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Role of FGF23 and alkaline phosphatase in bone health: Case-based clinico-physiologic discussion

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ABSTRACT

Proper bone development requires the coordinated and calibrated action of various cells, hormones, enzymes and nutrients. In this paper, we present two clinical cases of metabolic bone disorders – one with excessive fibroblast growth factor-23 (FGF23) and the other, with low alkaline phosphatase. FGF23 and alkaline phosphatase are not-so-well-known players in bone health. This paper puts the spotlight on these two, and discusses their role in bone development, and how abnormal levels lead to disease.

INTRODUCTION

The well-known hormones affecting bone health are calcium, vitamin D, parathyroid hormone and estrogen which influence the osteoblasts, osteocytes and osteoclasts. (Florencio-Silva et al. 2015) This article intends to introduce two not so well-known players in bone health, specifically fibroblast growth factor-23 (FGF23) and alkaline phosphatase.

Objectives:

This paper aims to (1) present two clinical cases with metabolic bone disorders, (2) discuss the physiologic role of FGF23 in bone development, as seen in a case with excessive FGF23, and (3) discuss the physiologic role of alkaline phosphatase in bone development, as seen in a case with low alkaline phosphatase.

MATERIALS AND METHODS

Study Design
Case report of 2 patients and review of literature

Methodology
A comprehensive history and physical examination were performed on two patients referred for evaluation and co-management at the University of the Philippines – Philippine General Hospital. . Laboratory test results were interpreted. All available clinical information was analyzed, and a logical diagnosis was made. Patients were managed and followed-up accordingly. Their clinical cases are written up here. Review of literature was also done and a discussion of the importance of FGF23 and alkaline phosphatase in bone health is presented.

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KEYWORDS

Fibroblast growth factor 23, alkaline phosphatase, bone, fracture, osteomalacia

RESULTS AND DISCUSSION

Case 1

The full details of this patient have been extensively discussed in a separate publication by the primary author. (Sandoval et al 2017) Briefly, a Filipino male in his 30s consulted for "nakukuba at masakit ang mga buto". He had low back pain for the past 5 years, associated with hunchback deformity, and progressive loss of height. He has lost 14 cms over 5 years.

On physical examination, he had severe kyphosis and pectus carinatum (pigeon chest deformity). Inspection of the oral cavity showed a pinkish, fleshy mass at the floor of the tongue. This was smooth, not bleeding, not painful, did not have necrosis and not foul-smelling. It was not impairing with his speech or chewing.

Biochemically, serum calcium levels were normal to high, measured at 2.38 to 2.65 mmol/L (normal range: 2.10 – 2.55). His serum phosphate was consistently low and ranged from 0.28 to 0.64 mmol/ (normal range: 0.81 – 1.49). Serum creatinine was normal. Intact Parathyroid hormone was high at 173.5 pg/mL (normal range: 10 – 65). Serum alkaline phosphatase was also high at 243 IU/L (normal range: 38-126). 25-OH vitamin D was low at 13.86 nmol/L (normal range: >80).

With these biochemical findings, the initial impression was primary hyperparathyroidism characterized by an excess of parathyroid hormone leading to high serum calcium, low serum phosphorus and bone deformities. However, on further workup, ultrasound did not reveal any enlarged parathyroid, while parathyroid scintigraphy did not reveal any hyperfunctioning parathyroid gland.

X-ray showed pathognomonic findings in osteomalacia called pseudo-fractures or Looser zones at his ulnae, 4th metacarpals, and 4th metatarsals. Bone densitometry showed low bone mass for age, with Z-score as low as -5.0.

Because of the consistent hypophosphatemia, measures of renal phosphate wasting were ascertained. (Payne 1998)

Tubular phosphate reabsorption (TRP) was computed using the formula:

TRP= 1- [(serum creatinine x urine phosphate)/(urine creatinine x serum phosphate)]

This patient had a value of 0.8745.

Tubular maximum reabsorption of phosphate corrected for GFR (TmP/GFR) was computed using the formula:

TmP/GFR = a x serum phosphate,
where a = (0.3 x TRP) / [1- (0.8 x TRP)]

TmP/GFR was found to be low at 0.54, (normal range for age and sex: 1.00 to 1.35). This indicates that reabsorption of phosphate by the proximal convoluted tubule is low. Hence, the patient was excessively excreting phosphate through his urine.

Incision biopsy of the mass in the oral cavity showed peripheral fibroma.

With these laboratory findings, the final diagnosis was tumor-induced osteomalacia (TIO).

The patient eventually underwent excision of the oral mass. Histopathology showed that the tumor was composed of whorls of fibroblasts, and adjacent areas showing tissues that resemble bone and cartilage. With these features, final histopathologic diagnosis was an ossifying peripheral fibroma.

Despite the persistently low serum phosphate levels, the patient was not yet given phosphorus or vitamin D supplements. The only intervention performed on him was the excision of the mass. One day after surgery, serum phosphate already increased by three times, and by day 2, it already reached normal levels and was sustained thereafter. The measures of serum phosphate wasting, TRP and TmP/GFR, both increased by the fifth day post-op with TmP/GFR, now within normal range.

TIO is a rare paraneoplastic syndrome wherein a tumor produces a hormone that causes excessive phosphate excretion, called a phosphatonin. It can be from various histologies, with the tumors being mesenchymally-derived (phosphaturic mesenchymal tumors), a fibroma included. Chronic hypophosphatemia leads to defective bone mineralization, also known as osteomalacia. It was in the year 2001 that the phosphatonin in TIO was extracted, and its complementary DNA was found to be identical with the already known molecule FGF23. (Shimada et al. 2001).

Final Diagnosis: Tumor-induced osteomalacia

Discussion on Fibroblast growth factor-23

FGF23 has the largest chemical structure in the fibroblast growth factor family. The FGF23 gene is in human chromosome 12. It does not have a heparin binding portion, making it not attached to the extracellular matrix, and thus it is soluble and able to act as a hormone. All the other fibroblast growth factors act locally because of that heparin binding portion. The FGF23 gene is transcribed into FGF23 mRNA which in turn is translated to an FGF23 protein, which has 251 amino acids. On its N-terminal, it has a signal peptide. In the middle, it has an FGF homology region, which is similar to all fibroblast growth factors. The uniqueness of FGF23 lies on its C-terminal, which is the Klotho interaction region. Under normal conditions, FGF23 is produced by osteocytes and osteoblasts in bone. It is secreted in lower concentrations by the salivary glands, the stomach, skeletal muscle, the brain, mammary gland, heart, and liver [Bhattacharrya et al. 2012, Komaba and Fukagawa 2009)].

FGF23's receptor is the FGF receptor, which is the receptor for all fibroblast growth factors. However, the FGF23 receptor must have alpha-Klotho as a necessary or obligate co-receptor. Additionally, FGF23 acts only on cells that express the FGF receptor-Klotho complex, and this would be the kidneys and the parathyroids. The FGF receptor and Klotho must be complexed with each other for FGF23 to exert its biological actions. The term "Klotho" is not an abbreviation, but it is the name of a Greek goddess that spins the thread of life. (Juppner 2010).

FGF23 inhibits the sodium-inorganic phosphate 2a and 2c transporters (Na-Pi2a and Na-Pi2c) present in the proximal convoluted tubule of the kidneys. Inhibition of these transporters leads to impairment of renal phosphate reabsorption. Consequently, there is increased phosphate excretion leading to low serum levels of phosphate. In addition, FGF23 also inhibits the enzyme 1-alpha-hydroxylase. Hence, there is a decreased production of the active form of vitamin D, calcitriol. This leads to decreased phosphate reabsorption in the GI tract, and this also contributes to lower serum phosphate levels (Fukumoto 2010). Factors that increase FGF23 would be high serum phosphorus and high active vitamin D, while the opposite would decrease FGF23. FGF23 is inactivated or cleaved by several enzymes: furin-like protease, GalNAc transferase 3 dentin matrix protein 1 (DMP1) and phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX). It has a half-life of 58 minutes (Bhattacharyya et al. 2012).

The clinical conditions associated with FGF23 abnormalities are 1) excessive neoplastic FGF23 production, that is tumor-induced osteomalacia, exemplified by this patient's case, 2) mutations that prevent cleavage of FGF23 exemplified by autosomal dominant hypophosphatemic rickets, and 3) mutations that inactivate the proteases of FGF23 exemplified by autosomal-recessive hypophosphatemic rickets and X-linked hypophosphatemic rickets (Bhattacharyya et al. 2012).

Going back to the patient's case:
FGF23 assay is not available in the Philippines. Even in the US, it is not widely commercially available and is limited to research endeavors. It is for these reasons that FGF23 was not measured in this case. Shimada et al. (2001), however, have established that FGF23 is the phosphatonin implicated in cases of tumor-induced osteomalacia.

Being a phosphaturic hormone, elevations in PTH can also contribute to the low TmP/GFR. However, for this particular case, the normalization of TmP/GFR with just surgical resection of the oral mass as the only intervention, proves that the oral mass was the source of a phosphaturic substance, and not the parathyroids. This patient was not given interventions that decrease PTH secretion such as the administration of cinacalcet or the performance of parathyroidectomy.

The hypophosphatemia can be explained by the patient's vitamin D deficiency which is common among Filipino adults. The prevalence of combined vitamin D insufficiency and deficiency in Filipino adults is high at 48.7% (Angeles-Agdeppa, 2018). However, the patient's clinical presentation (hunch back and chest deformity, loss of height and bone pain) is not seen in the same proportion of the Filipino population, making us suspect that there is another entity responsible for the patient's signs and symptoms.

Vitamin D deficiency can explain the low phosphorus but it could not explain the low TmP/GFR. Patients with low serum phosphorus due to decreased intestinal absorption are expected to have normal or even high TmP/GFR as the kidneys would be able to conserve this deficient nutrient.

On follow-up, he has no more bone pains. He can now walk, run, and ride a motorcycle without assistance. The kyphosis persists, however, and serum phosphorus remains normal even without phosphorus supplementation.

He said *"Doc, bumilib sa akin yung mga kaibigan ko. Limang taon daw nila nakita na ako ay nanghihina at di makalakad dahil sa sakit. Dahil sa pagpunta ko sa inyo, nalaman ko ang sakit ko. Yung lang daw pa lang pagpapa-opera ko sa bibig and magpapagaling sa akin."* (Doc, my friends were amazed. They have seen me weak and unable to walk because of pain for the past 5 years. After we consulted your team, that is the only time I knew what was wrong with me. It is astonishing that it is just the surgery on my mouth that will solve all my woes!)

Case 2
A 44-year-old premenopausal Filipino female from Batanes was of good functional capacity, and independent in activities of daily living until the day of injury. She was just hugging and carrying her four-year-old child while standing, when she slipped and fell on her back. There was immediate left lower extremity pain and difficulty standing up. She was brought to a local hospital where the x-ray showed a complete, displaced, transverse, subtrochanteric or diaphyseal femoral fracture on the left (Figure 1). On the right femur, there was an area of focal periosteal thickening associated with a lucent perpendicular line ("beaking"), which represents an impending fracture (Figure 2).

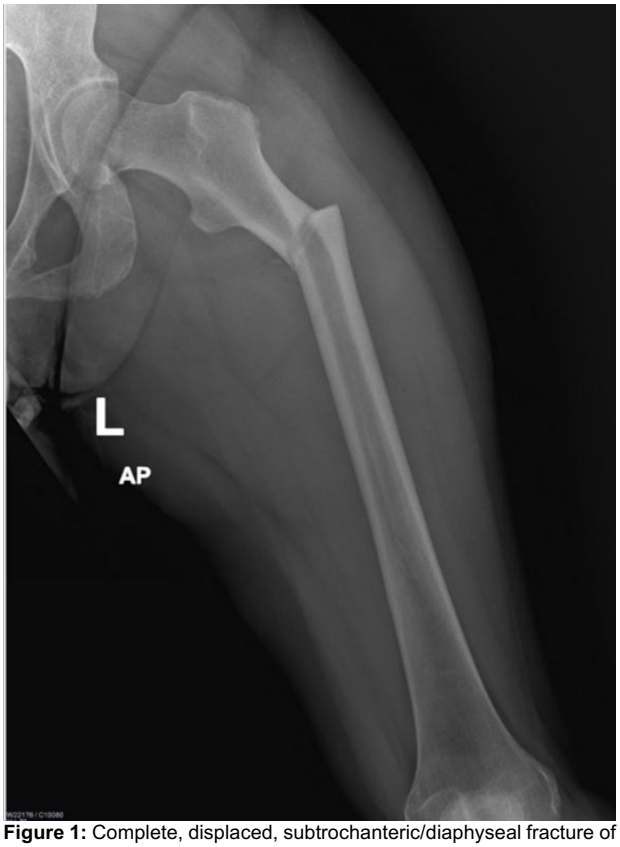

Figure 1: Complete, displaced, subtrochanteric/diaphyseal fracture of the left femur

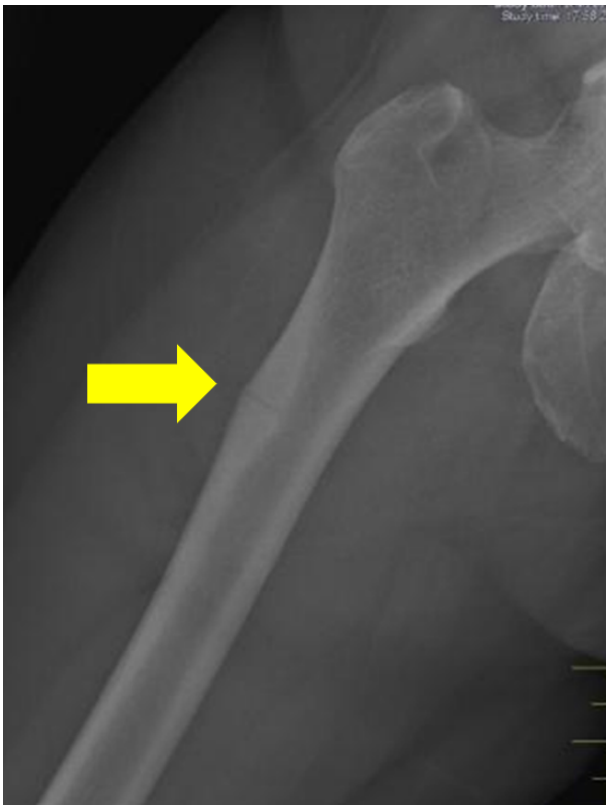
Figure 2: Periosteal thickening with a lucent perpendicular line at the subtrochanteric / diaphyseal area of the right femur.

Interesting in her medical history was that the patient was completely edentulous since age 16. She lost all her teeth by that age. When it comes to the family history, the father had a fracture, but already when he was already at age 81. Interestingly, the daughter, who is now 16 years old, has also prematurely lost all her teeth.

Her skull x-ray shows the complete absence of maxillary and mandibular teeth. (Figure 3)

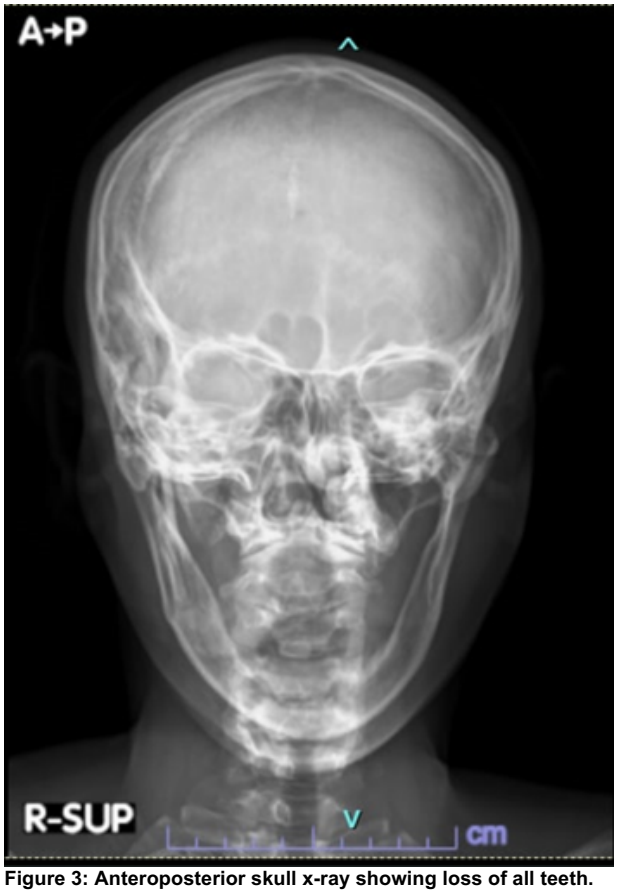

Figure 3: Anteroposterior skull x-ray showing loss of all teeth.

Biochemically, she had normal serum creatinine and estimated glomerular filtration rate. Total calcium levels fluctuated within the normal range while one determination was low, ranging from 1.96 to 2.25 mmol/L (normal: 2.20 - 2.60). Ionized calcium was slightly low at 1.12 mmol/L (normal: 1.15 – 1.33). For serum phosphorus, there was one determination which was low, but another determination was elevated (0.79 and 1.63 mmol/L (normal: 0.81 – 1.45 mmol/L). To settle the issue, measures of renal phosphate wasting were again computed like in Case 1. Her TmP/GFR was elevated at 1.83 (normal rage for sex and age: 0.88 – 1.42), meaning her kidneys were able to reabsorb phosphate and that she was not losing phosphate in the urine. Parathyroid hormone was normal. 25-hydroxyvitamin D was also low at 16.87 ng/mL (normal >30). A very prominent finding was a low serum alkaline phosphatase on repeated measures: <20 and 22 U/L (normal: 38-126). Bone-specific alkaline phosphatase (BSAP) was also low at 1.12 ng/mL (normal: 6.0 – 22.7).

Dual energy x-ray absorptiometry (DXA) showed normal bone density. Bone biopsy did not show any neoplastic process.

The clinical features of fragility fracture, premature loss of all teeth, and consistently low levels of serum alkaline phosphatase in this adult patient led to the diagnosis of adult hypophosphatasia. There is suspicion of this being a heritable condition with autosomal dominant mode of inheritance as the daughter also has similar symptoms.

Final diagnosis: Adult hypophosphatasia

Discussion on Alkaline Phosphatase

Alkaline phosphatase is not just one enzyme but a group of isoenzymes attached to the outer surface of the cell membrane (ectoenzyme). It is anchored to the cell membrane by glycosylphosphatidylinositol (GPI). It is called "alkaline" because in vitro, it functions optimally at pH 10 (Cole et al. 2015).

There are two types of alkaline phosphatase: tissue non-specific alkaline phosphatase (TNAP) and tissue-specific alkaline phosphatase (TSAP). TNAP is expressed in various tissues such as the liver (sinusoidal cells), kidney (proximal convoluted tubule cells), skeletal tissues (osteoblasts) and nervous system. Even if expressed in different tissues, they have the same amino acid sequences and are derived from the same gene (ALPL). They differ in post-translational modification, specifically glycosylation and sialylation. The second type, the tissue-specific alkaline phosphatases, are expressed in the syncytiotrophoblast of the placenta, testes/germ cell and intestines. The enzymes expressed in these tissues have varying amino acid sequences and are encoded by different genes (Rader 2017).

The various isozymes can be classified into heat-stable and heat-labile. Heat-stable or thermostable means that enzymatic activity remains at temperatures above 65 degrees C. Heat-labile forms lose their activity above this temperature. Placental and germ cell alkaline phosphatase are heat-stable, while the intestinal and liver/bone/kidney (also known as nonspecific) isozymes are heat-labile. Specifically for the heat-labile liver/bone/kidney isozyme which is the type deficient in this case being discussed, it takes just 1.0 minute for the enzyme to lose activity at 65 degrees C, but it remains active for 7.4 minutes at a lower temperature of 56 degrees C (Sharma et al., 2014).

Aside from thermostability, the various enzymes can be differentiated by their sensitivity to inhibition by different molecules. For example, the liver/bone/kidney (nonspecific) isozyme is easily inhibited by L-homoarginine and levamisole, while the intestinal and placental isozymes are easily inhibited by L-phenylalanine and L-phenylalanineglycylglycine (Sharma et al., 2014).

Even if alkaline phosphatase is anchored to the cell membrane, it can also be secreted into the blood circulation. Its serum levels can be measured: 50% comes from bone and the other half comes from the liver. A small percentage comes from the intestines (Haarhaus et al. 2020).

Alkaline phosphatase increases when there is increased osteoblast activity seen during periods of growth. Its levels are highest around age one and also at around age 12 during puberty. Its levels are actually at their lowest during adulthood. Alkaline phosphatase levels are 2-3x elevated in childhood and adolescence compared to adulthood. A second physiologic condition that is associated with increased alkaline phosphatase is after fat intake, particularly among those with blood types B and O. This rise is a contribution of the intestinal isoform of the enzyme. Because of this, fasting is recommended if alkaline phosphatase is to be measured in serum. A third condition associated with physiologic increase in this enzyme is during the third trimester of pregnancy. (Turan et al. 2011). Menopause is the fourth physiologic condition associated with an increase in alkaline phosphatase activity. This is due to increased bone turnover as evidenced by an increase specifically in the bone-specific isozyme (Crilly et al., 1980; Mukaiyama et al., 2015).

In bone, alkaline phosphatase can be demonstrated by immunohistochemistry to be present in the surface of osteoblasts and also in osteoid or newly-formed bone.(Miao and Scutt 2002) Since alkaline phosphatase parallels osteoblast activity, it is considered as a marker of bone formation (Kuo and Chen 2017).

Pathologic conditions associated with elevated alkaline phosphatase levels include bone metastases, Paget's disease, osteosarcoma, healing fractures, hyperparathyroidism, hyperthyroidism and osteomalacia. Conditions associated with low alkaline phosphatase levels are Wilson's disease, zinc deficiency, pernicious anemia, hypothyroidism and congenital hypophosphatasia, the last being the diagnosis in Case 2.

Alkaline phosphatase catalyzes the hydrolysis of pyrophosphate into two molecules of inorganic phosphate. The inorganic phosphate molecules then combine with calcium to form hydroxyapatite, which is the building block of bone. Thus, if there is decreased enzymatic activity of alkaline phosphatase, pyrophosphate will not be cleaved, inorganic phosphate will not be released and hydroxyapatite will not be produced, leading to weak bones and teeth (Orriss et al; 2016, Sekaran et al. 2021).

Going back to the patient's case:
She underwent intramedullary nailing of the left femur using a proximal femur nail with bone grafting, and prophylactic fixation using a proximal femur locking plate on the right.

At present, there is no effective treatment yet for adult hypophosphatasia.

The patient has not realized that the premature loss of all of her teeth in her teenage years was an early manifestation of her condition. She attributed the loss of teeth to just malnutrition since they live in the isolated island province of Batanes. She is worried that her daughter might have inherited her condition, and she will bring her for consultation as well.

CONCLUSION

Learning Points for Case 1:
FGF23 lowers serum phosphate levels by inhibiting renal reabsorption and intestinal absorption of phosphate. This is another hormone that affects bone, aside from the commonly known PTH, Vitamin D and estrogen. Phosphorus, in the form of phosphate, is as important as calcium in bone mineralization. Bone, the natural source of FGF23, can be considered an endocrine gland.

Learning points for Case 2:
Alkaline phosphatase is an enzyme that releases inorganic phosphorus from pyrophosphate. In bone, low levels of alkaline phosphatase means phosphorus is not made available for the synthesis of hydroxyapatite. Thus, low levels of alkaline phosphatase impair bone and tooth mineralization by osteoblasts, leading to fragility fractures and premature loss of teeth.

ETHICAL CONSIDERATIONS

Patient in Case 1 already provided informed consent for the publication of the original detailed case report which is reference #12. Patient in Case 2 provided informed consent for the publication of her case report in this article. This paper has been registered with the Research Grants Administration Office of the University of the Philippines Manila (RGAO registration number 2024-0164).

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CONFLICT OF INTEREST

Both authors have no potential conflicts of interest to disclose.

CONTRIBUTIONS OF INDIVIDUAL AUTHORS

MASS was involved in the care of both patients, collected pertinent clinical information, interpreted and synthesized all available clinical information, performed a review of literature, and drafted the manuscript. IAT was involved in the care of the patient in Case 2, reviewed the draft manuscript, provided additional intellectual inputs to the manuscript, and approved the final draft.

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