of micro RNAs (mi R 21, mi R 133a, and miR 422a) as molecular marker for Osteoporosis diagnosis and monitoring.

The most commonly used tool for molecular marker which has been summarized in Figure 5 indicates a relative expression of circulating microRNAs (miR-21, miR-133a, and miR-422a) in ten Osteoporotic samples. In most samples, miR-21 has the highest expression level, followed by miR-422a and then miR-133a. The expression of these microRNAs increases in later samples, implying increased bone remodeling activity. These microRNAs are involved in the control of osteoblasts and osteoclasts and are thus potentially useful molecular biomarkers for the early detection of osteoporosis progression (Seeliger et al., 2014).

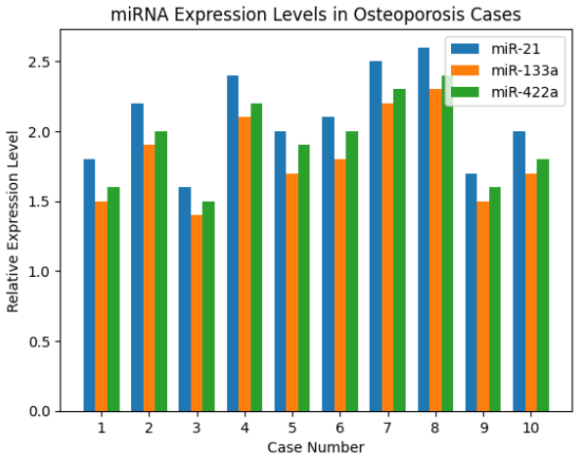

Figure 5: Comparative analysis of Osteoporotic Fracture Risk Assessment Tools.

Risk Assessment Strategies for Predicting Osteoporotic Fractures:

In osteoporosis risk assessment is a critical clinical tool for determining fracture risk and for identifying patients' condition with suffering from bone loss. Osteoporosis is a medical condition that advances in most patients without any signs or symptoms until a fracture takes place, which makes it vital to carry out risk assessment to ensure timely intervention for prevention and treatment. Risk assessment for osteoporosis is normally carried out by using risk factors, bone density scanning, and risk prediction tools. Bone density scanning is normally performed by using dual-energy X-ray absorptiometry, which generates results in terms of T-scores to show the status of bone density in patients. According to clinical guidelines, when the T-score is equal to or less than -2.5, it means that the patient is suffering from osteoporosis, whereas when it ranges from -1 to -2.5, it means that the patient is suffering from osteopenia. In addition to BMD, several clinical factors are also known to be important in the prediction of fracture risk. These factors are: Progressive age, Feminine, Short physique mass index, Family history for hip fractures as discussed in Table 3. History of previous fragility fractures, Smoking, Heavy drinking, Glucocorticoid therapy, Rheumatoid arthritis, Secondary causes of bone loss, are assessed in order to identify individuals who need further investigation and management. To improve the accuracy of the prediction of fracture risk, several risk assessment tools are now being commonly used in clinical practice (Johansson et al 2014). Similarly, a comparative assessment of commonly used tool for risk strategies has been explained in Figure 6. The pie chart indicates the proportional distribution of 3 utmost commonly used fracture risk assessment tools: that are FRAX, Garvan Fracture Risk Calculator and Q Fracture. Out of these three fracture risk assessment tools, the Garvan calculator has the largest proportion at 35.2%, implying a slightly higher contribution in fracture risk prediction. In contrast, the proportion of the QFracture tool is 33.1%, implying a similar level of contribution in the estimation of fracture risk using clinical risk factors for osteoporotic fractures. In addition, the FRAX tool has a slightly lower proportion at 31.7%, implying a similar level of contribution but slightly lower compared to the other two fracture risk assessment tools. In summary, the pie chart indicates that the three fracture risk assessment tools have almost equal contributions to fracture risk prediction.

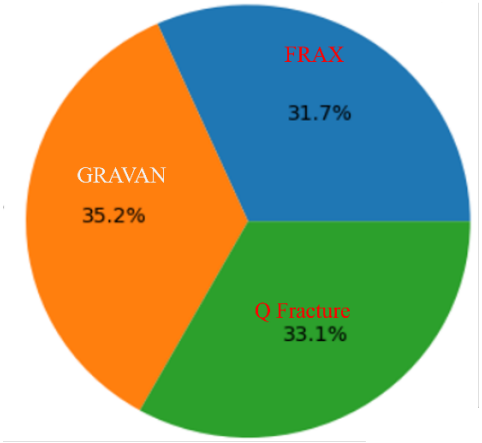

Figure 6: Comparative Distribution of Fracture Risk Assessment

It calculates the ten-year prospect for foremost osteoporotic fractures with hip fractures constructed by the assemblage of clinical risk factors and BMD results. Another tool is the Garvan fracture risk calculator and QFracture, which includes other risk factors such as falls and co-morbidities. Assessment of risk plays a vital role in the early detection, prevention of fractures, and management of osteoporosis. By identifying individuals at a higher risk, healthcare providers can advise on lifestyle changes, medication, and monitoring to minimize the chances of fractures in osteoporosis patients.

Table: 3

Case no	Sex	Age	BMI	Previous fracture	Smoking	FNB (g/cm^2)	FRAX (%)	Garvan (%)	Q Fracture (%)	Risk category
1.	M	58	23.5	N	N	0.78	8.4	9.1	8.6	Low
2.	M	63	22.2	Y	Y	0.71	16.5	18.3	17.4	Moderate
3.	M	55	24	N	N	0.83	6.9	7.5	7.0	Low
4.	M	67	21.6	Y	Y	0.65	22.8	26.5	25.1	High
5.	M	60	23.1	N	Y	0.74	12.6	14.2	13.6	Moderate
6.	F	57	22.3	Y	N	0.69	18.7	19.6	18.3	Moderate
7.	F	64	21.4	Y	Y	0.62	24.9	28.3	26.9	High
8.	F	54	23.8	N	N	0.81	7.2	8.0	7.6	Low
9.	F	68	20.9	Y	Y	0.60	27.6	31.2	29.8	High
10.	F	59	22.7	N	N	0.72	13.5	15.0	14.4	Moderate

Pre-Treatment and Risk Awareness

As indicated in the table, fracture risk increases with age, BMI, previous fractures, smoking, and decreased bone density. All three tools, FRAX, Garvan, and QFracture, show a similar pattern of fracture risk estimation. Higher percentages of fracture risk are evident in female patients of advanced age due to bone loss after menopause, which contributes to the progression of osteoporosis. Patients who are at a high risk of fracture (>20%) need to be intervened with lifestyle changes and pharmacological interventions to avoid fractures

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DISCUSSION

Recent advances in diagnostic technologies have improved the early detection of osteoporosis. In past, investigation of osteoporosis was constructed on the assessment of bone density, restrained as bone mineral density (BMD), consuming a scheme acknowledged as dual energy X ray absorptiometry (DXA). This method remains "gold standard" in diagnosis of osteoporosis, as it provides T-scores used to classify bone health, with a T-score of ≤ -2.5 demonstrating osteoporosis, whereas a score of -1 to -2.5 indicates as osteopenia (Kanis et al., 2013). However, various studies have shown that fracture risk cannot be fully explained by BMD, as bone strength also depends on the microarchitecture of the bone. In this regard, the advanced imaging techniques such as High- Resolution Peripheral Quantitative Compound Tomography (HR-pQCT) in addition Quantitative Computed Temography (QCT) consume in place of DEXA scans. HR-pQCT helps in visualizing bone microarchitecture in three dimensions, while QCT supports in quantifying bone mineral density in three dimensions. Boutroy et al. (2005) found a strong correlation between bone microarchitecture constraints such as trabecular thickness and cortical porosity measured by HR-pQCT with bone strength or fractures. In addition to these imaging techniques, biochemical bone turnover markers such as osteocalcin, bone alkaline Phosphate (BALP), procollagen type 1 N terminal pro-peptide (PINP), C terminal telopeptide (CTX) and N terminal telopeptide (NTX) supports in estimating bone remodeling activity. According to Vasikaran et al. (2011), these bone turnover markers can be used for monitoring disease progression or response to therapy. Similar findings by other researchers such as Seeliger et al. (2014) indicate the potential role of molecular biomarkers such as circulating microRNAs in the early diagnosis of osteoporosis.

CONCLUSION

In recent years, advances in diagnostic techniques for osteoporosis have greatly helped in its management.

Although the conventional approaches like Dual Energy X ray Absorptiometry (DXA) have been recognized as the gold standard intended for the assessment of bone mineral density, progressive image sense modality like High Resolution Peripheral Quantitative Compound Tomography (HR-pQCT), Quantitave Compound Tomography (QCT), and Magnetic Resonance Imaging (MRI) support in the depth analysis of the bone microarchitecture and bone strength. Biochemical bone turnover markers and molecular biomarkers like circulating microRNAs help in a more detailed analysis of bone remodeling mechanisms. Together with fracture probability prediction tools like FRAX, Garvan, and QFracture algorithms, these advanced diagnostic techniques help in a holistic approach for the early diagnosis and clinical management of osteoporosis.

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