ASARM peptides: PHEX-dependent and -independent regulation of serum phosphate

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David V, Martin A, Hedge A-M, Drezner MK, Rowe PS. ASARM peptides: PHEX-dependent and -independent regulation of serum phosphate. Am J Physiol Renal Physiol 300: F783–F791, 2011. First published December 22, 2010; doi:10.1152/ajprenal.00304.2010.—Increased acidic serine aspartate-rich MEPE-associated motif (ASARM) peptides cause mineralization defects in X-linked hypophosphatemic rickets mice (HYP) and “directly” inhibit renal phosphate uptake in vitro. However, ASARM peptides also bind to phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) and are a physiological substrate for this bone-expressed, phosphate-regulating enzyme. We therefore tested the hypothesis that circulating ASARM peptides also “indirectly” contribute to a bone-renal PHEX-dependent hypophosphatemia in normal mice. Male mice (n = 5; 12 wk) were fed for 8 wk with a normal phosphorus and vitamin D3 diet (1% P, diet) or a reduced phosphorus and vitamin D3 diet (0.1% P, diet). For the final 4 wk, transplantation of mini-osmotic pumps supplied a continuous infusion of either ASARM peptide (5 mg·day⁻¹·kg⁻¹) or vehicle. HYP, autosomal recessive hypophosphatemic rickets (ARHR), and normal mice (no pumps or ASARM infusion; 0.4% P, diet) were used in a separate experiment designed to measure and compare circulating ASARM peptides in disease and health. ASARM treatment decreased serum phosphate concentration and renal phosphate cotransporter (NPT2a) mRNA with the 1% P, diet. This was accompanied by a twofold increase in serum ASARM and 1,25-dihydroxy vitamin D3 [1,25 (OH)₂D₃] levels without changes in parathyroid hormone. For both diets, ASARM-treated mice showed significant increases in serum fibroblast growth factor 23 (FGF23; +50%) and reduced serum osteocalcin (−30%) and osteopontin (−25%). Circulating ASARM peptides showed a significant inverse correlation with serum P, and a significant positive correlation with fractional excretion of phosphate. We conclude that constitutive overexpression of ASARM peptides plays a “component” PHEX-independent part in the HYP and ARHR hypophosphatemia. In contrast, with wild-type mice, ASARM peptides likely play a bone PHEX-dependent role in renal phosphate regulation and FGF23 expression. They may also coordinate FGF23 expression by competitively modulating PHEX/DMP1 interactions and thus bone-renal mineral regulation.

Among these proteins, MEPE was cloned from a tumor-related acidic serine aspartate-rich motif (ASARM) peptide is responsible for inhibition of mineralization in HYP osteoblasts (37). We also showed that PHEX, a membrane protein present in osteocytes and osteoblasts, is able to bind to MEPE via the ASARM motif (31, 37, 51). This interaction could prevent proteolysis of MEPE and release of protease-resistant phosphorylated ASARM peptides into bone and circulation (49). We previously showed in vitro and in vivo that ASARM peptide is responsible for inhibition of mineralization in HYP osteoblasts (37). This is further supported by the observation that ASARM peptides can regulate PHEX expression and activity (2, 10, 31, 37, 51). In HYP, defective PHEX (null activity) is accompanied by increased activities from other bone proteases (16, 37–39, 48) and increased MEPE expression (4, 9, 30, 37, 48, 49, 66). This causes the release of excessive amounts of protease-resistant ASARM peptides from MEPE and likely DMP1 (4, 9, 13, 30, 37, 48, 49, 66). These peptides are candidates for the growth and mineralization defects in vivo (37). Specifically, ASARM peptides are potent inhibitors of mineralization (2, 7, 13, 31, 37, 51, 52) and administration in vitro induces increased expression of fibroblast growth factor 23 (FGF23), a potent phosphatonin (31, 37). ASARM peptides likely induce increased FGF23 expression by competing with other PHEx substrates and/or disrupting PHEx activity (2, 10, 31, 37, 51). It remains to be determined how loss of PHEx activity induces increased FGF23 expression.

Although the ASARM model is compelling, specific in vivo questions remain. For example, several studies confirm full-length MEPE inhibits intestinal/renal phosphate transport and mineralization in vivo and in vitro (14, 36, 49, 52, 56). These studies consist of bolus injections or direct perfusion in rats and mice using recombinant MEPE protein. In vitro studies using ASARM peptides show similar results (1, 2, 31, 37, 48, 51, 52, 66).
ASARM peptides

Mice consisted of four groups (ASARM peptide [NH2-RDDSSESSDSGS(PO3H2)SS(PO3H2)ES-0.1% Pi diet and 1% Pi diets, respectively (wild-type mice were used (MAL Care and Use Committee. Twenty 12-wk-old male C57B/L6 protocols were approved by the University of Kansas Institutional Animal Care and Use Committee. Twenty 12-wk-old male C57B/L6 wild-type mice were used (without Alzet pumps or ASARM infusion; n = 5/group) for the Alzet pump infusion study with 30 control untreated mice (without pumps or infusion). A total of 15 control mice (no pumps or treatment) were used for the 0.1% P, diet and 1% P, diets, respectively (n = 15). The pump-treated mice consisted of four groups (n = 5) as follows: 1) 1% P, diet vehicle (V), 2) 1% P, diet ASARM infused, 3) 0.1% P, diet V infused, and 4) 0.1% P, diet ASARM infused. Animals were individually housed and fed ad libitum either a phosphate and vitamin D3-deplete diet (0.1% P,) or a phosphate and vitamin D3-replete diet (1% P,) for 2 mo. The 1% P, diet contained 1% phosphorus and 2.4 IU/g vitamin D3 diet (Harlan Teklad Rodent Diet 8604, Indianapolis, IN), and the 0.1% P, diet contained 0.1% of phosphorus and 1 IU/g vitamin D3 diet (Test Diet AIN-93M, Richmond, IN). During the last month of the respective diets, mice were also infused using Alzet osmotic pumps (Durect, Cupertino, CA) with ASARM peptide (5 mg day1 kg1) or V (HEPES-buffered saline). Untreated C57B/L6 12-wk-old male mice (without Alzet pumps or ASARM infusion; n = 15) were also included as additional controls.

ASARM peptide [NH2-RDDSSESSDSGS(P03H2)SS(P03H2)ES-(P03H2)2GD-OH] was synthesized using standard techniques and purchased from neo-MPS Biosystems (Multiple Peptide Systems, San Diego, CA) as described previously (37, 51). Peptide purity was greater than 80% via HPLC, ion exchange, and also mass spectrometry. HYP (66) and ARHR mice (DMPI null) (18) were age and gender matched (male; 12 wk). Sera were collected as described for the wild-type mice. HYP mice, DMPI-null mice (ARHR), and wild-type littermates (CSBL6, backgrounds, 6 wk) were compared separately to the Alzet pump and control mice group and were not treated with pumps or ASARM peptides. Also, these mice (HYP, ARHR, and wild-type) were fed a 0.4% Pi diet (Lab Diet no. 5001; PMI LabDiet, St. Louis, MO) since this diet was optimal for mutant mice viability.

Serum and urine measurements. Blood samples were collected in separator tubes and urine was collected overnight in metabolic cages. Serum and urine measurements. Blood samples were collected in separator tubes and urine was collected overnight in metabolic cages.

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**Statistical analysis.** Statistical analysis was performed using statistical software STATISTICA (StatSoft, Tulsa, OK) or PRISMS (GraphPad Software, La Jolla, CA). Differences between groups were initially analyzed by two-way ANOVA. When F values for a given variable were found to be significant, the sequentially rejecting Bonferroni-Holm test was subsequently performed using the Holm’s adjusted P values. Results were considered to be significantly different at P < 0.05.

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the 1% Pi. Also, the ASARM-treated 0.1% Pi group had increased phosphaturia compared with the 0.1% Pi, V and control mice (Fig. 1B). The hypophosphatemia and renal phosphate leak was mirrored by a significant decreased expression of NPT2a mRNA (Fig. 1C). Consistent with this finding, a significant inverse correlation between serum Pi, and serum ASARM peptides occurred with V mice and control mice. The inverse correlation between serum Pi, and serum ASARM holds for different ages and diets (Fig. 2, A and B). In agreement with these observations, an opposite positive correlation between urinary ASARM peptides and FEP occurred with V and control mice (Fig. 2C). In contrast, no significant correlations were observed between serum Pi, and serum ASARM in mice treated with synthetic ASARM peptides (osmotic pumps, both diets; Fig. 2D), HYP mice, or DMP1 mice (data not shown). This was despite the hypophosphatemia and increased FEP relative to V and control groups. The lack of correlation in ASARM-treated wild-type mice is likely due to ASARM supersaturation and a threshold effect. In HYP mice and DMP1-null mice, a more complex mechanism is likely due to the constitutive overexpression of FGF23 and mutations in PHEX and DMP1, respectively. This interpretation is congruent with the strong correlations between ASARM peptides (serum and urine) and serum Pi, or FEP in normal mice and V mice on all diets. Specifically, the untreated normal mice have lower subthreshold levels of endogenous ASARM peptides.

**Dietary Pi, and 1,25 (OH)_2D_3 alter serum and urinary ASARM peptide levels.** On both diets, ASARM peptide-treated mice displayed a greater than twofold increase in serum ASARM levels (P < 0.05) compared with the V-treated animals (Fig. 3A). Also, a significant 0.5-fold increase in serum ASARM peptides occurred with both the ASARM-treated and V mice fed the 0.1% Pi, diet relative to matched groups on the 1% Pi, diet (Fig. 3A). A significant decrease in urinary ASARM peptides (corrected for creatinine) occurred with V-treated mice fed the 0.1% Pi, diet. In contrast, urinary ASARM peptide levels remained the same for both diets with ASARM-treated mice (Fig. 3B). Thus, on the 0.1% Pi, diet, urinary ASARM levels were significantly higher with ASARM-treated mice relative to V-treated mice. Of note, with control mice (without osmotic pumps) and V mice (with osmotic pumps) on both diets, an inverse correlation between serum ASARM and urinary ASARM peptides occurs (Fig. 3, C, D, and E). However, the correlation is weaker with mice on the 0.1% Pi, diet.

In contrast, ASARM-treated mice showed a nonsignificant trend toward a positive correlation between serum ASARM and urinary ASARM (Fig. 3F). In conclusion, these data demonstrate ASARM peptide levels are subject to dietary Pi, and vitamin D3.

**Increased ASARM peptides in HYP and ARHR correlate with phenotype.** Serum Pi, levels of DMP1(null) mice (ARHR) were significantly higher than HYP mice and significantly lower than wild-type mice fed the same diet. The converse was true for serum ASARM peptide levels. Indeed, an inverse correlation between serum Pi, and serum ASARM peptides mirrored the phenotypic severity of the hypophosphatemia (Fig. 4, A, B, and C).

**ASARM regulates the 1,25(OH)_2D_3/FGF23/PTH system.** ASARM treatment led to a significant twofold increase in 1,25 (OH)_2D_3 serum levels in mice fed the 1% Pi, diet. In contrast, there were no significant differences in serum 1,25 (OH)_2D_3 between both ASARM-treated and V groups on the low-phosphate diet (Fig. 5A). However, V and ASARM-treated mice fed the 0.1% Pi, diet had a significant two- and fourfold decrease in 1,25 (OH)_2D_3 serum levels, respectively (relative to 1% Pi, diet-fed mice). This was because of the severely decreased dietary vitamin D3 composition of the 0.1% Pi, diet. In accord with the low dietary vitamin D3, a twofold increase (P < 0.05) in serum parathyroid hormone (PTH) levels for V-treated animals occurred with the 0.1% Pi, diet (Fig. 5B). In contrast, ASARM-treated animals retained uniform PTH levels on both diets. Increased phosphorus excretion was concordant with increased FGFR3 serum levels in both ASARM-treated groups compared with their diet-matched V groups (P < 0.05; Fig. 5C). A marked decrease in FGFR3 levels occurred in both 0.1% Pi, diet groups compared with the 1% Pi, diet-fed mice. Also, for both diets, a significant increase in serum FGFR3 levels occurred with ASARM-treated vs. V mice. The increase was more marked with the 1% Pi, diet and two-way ANOVA analysis showed a significant ASARM peptide-dependent effect on FGFR3 levels (P = 0.0037). FGFR3 levels in HYP and
marked significant decrease in urinary and serum OPN levels occurred with ASARM-treated animals relative to control and V mice (Fig. 5, D and E). In contrast, no significant differences occurred with ASARM-treated mice fed the 0.1% P diet relative to control and V mice. Of note, OPN levels (sera and urine) were decreased significantly in V-treated and control animals fed the 0.1% P diet relative to the 1% P diet (Fig. 5, D and E). This diet-associated decrease did not occur with ASARM-treated mice (only with the wild-type mice). Specifically, the relative OPN levels on 1% P, and 0.1% P, diets remained unchanged with ASARM-treated mice (Fig. 5, D and E).

**DISCUSSION**

The ASARM motif is released as a small protease-resistant ASARM peptide following degradation of MEPE and other SIBLINGs (e.g., DMP1) by osteoblastic proteases (9, 37, 48, 49). The abundance of these peptides in hypophosphatemic and bone mineralization disorders (8, 9, 48, 66) suggests they play a key role in phosphate and bone-mineral homeostasis. To our knowledge, this is the first study establishing ASARM as a phosphaturic peptide that induces hypophosphatemia in vivo.
Fig. 5. ASARM peptides induce diet-dependent changes in 1,25 dihydroxy vitamin D3 [1,25(OH)2D3], parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and osteopontin (OPN) levels. A, B, C, D, and E: sera or urine chemistries (as indicated) for 1,25(OH)2D3, PTH, FGF23, and OPN. Mice were fed the 1% Pi diet or the 0.1% Pi diet as labeled on the x-axis (n = 5; ASARM, vehicle, and control). Diagonally striped columns represent control mice without osmotic pumps, filled columns represent osmotic pump ASARM peptide-infused mice. The significant differences in metrics between ASARM-treated and vehicle-treated mice on both 1% Pi and 0.1% Pi diets are numbered on the graph (P value, 1-way ANOVA with Newman-Keuls multiple comparison test). P values of <0.05 are considered significant and are also highlighted with *. Arrows highlight the columns compared by 1-way ANOVA and Newman-Keuls posttest. Broken lines highlight cross comparisons for more than one column where the significance or nonsignificance computation is identical. Finally, for all metrics, 2-way ANOVA confirmed significant ASARM treatment-dependent changes between mice and control or vehicle mice (P < 0.05). For control mice or vehicle mice, 2-way ANOVA analysis showed significant diet-influenced changes for all metrics (P < 0.05). For ASARM-treated mice, 2-way ANOVA showed significant diet-influenced changes for all metrics (P < 0.05) except for serum PTH and serum/urine OPN. Note, all mice are male 19-wk and C57BL/6 strains. Control mice are identical. Finally, for all metrics, 2-way ANOVA confirmed significant ASARM treatment-dependent differences between mice and control or vehicle mice (P < 0.05). For control mice or vehicle mice, 2-way ANOVA analysis showed significant diet-influenced changes for all metrics (P < 0.05). For ASARM-treated mice, 2-way ANOVA showed significant diet-influenced changes for all metrics (P < 0.05) except for serum PTH and serum/urine OPN. Note, all mice are male 19-wk and C57BL/6 strains. Control mice are normal mice without osmotic pumps, vehicle, or synthetic ASARM peptide infusion.

Our study shows a significant decrease (~97%; P < 0.05) in NPT2a renal phosphate transporter mRNA expression is likely responsible for the lowered serum P1. However, altered NPT2c expression may also be involved since both NPT2a and NPT2c renal phosphate transporters are decreased in several familial and oncogenic hypophosphatemic bone mineralization disorders including HYP, ADHR, ARHR, and TIO (27, 45, 49, 59). As reported previously, we found increased serum ASARM peptide levels in mice with HYP relative to normal mice (2, 9, 31, 37, 48, 66). For the first time, we also confirm serum ASARM peptide epitopes are increased in mice with autosomal recessive hypophosphatemic rickets (ARHR or DMP1-null mice; Fig. 4). Intriguingly, the ARHR hypophosphatemia was intermediate to wild-type and HYP and this correlated with circulating ASARM peptide levels. Thus, we provide further evidence that shows ASARM peptides play a major role in the bone-renal pathophysiology of familial and oncogenic hypophosphatemic disorders.

Fig. 6. PHEX, DMP1, matrix extracellular phosphoglycoprotein (MEPE), and ASARM peptides are proposed to dynamically regulate FGF23 expression in bone. An indirect pathway (A) predominates in normal physiology and a component direct pathophysiological pathway (B) predominates in familial and tumor forms of rickets/osteomalacia with hypophosphatemia [HYP, autosomal recessive hypophosphatemic rickets (ARHR), ADHR, and tumor-induced osteomalacia for example]. A: indirect ASARM pathway: 1) PHEX (a Zn metalloendopeptidase) is proposed to interact with DMP1 by binding to the DMP1-ASARM motif located at the COOH-terminal region of DMP1 (see also Fig. 7). The PHEX-DMP1 binding initiates a signaling pathway that reduces FGF23 expression. Note that in support of this, in XLH and ARHR, mutations in “PHEX or DMP1” result in hypophosphatemia through increased FGF23 expression and stability (overlapping pathophysiologies) (18, 24, 35). Also, PHEX binds with high affinity and specificity to ASARM peptides or ASARM protein motifs (MEPE, DMP1, and osteopontin derived) and MEPE protein (1, 2, 37, 51). PHEX cleaves ASARM peptides, the only known physiological substrate for PHEX (1, 2, 10, 37, 51). Also, SIBLINGs (like DMP1) activate PHEX-related Zn metalloproteinases via their binding interactions (17, 25). DMP1 for example binds and activates a PHEX-related Zn metalloproteinase 9 (MMP9) (17). Finally, in the intraditio addition of recombinant DMP1 to UMR-106 cells causes a dose-dependent decrease in FGF23 expression (mRNA and protein) (54). ASARM peptides are proposed to competitively displace the DMP1-PHEX complex in “normal mice” by forming a high-affinity/specificity PHEX-ASARM complex (37, 51) that is slowly hydrolyzed (low Kcat/Km) by PHEX (1, 2, 10). 2) This causes an upregulation of FGF23. Increased FGF23 expression leads to reduced 1,25 vitamin D3, reduced NPT2a expression, and hypophosphatemia. The competitive displacement of DMP1 by ASARM peptides provides an additional “bone” fine tuning of FGF23 and renal phosphate mineral homeostasis. B: direct pathophysiological ASARM pathway that is independent of FGF23, PHEX, and DMP1 is proposed to occur in familial HYP, ARHR, and ADHR. For example, in XLH and ARHR, expression of MEPE and several bone proteases including cathepsins, ECEL1/DINE, and NED are markedly increased (37–39, 48, 55) resulting in excess ASARM peptide production and inhibition of mineralization (2, 9, 37, 48, 66). In these diseases, specific cleavage of MEPE and/or other bone SIBLING proteins (DSPP, OPN, DMP1, etc.) generates an excess of free protease-resistant ASARM peptides (37, 48). ASARM peptides are acidic, highly charged, with low PIs and are extraordinarily resistant to a wide range of proteases and have physicochemical similarities to bisphosphonates, phosphonoformic acid (PFA), and phosphonoacetic acid (PAA). Also, they share biological properties in vivo and in vitro with bisphosphonates, PFA, and PAA in that they all inhibit mineralization and interfere with renal phosphate handling and vitamin D metabolism (6, 28, 32–34, 40–42, 57, 58, 60, 61, 63). Much work remains to be done to confirm the proposed speculative model presented in the above scheme.
In this study, ASARM-induced hypophosphatemia in wild-type mice on a normal diet (1% P) was accompanied by an increase in serum 1,25 (OH)2D3. This increase in 1,25 (OH)2D3 is consistent with our previous in vivo findings following bolus injections of full-length recombinant MEPE in wild-type mice (52). Also, the vitamin D receptor-null mouse has increased MEPE expression (44), and 1,25 (OH)2D3 suppresses MEPE expression in vitro (3). Of note, the increase in ASARM peptide levels observed in the V mice on a combined low-phosphorus and low-vitamin D3 diet (0.1% P) suggests that P and 1,25 (OH)2D3 are potent inhibitors of ASARM production under physiological conditions. Since ASARM peptides are derived in part by cleavage of MEPE by cathepsins and other osteoblastic proteases (8–10, 16, 37–39, 48, 49), this increase was likely sourced from the endogenous biological pool of peptides.

The ASARM-induced, increased serum 1,25 (OH)2D3 contrasted with the inappropriately normal levels of 1,25 (OH)2D3 found in HYP mice with pathologically increased endogenous ASARM peptides (15). However, ASARM treatment of normal mice (both diets) mirrored the increased FGF23 reported for HYP mice (9, 31, 37, 48, 66) and was uniform with our previous ASARM peptide in vitro findings (31, 37). Notably, the increased serum FGF23 is consistent with the known feedback mechanism designed to suppress inappropriate increases in serum 1,25 (OH)2D3 (53). In contrast, PTH levels remained unchanged in the ASARM peptide-treated mice on the normal 1% P diet. This was likely also due to the ASARM-mediated increase in serum 1,25 (OH)2D3. The ASARM-induced hypophosphatemia [despite the increased serum 1,25(OH)2D3] is evidence for a direct suppression of renal P transport due to increased FGF23. Indeed, several studies report FGF23 interacts with Klotho to directly suppress renal NPT2A expression in the brush border of renal proximal convoluted tubules (45). Likewise, ASARM peptides (in vitro) and MEPE (in vivo and in vitro) directly inhibit Na-dependent P uptake in renal cells (14, 36, 49, 51, 52, 56).

ASARM peptides bind with high specificity to PHEX and some of the ASARM peptide biological effects are mediated through a PHEX-ASARM interaction that includes regulation of FGF23 expression (31, 37, 51). However, although the evidence presented from our studies and others show compellingly ASARM peptides affect phosphate regulation indirectly through a PHEX/FGF23/DMP1 pathway, there is also evidence of direct inhibition. Specifically, ASARM peptides and recombinant MEPE directly inhibit P uptake in renal cell cultures and recombinant MEPE inhibits P uptake in renal micropuncture experiments (14, 36, 48, 51, 52, 56, 62). The direct inhibition is likely initiated by physicochemical mechanisms similar to that described for etidronate and foscarne
Since MEPE ASARM peptides are mineralization inhibitors (2, 7, 13, 31, 37, 51, 52), their presence in urine may well help suppress renal calcification (13). Indeed, we recently showed mice overexpressing MEPE contained increased urinary ASARM peptides and were resistant to diet-induced renal calcification (13). Also, OPN (a related SIBLING protein) has been implicated as a component player in the exquisitely complex multistep process of renal stone formation (11–13, 21, 23, 43, 64). Remarkably, our data show synthetic ASARM peptides suppress significantly serum/urine OPN levels (protein) in mice fed the 1% Pi diet. This is consistent with our earlier studies with MEPE transgenic mice that showed marked suppression of renal calcification with increased urinary ASARM peptides and altered OPN (13). More studies are required, however, to confirm a direct mechanistic role for OPN and acidic ASARM peptides.

Figure 6 illustrates a scheme that proposes a physiological role for ASARM peptides and Fig. 7 shows the extended cross species homologies of the DMP1 and MEPE ASARM regions. Specifically, FGF23 expression and processing are regulated by competitive displacement of the DMP1-PHEX complex by free ASARM peptides. A feedback regulatory loop involving FGF23, 1,25(OH)2D3, ASARM peptides, and PHEX orchestrates this pathway as explained in Fig. 6. Thus, we propose a novel pathway linking bone mineralization, bone turnover, and phosphate requirement across a bone-renal axis. More work is needed to confirm this pathway particularly the proposed interactions between DMP1 and PHEX through the DMP1-ASARM motif. Compelling support for the model is provided by the demonstration that PHEX and DMP1 mutations lead to identical pathophysiological (18, 24, 35) and PHEX binds/ hydrolyzes ASARM peptides (1, 2, 10, 37, 51). To date, ASARM peptides are the only known physiological substrate for PHEX (1, 2, 10, 37, 48, 51).

To conclude, our study shows for the first time ASARM peptide(s) from MEPE and likely other SIBLING proteins (DMP1, for example) are phosphaturic agents in vivo. Also, these peptides likely play an indirect PHEX-dependent in vivo regulatory link between DMP1, FGF23, and bone-renal mineral regulation in normal mice. Contrasting with normal mice, HYP and ARHR mice have defective PHEX and DMP1, respectively. Because of this, there is no PHEX-DMP1 interaction and FGF23 is therefore constitutively overexpressed. Also, the FGF23 overexpression is independent of an upstream ASARM-regulated PHEX/DMP1 interaction. However, both mutant mice (HYP and ARHR) overexpress ASARM peptides due to abnormal bone protease expression (16, 37–39, 48) and increased MEPE expression (4, 9, 30, 37, 48, 49, 66). In this abnormal context, ASARM peptides likely play a direct but component “PHEX-independent” part in the hypophosphatemic pathophysiology. Specifically, in HYP and ARHR, FGF23 is the chief hypophosphatemic stimulus and ASARM peptides exacerbate the renal phosphate leak by virtue of their over- abundance and intrinsic, hypophosphatemic, physicochemical properties.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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