RESEARCH ARTICLE

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LABORATORY FOLLOW-UP OF POSTMENOPAUSAL OSTEOPOROSIS BY RECENT MOLECULAR TECHNIQUES: AN ACADEMIC COMMENTARY

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Abstract

Postmenopausal osteoporosis (PMO) is a systemic skeletal disorder characterized by reduced bone mass and microarchitectural deterioratio n of bone tissue, leading to increased fragility and fracture risk. The decline in estrogen levels after menopause accelerates bone remodelin, favoring osteoclastic bone resorption over osteoblastic bone formation. Osteoporotic fractures remain a major cause of morbidity, mortality, and healthcare expenditure worldwide. While dual- energy X- ray absor Ptiometry (DXA) remains the gold standard for diagnosis and monitori ng, growing evidence suggests that molecular laboratory techniques can provide earlier and more sensitive insights into bone metabolism, treatment response, and fracture risk. Recent advances in molecular diagnostics, including bone turnover biomarkers, genomics, epigenomi cs, transcriptomics, proteomics, metabolomics, and liquid biopsy appro aches, are transforming the laboratory follow-up of postmenopausal osteoporosis.

Introduction:-

Limitations of Conventional Monitoring:

The routine follow-up of osteoporosis relies heavily on serial bone mineral density (BMD) measurements using DXA. However, significant changes in BMD may require one to two years to become detectable. Moreover, BMD does not fully capture bone quality, remodeling dynamics, or treatment responsiveness. Consequently, there is increasing interest in molecular biomarkers that reflect real-time skeletal metabolism and allow earlier therapeutic assessment (1,2).

Bone Turnover Markers: Current Molecular Standards:

Bone turnover markers (BTMs) represent the most established molecular tools in osteoporosis follow-up. They provide information about the rates of bone formation and resorption, often changing within weeks or months after therapeutic intervention.

Among bone formation markers, procollagen type I N-terminal propeptide (PINP) is currently recommended by several international organizations as a reference marker. PINP reflects collagen synthesis by osteoblasts and correlates with bone formation activity. Antiresorptive therapies such as bisphosphonates and denosumab typically reduce PINP concentrations within 3–6 months, allowing early assessment of treatment efficacy (3).

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For bone resorption, C-terminal telopeptide of type I collagen (CTX) is the most widely utilized marker. CTX reflects degradation of type I collagen and rapidly decreases following antiresorptive treatment. Monitoring serum CTX can identify poor adherence to therapy, inadequate response, or secondary causes of ongoing bone loss.

Automated immunoassays have improved analytical precision and standardization of BTM measurements. Recent studies suggest that integrating PINP and CTX with DXA measurements enhances prediction of fracture risk and therapeutic response compared with imaging alone.

Genomic Approaches in Osteoporosis Follow-up:
Genetic factors account for approximately 50–85% of the variability in bone mass and fracture susceptibility. Advances in next-generation sequencing (NGS) and genome-wide association studies (GWAS) have identified hundreds of loci associated with osteoporosis risk.

Genes involved in the Wnt signaling pathway, including LRP5, WNT16, and SOST, play critical roles in bone formation. Variants in RANK, RANKL, and OPG genes influence osteoclast differentiation and activity (4). Molecular follow-up increasingly incorporates genetic profiling to identify individuals who may exhibit differential responses to antiosteoporotic therapies.

Polygenic risk scores (PRS) have emerged as promising tools for stratifying fracture risk. By combining multiple genetic variants, PRS may identify women at high risk before significant bone loss occurs. Although currently more useful for risk prediction than longitudinal monitoring, genomic data may facilitate personalized follow-up strategies in the near future.

Epigenetic Biomarkers:
Epigenetic modifications represent reversible alterations in gene expression without changes in DNA sequence. DNA methylation, histone modifications, and non-coding RNAs have been implicated in postmenopausal bone loss.

Recent studies have demonstrated altered methylation patterns in genes regulating osteoblast differentiation and osteoclast activity. Hypermethylation of osteogenic genes may contribute to impaired bone formation during aging and estrogen deficiency.

Particularly noteworthy are microRNAs (miRNAs), small non-coding RNAs that regulate post-transcriptional gene expression. Numerous circulating miRNAs have been associated with osteoporosis, including miR-21, miR-29b, miR-133a, miR-148a, and miR-503 (2,3).

Changes in circulating miRNA profiles often precede detectable alterations in BMD. Consequently, serial measurement of osteoporosis-related miRNAs has emerged as a promising laboratory tool for monitoring disease progression and therapeutic response. Several investigations have shown that antiresorptive and anabolic treatments induce characteristic changes in miRNA expression patterns.

Transcriptomic Monitoring:
Transcriptomic technologies evaluate gene expression across thousands of genes simultaneously. RNA sequencing (RNA-seq) has enabled comprehensive characterization of molecular pathways involved in bone remodeling.

Peripheral blood mononuclear cells have become an accessible source for transcriptomic studies in osteoporosis. Differential expression of genes involved in osteoclastogenesis, inflammation, and Wnt signaling has been observed in postmenopausal women with osteoporosis.

Longitudinal transcriptomic monitoring may provide insights into treatment responsiveness. For example, changes in expression of osteogenic transcription factors such as RUNX2 and SP7 may reflect anabolic responses to agents such as teriparatide or romosozumab. Although still largely confined to research settings, transcriptomic profiling has substantial potential for precision osteoporosis management (4,5).

Proteomic Innovations:
Proteomics examines the entire spectrum of proteins expressed within biological systems. Advances in mass spectrometry have enabled identification of novel protein biomarkers associated with skeletal health.

Several candidate proteins have shown promise in osteoporosis monitoring:
These include:

- Sclerostin
  Dickkopf-related protein 1 (DKK1)
- Osteoprotegerin (OPG)
- Receptor activator of nuclear factor-kappa B ligand (RANKL)
- Osteocalcin
- Periostin

Sclerostin and DKK1 are particularly important because they inhibit Wnt-mediated bone formation. Changes in circulating concentrations may provide valuable information regarding anabolic treatment effects. High-resolution proteomic analyses have also identified inflammatory proteins and extracellular matrix components associated with fracture risk. Multiplex protein panels may eventually provide superior prognostic accuracy compared with single biomarker approaches (6).

Metabolomics and Osteoporosis Follow-up:
Metabolomics involves comprehensive analysis of small-molecule metabolites in biological samples. Since bone remodeling influences numerous metabolic pathways, metabolomic profiling offers unique insights into skeletal physiology.

Recent investigations have identified characteristic metabolic signatures associated with osteoporosis, including alterations in:

- Amino acid metabolism
- Lipid metabolism
- Energy metabolism
- Oxidative stress pathways

Metabolites such as citrate, hydroxyproline derivatives, lysophosphatidylcholines, and specific lipid species have shown associations with bone turnover and fracture risk. Importantly, metabolomic changes often occur earlier than detectable alterations in BMD, making them attractive candidates for monitoring treatment response. Machine-learning algorithms applied to metabolomic datasets have demonstrated promising predictive performance for fracture risk stratification.

Extracellular Vesicles and Liquid Biopsy Technologies:
One of the most exciting developments in osteoporosis research is the application of liquid biopsy technologies. Extracellular vesicles (EVs), including exosomes, are released by osteoblasts, osteoclasts, osteocytes, and other tissues. These vesicles contain proteins, messenger RNAs, microRNAs, and other signaling molecules that reflect cellular activity (6). Analysis of exosomal cargo provides a noninvasive window into skeletal metabolism. Recent studies have identified osteoporosis-associated exosomal miRNAs that correlate with bone density, fracture risk, and treatment outcomes. Because exosomes protect their molecular contents from degradation, they may offer superior analytical stability compared with conventional circulating biomarkers. Although currently investigational, EV-based diagnostics may become an important component of future osteoporosis follow-up protocols.

Artificial Intelligence and Multi-Omics Integration:
The growing volume of molecular data generated by genomic, transcriptomic, proteomic, and metabolomic technologies has stimulated the development of artificial intelligence (AI)-driven analytical approaches (7). Machine-learning algorithms can integrate multiple biomarker categories with clinical variables, DXA results, and fracture history. Such multi-omics models have demonstrated improved predictive performance for fracture risk and treatment response compared with traditional assessment methods. Future laboratory follow-up may involve individualized molecular profiles that dynamically guide therapeutic decisions. Patients could receive personalized monitoring schedules based on integrated molecular risk assessments rather than fixed imaging intervals.

Challenges and Future Perspectives:
Despite substantial progress, several challenges remain before advanced molecular techniques can be routinely incorporated into clinical practice. Standardization of assays, establishment of reference intervals, biological variability, and cost considerations continue to limit widespread implementation. Many candidate biomarkers have

been identified in relatively small cohorts and require validation in large, multicenter studies. Furthermore, regulatory approval and harmonization of laboratory methodologies will be necessary before molecular markers can be incorporated into international osteoporosis guidelines. Nevertheless, the trajectory of research strongly suggests that molecular diagnostics will play an increasingly important role in osteoporosis management. Future monitoring strategies will likely combine DXA with selected molecular biomarkers, enabling earlier detection of treatment failure, improved adherence assessment, and personalized therapeutic optimization (8).

Conclusion:-

The laboratory follow-up of postmenopausal osteoporosis is undergoing a significant transformation driven by advances in molecular medicine. While bone turnover markers such as PINP and CTX currently represent the most clinically established tools, emerging technologies including genomics, epigenomics, transcriptomics, proteomics, metabolomics, and extracellular vesicle analysis offer unprecedented insights into skeletal biology (8,9). These approaches have the potential to detect treatment responses earlier than conventional imaging, improve fracture risk prediction, and facilitate personalized therapeutic strategies. As standardization and validation efforts continue, molecular techniques are expected to become integral components of precision medicine approaches for the long-term management of postmenopausal osteoporosis (9).

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