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COMENTARIOS BIBLIOGRÁFICOS / *Bibliographical Comments*

COMENTARIOS DE TRABAJOS PRESENTADOS EN LA ASBMR 2015 DISCUTIDOS POR EXPERTOS

Natural history and prognostic factors of fibrous dysplasia of bone in a modern cohort of 372 patients. The Francedys Study

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Síntesis del trabajo: la displasia fibrosa (DF) es una rara enfermedad del hueso responsable de fracturas, dolor óseo y deformidad, cuyo pronóstico es difícil de establecer. El objetivo fue analizar la base de datos del *French National Reference Center* para DF establecida a partir de historias clínica electrónicas estandarizadas. Se realizó un análisis estadístico descriptivo de las diferentes formas clínicas de DF y se examinaron los factores pronósticos a través de un análisis de regresión múltiple logarítmica. En esta nueva cohorte de 372 pacientes (reclutados después de 1990), la edad promedio de diagnóstico fue de 23 años. Los síntomas relevantes (edad promedio=18 años) fueron dolor en un 44% de los pacientes y fracturas en un 9%. El diagnóstico fue fortuito en el 25% de los casos. El 58% de los pacientes presentaron la forma monostótica y el 42%, la forma poliostótica. El fémur resultó el hueso más afectado (44% de los pacientes), seguido por el cráneo (38%). El 12% de los pacientes tenía el síndrome de McCune-Albright (MAS). En 211 pacientes, con un período de seguimiento promedio de 7 años, se observó una incidencia del 17% de fracturas por fragilidad ósea y el 51% de los pacientes no presentaron dolor óseo al final del seguimiento (con tratamiento con bifosfonatos o sin él). En el 30% de los pacientes se observó retraso en el diagnóstico, definido por un intervalo igual a 6 meses o mayor entre el primer síntoma y el diagnóstico. La edad temprana de diagnóstico, la pérdida tubular de fósforo, la forma poliostótica y la prevalencia de fracturas fueron los predictores de peor pronóstico, pero al realizar un modelo de regresión multivariada solo la forma poliostótica fue el único predictor significativo (OR=2,04 [1,29; 3,27]). Se señalan como predictores de tratamiento quirúrgico la edad temprana de diagnóstico, la forma poliostótica, la pérdida tubular de fósforo, MAS y la prevalencia de fractura, pero ninguno pudo emerger como un predictor significativo en un análisis multivariado. En conclusión, en un centro de referencia nacional de DF, la incidencia de fractura fue de uno de cada seis pacientes en seguimiento. La forma poliostótica constituyó el principal factor de riesgo para una evolución de la enfermedad poco favorable.

Comentario de experto: este es un trabajo interesante ya que pocos grupos referentes en displasia fibrosa en el mundo presentan una casuística tan importante como la ofrecida en éste. Este hecho es de vital importancia, ya que permite obtener conclusiones sólidas sobre la historia natural de esta rara enfermedad ósea. Como señalan los autores, la forma poliostótica es el único predictor de peor pronóstico identificado. Sin embargo, es muy interesante desde el punto de vista clínico que el dolor haya estado presente en el 44% de los pacientes. Este hecho constituye una llamada de atención para los médicos en general, ya que este síntoma es uno de los motivos de consulta más frecuentes en la práctica clínica. Otro dato interesante es que el diagnóstico fue fortuito en el 25% de los casos, lo que nos indica una baja sospecha diagnóstica de esta enfermedad. Por lo tanto, el mayor conocimiento de la historia natural de la displasia fibrosa permitirá sospechar el diagnóstico, confirmarlo adecuadamente y establecer un tratamiento apropiado para cada paciente.

Effects of abaloparatide on major osteoporotic fracture incidence in postmenopausal women with osteoporosis. Results of the phase 3 ACTIVE trial.

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Síntesis del trabajo: Abaloparatide (ABL) es una droga anabólica ósea, análoga de la PTHrp desarrollada para el tratamiento de la osteoporosis posmenopáusica. El estudio de fase III llamado ACTIVE demostró que ABL fue eficaz para la reducción de la incidencia de nuevas fracturas vertebrales, no vertebrales y clínicas, con aumento significativo de la densidad mineral ósea de columna lumbar, cuello femoral y fémur o cadera total. Este estudio fue realizado a doble ciego, y controlado por placebo, con el objetivo de evaluar la prevención de fracturas en mujeres con osteoporosis posmenopáusica, las que fueron aleatorizadas para recibir 80 µg diarios de ABL, por vía subcutánea, durante 18 meses contra un grupo apareado que recibió placebo subcutáneo. Al mismo tiempo, un tercer grupo de mujeres recibieron 20 µg diarios de teriparatida (TPTD) por vía subcutánea, en forma abierta. Todas recibieron suplementos de calcio y vitamina D. De las 2463 mujeres aleatorizadas, 1901 (77,9%) completaron el estudio. No hubo diferencias demográficas basales significativas entre los grupos. El 44,5% de las pacientes tenía una fractura vertebral preexistente y el 46,8% había sufrido recientemente una fractura no vertebral.

Ante el alto riesgo de morbimortalidad por la aparición de fracturas clínicas osteoporóticas mayores (cuello humeral, muñeca, cadera y vértebras) se describe en este póster su ocurrencia luego de 18 meses de seguimiento dentro del estudio ACTIVE. En el grupo tratado con ABL hubo una reducción significativa de la ocurrencia de fracturas osteoporóticas mayores (67%) comparado con el grupo placebo. En el grupo tratado con ABL (n: 824), la tasa de fracturas fue del 1,2% (HR 0,33, 95% IC 0,16-0,68), mientras que en el grupo placebo (n=821) la tasa de fractura fue del 3,8% (p=0,0014). Durante el seguimiento a 18 meses no fue significativa la acción de TPTD (n=818, tasa de fractura: 2,7%), comparado con placebo (HR 0,7, 95% IC 0,41-1,21, p=0,2028) en relación con la aparición de fracturas clínicas osteoporóticas mayores. Ocurrieron 34 fracturas osteoporóticas mayores en el grupo placebo, 10 en el grupo con ABL y 23 con TPTD. La diferencia entre ABL y TPTD fue significativa, ya que se obtuvo mejor respuesta en el tratamiento con ABL (p=0,0437). La curva de registro de fracturas muestra que el tiempo

hasta la aparición de fracturas clínicas fue mayor en el grupo ABL en relación con placebo y TPTD.

Luego de 18 meses, abaloparatide fue segura y eficaz para reducir la incidencia de fracturas clínicas osteoporóticas mayores en mujeres posmenopáusicas comparada con placebo y TPTD.

Comentario del experto: hasta ahora solo están aprobadas y disponibles como drogas anabólicas puras la teriparatida o PTH 1-34 y la PTH intacta 1-84. Ambas como medicaciones subcutáneas diarias. En la Argentina solo está disponible la teriparatida, por lo que la llegada en un futuro de nuevas opciones anabólicas como abaloparatide ampliaría las escasas opciones terapéuticas anabólicas óseas. Si bien la aplicación nasal de teriparatida fue eficaz para mejorar la densidad mineral ósea, no hay estudios de eficacia en cuanto a la reducción de riesgo de fracturas y aún no está disponible. Abaloparatide es una molécula con características propias de la teriparatida y el agregado de aminoácidos de la PTH rp que potenciarían su actividad anabólica ósea. Los resultados parecerían mejores que los logrados con teriparatida, pero muchas veces el diseño limitado en tiempo del estudio no permite obtener conclusiones definitivas. El desafío es, sin dudas, la correcta indicación de estos fármacos y la eficacia a largo plazo, luego de la suspensión del tratamiento.

MicroRNAs and bone biology: summary of microRNA-related abstracts presented at the 2015 Annual Meeting of the American Society for Bone and Mineral Research

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Introduction

MicroRNAs (abbreviated miRs) are small non-coding RNA molecules (containing about 22 nucleotides) found in plants, animals, and some viruses, which mediate RNA silencing and post-transcriptional regulation of gene expression. miRs play critical roles in regulating cell processes including growth, development, and disease. Recent studies have started to uncover the role of miRs in skeletal biology (1), but our understanding of the actions of miRs in bone is still limited, as evidenced by the high number of abstracts presented at the last meeting of the American Society for Bone and Mineral Research (ASBMR), and reported in the Supplementary Issue 1 of the Journal of Bone and Mineral Research (JBMR vol 30, 2015). We have summarized the main findings of each abstract.

The microRNA miR-23a cluster regulates the differentiation of osteoblasts into osteocytes

This study found that miR-23a overexpressing transgenic mice exhibited low bone mass and a significant decrease in osteocyte density. It was found that the miR-23a cluster was involved in regulating osteocyte differentiation by targeting Prdm16 in the TGF-β signaling pathway.

Discovery of microRNAs in synovium in regulating inflammation leading to bone erosion in rheumatoid arthritis

This study demonstrated that miR-221, derived from inflamed synovial tissues in patients with rheumatoid arthritis, is involved in the regulation of skeletal signaling pathways. MiR-221 regulated osteoblast differentiation and mineralization through the suppression of DKK2 and the Tcf-1, a Wnt downstream target.

The Wnt-miR-218-axis promotes breast cancer-induced osteolytic disease

This study found that Wnt signaling increased cancer-induced osteolytic disease and the

metastatic characteristics of breast cancer cells through the activation of miR-218 expression. Providing a potential therapeutic mechanism to prevent advancement of the disease.

Conditional disruption of miR17~92 in osteoclasts results in activation of functional activity of osteoclasts and substantial loss of trabecular bone in mice

This study investigated the possible role of miR17~92 on bone resorption, through the analysis of the skeletal phenotypes associated with the conditional osteoclast specific deletion (cKO) of the miR17~92 cluster. The miR17~92 cluster was shown to increase osteoclast activity, but did not alter the process of osteoclastogenesis.

Osteoclast-derived exosomal miR-214 inhibits osteoblastic bone formation

This study examined the role of osteoclast-derived exosomal miR-214 on osteoblast activity, through two different studies including the generation of an osteoclast specific overexpressing miR-214 knock-in mouse model and treatment with PKH67-exosomes. Both of these experiments resulted in disorganized trabecular bone, decreased bone mass, and low bone formation. Demonstrating the ability of osteoclast-derived exosomal miR-214 to inhibit bone formation.

MiR-144 inhibits tumor growth and metastasis in osteosarcoma via targeting ROCK1

This study investigated the role of miR-30s in the formation of osteolytic lesions, through experiments examining bone lesion formation in immunodeficient mice injected with MDA-BO2 osteopetrotic cancer cell lines with and without a miR-30s containing retroviral vector. The results demonstrate that increased miR-30s expression reduces the invasion of breast cancer cells into the bone marrow and controls the formation of skeletal lesions in animals with tumors.

Mechanical unloading sensitive miR-138 targets MACF1 to regulate bone formation

This study aimed to determine the regulatory role of specific miRs involved in MACF-1 induced osteogenesis in hind limb unloading (HLU) mice. MiR-138 was found to negatively regulate MACF-1, inhibiting osteoblast activity and matrix mineralization resulting in the inhibition of bone formation, which could be partially reversed in vivo through pretreatment with antagomir-138.

Matrix vesicles mediate the cell-to-cell transmission of microRNA-125b as an inhibitor of osteoclastic bone resorption

This study determined that miR-125b and let-7c were selectively transported into the matrix vesicles (MVs) that play critical roles in the first stages of bone mineralization. Transfection of miR-125b was sufficient to partially inhibited LPS-dependent osteoclastic osteolysis, suggesting that MV-mediated miRs transfer from osteoblasts to osteoclasts in a potential mechanism for cell-to-cell interactions between bone cells.

A novel role of miR-150 in bone homeostasis

This study demonstrated the role miR-150 plays in regulating bone homeostasis, through the regulation of osteoblast and osteoclast differentiation and activity. MiR-150 was shown to negatively regulate osteoactivin/gpnmb, a strong bone anabolic factor, leading to decreased bone mass in miR-150 knockout mice.

MicroRNA regulation of circadian rhythm in the osteoblastic lineage

This study demonstrated the role of miR-433 in regulating circadian rhythm in

osteoblastic cells through the control of rhythmic secretion of glucocorticoids. The authors hypothesized that miR-433 alters the sensitivity of peripheral tissues to changes in the circulating glucocorticoids, which leads to changes in bone metabolism.

miR-322 and Its target protein Tob2 modulate Osterix mRNA stability

This study performed a miR expression profile in BMP-treated cells demonstrating the role miR-322/Tob2 regulation plays in controlling osteogenesis. MiR-322 was shown to negatively regulate Tob2 allowing for increased stabilization of Osx mRNA, demonstrating a complex miR-transcription factor network involved in controlling the process of osteoblast differentiation.

Osteoclastic miR-214 targets PTEN to increase bone resorption

This study demonstrated the role of miR-214 in regulating bone resorption, establishing a relationship between increased osteoclastic miR-214 and bone resorption in postmenopausal osteoporosis and osteolytic bone metastasis. The mechanism for this increase in osteoclast differentiation and activity is through the direct interaction between miR-214 and PTEN.

Reduction in microRNA21 promotes apoptosis and increases RANKL in osteocytes: a mechanism for enhanced resorption in the absence of Cx43 in osteoblastic cells and with aging

This study demonstrated that osteocyte apoptosis observed in Cx43-deficient osteocytes results in the increased osteoclastogenic potential and miR-21 lies downstream of Cx43 in the regulatory pathways involved in osteocyte apoptosis. This study exposes a novel Cx43/miR21/RANKL pathway in osteocytes that could provide a potential target to treat bone fragility with aging.

NR2C2 gene regulated osteoblasts bone formation activity through mir34a TGIF signaling pathway

This study demonstrated that NR2C2 is involved in controlling lipid metabolism through the regulation of TGF-beta signaling via miR-34a. The new features of NR2C2 regulation of the TGF-beta signaling pathway provide new insights on the mechanisms underlying NR2C2 regulation of osteoblast activity.

Aging and caloric restriction significantly alter the microRNA cargo of exosomes and microvesicles in the bone marrow microenvironment

This study found that age did not alter the size or number of extracellular vesicles, (EVs), but significantly changed the miR profile of the EVs. The aged mice exhibited a significant increase in the miRs, miR-141, miR-19b, and miR-183, involved in suppressing osteoclastogenesis and caloric restriction, which has been shown to increase bone resorption, reversed the increase in these miRs miR-141, miR-19b, and miR-183.

The MicroRNA signatures in the patients with lumbar disc herniation

This study examined the miR expression profile in young and old samples with lumbar disc herniation (LDH) versus control aged matched samples. It was found the miR-224 was upregulated in the old samples and miR-130b and miR-147b were significantly downregulated in young samples, suggesting that these miRs might have a critical role in the molecular pathogenesis of LDH.

A transmembrane osteoclastic protein-tyrosine phosphatase (PTP-oc), a Positive regulator of osteoclast activity, is regulated post-transcriptionally in part by miR17 in osteoclastic cells

This study examined the underlying mechanisms involved in the regulation

of PTP-oc through the analysis of pre-miR17~92 transfected osteoclasts. The results from this study demonstrate a direct negative regulatory role of miR-17 on PTP-oc expression, regulating osteoclast function through the suppression of PTP-oc.

MicroRNA miR-30e-5p discriminates patients with idiopathic osteoporosis and low-traumatic fractures

This study examined the circulating miR profile of patients with idiopathic osteoporosis and found that miR-30e-5p was specifically upregulated in patients with low-traumatic fractures. This miR has been previously reported to repress osteogenic differentiation through IGF2 both in vivo and in vitro.

Specific microRNA signatures in CKD patients focusing on the risks of calcifications and ROD

The study examined the miR profile in late stage CKD patients and found various significantly down-regulated miRs, that have been shown to be related to vascular smooth muscle cell (VSMC) and bone metabolism, in the patient versus the control group. The altered miR profiles may provide an early diagnostic tool to identify late stage CDK patients with a high risk of bone demineralization or vascular calcification.

Pulsed electromagnetic fields (PEMF) enhance osteoblastic differentiation of human bone marrow stromal cells by activation of microRNA21 expression and the TGF-b signaling pathway

The findings from this study suggest that PEMF may affect hBMSC and regulate bone metabolism through miR-21, which directly acts on Smad7 reducing its expression. Reduced Smad7 results in the activation of the TGF-β signaling pathway and subsequent activation of Runx2.

MicroRNAs involved in bone metabolism are transported into matrix vesicles during bone formation

This study examined the miR expression profile in matrix vesicles (MVs) shown to play a critical role in bone formation and resorption. From the miRs that were identified to be found in MVs, eighty-one of miRs were identified to be downregulated and none of the miRs were found to be upregulated.

Murine microRNA 126-3p is upregulated by endothelin-1 signaling and mediates some of its pro-mineralization effects

This study demonstrated the role endothelin-1 (ET-1) signaling plays in the process of mineralization. ET-1 increases mineralization through the induction of SOST expression, by altering the expression of miR-126-3p.

MicroRNA profiling of the early phases of fracture repair

To determine the miR expression profile during the early stages of fracture healing, this study created femoral fractures in mice and isolated miR enriched RNA from intact and post fracture bones at days 1, 3, 5, 7, 11, and 14. The results from this study provide a complete analysis of the miR expression pattern observed during fracture repair, allowing for future determination of the roles of miRs in the underlying molecular mechanism involved in the early stages of fracture healing and providing possible therapeutic targets to treat delayed fracture healing.

Increased microRNA-34a expression levels in Paget's disease of bone

Through examining the expression of miR-21 and miR-34a in peripheral blood mononuclear cells isolated from individuals with Paget's disease of bone (PDB), it was determined that the expression levels of these particular miRNAs were increased in the patients with PDB compared to controls. There were no observed differences in

miRNA expression levels in monostotic versus polystotic PDB patients or with respect to the presence of the SQSTM1 mutation. The findings from this study demonstrate a negative correlation between the level of expression of miR-34 and the bone turnover rate.

MicroRNAs miR-29b-3p, miR-365a-3p, miR-550a-3p are correlated to histomorphometry and bone turnover markers in idiopathic osteoporosis

This study tested the correlation between specific bone circulating markers, miRs specific to bone, and bone histomorphometry parameters in pre-and post-menopausal men and women. It was determined that there was no significant alteration in bone specific miRs between the groups; however, increased expression of miR-29b-3p and miR-365-3p, was associated with known bone turnover regulators, and correlated with the bone turnover makers in the individuals with osteoporosis.

The tumor suppressor miRs-30-5p family in the control of metastatic bone disease

This study investigated the role of miRs one the engraftment of breast cancer cells in bone, to evaluate whether miR30s participate in the formation of bone micrometastases and subsequent osteolytic lesions. For this, miR30 was overexpressed in a breast cancer cell line. It was demonstrated that cells with increased miR30s expression induced osteolytic lesions that were smaller than control cells, associated with reduced tumor burden. The invasiveness of the breast cancer cells was also reduced in vitro when miR30 was overexpressed. On the other hand, low miR30 expression in primary tumors from patients was associated with poor relapse-free survival. These pieces of data suggest that miR30 controls breast cancer cell invasion in the bone marrow and the formation of bone lesions.

Human micro-RNAs miR-29b, miR-30c2 and miR-125b and their target genes are important modulators of bone metabolism

The human miRs miR-29b, 30c2 and 125b were shown to directly target multiple genes involved in bone homeostasis including COL1A1, RUNX2, and FRZB. Suggesting these particular miRs play a role in coordinating the activities of the critical regulators of osteoblast differentiation and the extracellular matrix proteins involved in modulating skeletal gene expression.

Curcumin promoting osteosarcoma cell death by activating miR-125a/ ERRa/ROS pathway

This study demonstrated that curcumin (Cur) suppressed ERRa expression through the upregulation of miR-125, which resulted in Cur induced osteosarcoma cell death. Providing evidence for a potential cancer therapy mechanism leading to the activation of miR-125/ERRa/ROS pathyway in osteosarcoma cells.

Mechanical responsive miR-365 contributes to osteoarthritis development

This study concluded that on of the key factors resulting in the destruction of osteoarthritic cartilage is the increased expression of miR-365 induced by the biophysical and biochemical factors that make up articular chondrocytes in humans. Suggesting the therapeutic potential of a miR-365 inhibitor to prevent cartilage degeneration.

Regulation of chondrocyte differentiation by miR-483

This study showed the pro-chondrogenic role miR-483 plays in promoting stem cell chondrogenic differentiation and hypothesized that the underlying mechanism involves increased responsiveness to the growth factors TGF-β3 and IGF1 and/or modifying Wnt signaling.

Elevated miR-214 level within osteoclasts associates with increased bone resorption in both postmenopausal osteoporosis and osteolytic bone metastasis

This study found that increased miR-214 levels in osteoclasts resulted in an increase in osteoclast activity in both post-menopausal osteoporosis and osteolytic bone metastasis cancer. Providing evidence for the role of miR-214 in these bone diseases characterized by increased bone resorption.

Targeted inhibition of miR-214 in osteoclasts suppresses bone resorption in both ovariectomy induced osteoporosis and osteolytic bone metastasis in vivo: A pilot study

This study examined the effects of inhibiting miR-214 in osteoclasts and showed that inhibition of miR-214 led to a suppression of bone resorption in ovarectomized and osteolytic bone metastasis mouse models. Highlighting the role of miR-214 in the process of bone resorption.

A network connecting KAT6A and the miR-665 regulates the odontoblast differentiation program

This study identified miR-655 as an inhibitor of odontoblast maturation through the reduction of KAT6A and RUNX2 expression. The mechanism underlying miR-655 in odontoblast differentiation involves the regulation of the genetic and epigenetic events required to maintain tooth formation and homeostasis.

Insulin receptor substrate 1 time-dependently regulates bone formation by controlling collagen I alpha 2 expression through miR-342

The findings from the study demonstrate that IRS-1 has the ability regulate bone formation in a time-dependent manner through the regulation Col1a2 expression through miR-342. It was shown that miR-342 inhibition lead to an increase in Col1a2 and ALP activity demonstrating a new mechanism for the insulin signal involved in the bone formation.

Expert Commentary

Mounting evidence indicates that miRs control the physiological function of osteoclasts, osteoblasts and osteocytes; as well as cartilage and tooth development. In addition, the reports presented at the ASBMR meeting assign a role of miRs in skeletal pathologies, from osteoarthritis to metastatic bone cancer. However, further studies are needed to fully understand the role of these non-coding small RNA fragments in bone biology in health and disease.

References

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