A RETROSPECTIVE STUDY OF THE BIOCHEMICAL AND RADIOLOGICAL PROFILE OF CHILDREN WITH GENETIC HYPOPHOSPHATEMIC RICKETS AND THEIR RESPONSE TO CONVENTIONAL TREATMENT

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Introduction

- Hypophosphatemic rickets is the commonest cause of rickets outside of the infant and toddler age groups in South Africa
- X-linked hypophosphatemic (XLH) rickets is the commonest genetic form of hypophosphatemic rickets.

- it is a disorder of renal phosphate wasting

- caused by loss of function mutation in the PHEX gene which leads to excess circulating FGF23 impairing proximal renal phosphate reabsorption.

- It also causes reduced 1α hydroxylation of 25(OH)D decreasing synthesis of active 1.25(OH)2D which further decreases phosphate reabsorption

Background

- Treatment of XLH consists of conventional therapy which includes multiple daily doses of phosphate and active vitamin D.
- Burosumab is a monoclonal antibody that targets FGF23 in patient with XLH
- Significant research exists on the response of hypophosphatemic rickets to Burosumab therapy which has shown that Burosumab effectively treats rickets, improves serum phosphate and increases height.
- Little is known about the response to conventional therapy in children with hypophosphatemic rickets residing in low-middle income countries and where Burosumab is currently not affordable.

Aim

- To assess the biochemical and radiological response of genetic forms of hypophosphatemic rickets, including XLH, to conventional therapy and to elicit the need for Burosumab.

Method

- Retrospective descriptive study
- Children under the age of 18 years
- Attending the Metabolic Bone clinic at Chris Hani Baragwanath Academic Hospital from 1st January 2006 till 30th April 2020.
- Diagnosed with “suspected” genetic hypophosphatemic rickets based on biochemical profile at baseline with high ALP, normal serum calcium and PTH and low phosphate levels
- With or without a positive family history of hypophosphatemic rickets
- Commenced on conventional treatment of phosphate and one alphacalcidol.

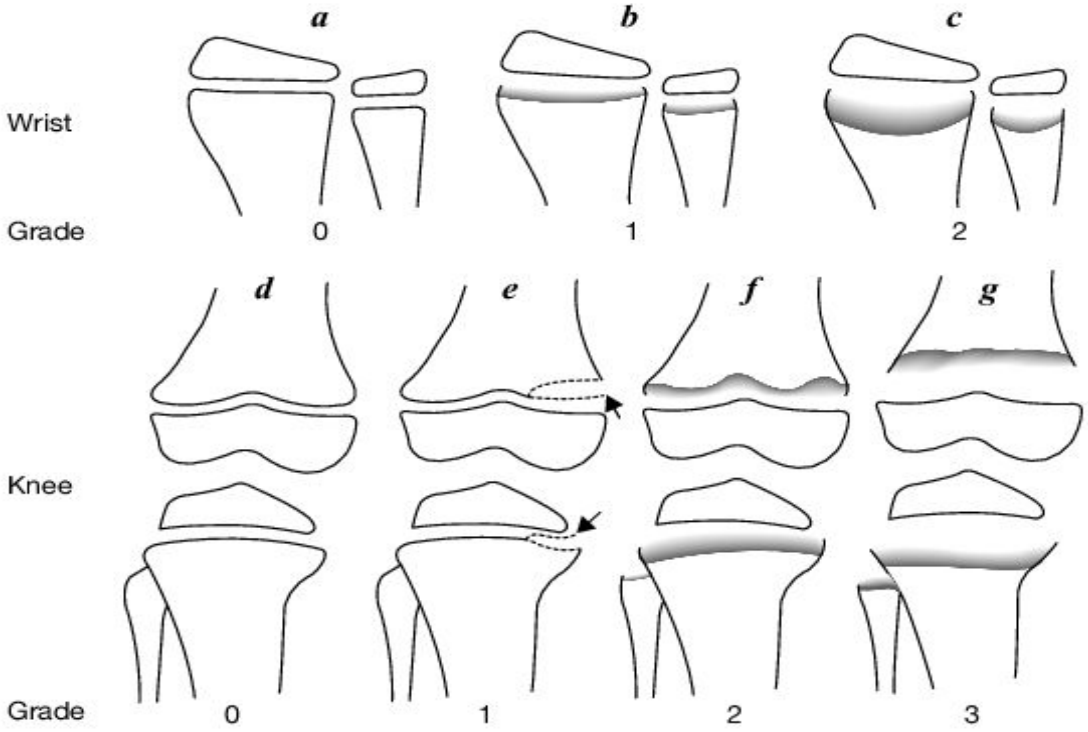
Exclusion criteria

- Calciopaenic rickets
- Hypophosphatemic rickets secondary to renal tubular acidosis (RTA).
- Hypophosphatemic rickets secondary to tumour-induced osteomalacia or fibrous dysplasia.
- Hypocalcaemia or hypercalcaemia, defined as serum calcium levels outside the age-adjusted normal limits
- Evidence of hyperparathyroidism.

Method

- The biochemical profile at the first visit was compared to the profiles at 3, 6, 9,12 months and longer, up until the last follow-up visit after starting treatment.
- The laboratory tests included for the study were : Serum phosphate, calcium, ALP and PTH.
- The Thacher radiological rickets severity score was utilized to assess the radiological changes of rickets at baseline and thereafter at 12 months and then yearly till the last available radiological assessment.

Thacher score



Wrist* Radius and ulna scored separately

Grade	Radiographic features
1	Widened growth plate, irregularity or fraying of metaphyseal margin, but without concave cupping
2	Metaphyseal concavity with fraying of margin

2 bones × 2 grade points = 4 points possible

Knee* Femur and tibia scored separately

Multiply the grade in part A by the multiplier in part B for each bone, then add femur and tibia scores together

A Grade	Degree of lucency and widening of zone of provisional calcification
1	Partial lucency, smooth margin of metaphysis visible
2	Partial lucency, smooth margin of metaphysis not visible
3	Complete lucency, epiphysis appears widely separated from distal metaphysis

B Multiplier	Portion of growth plate affected
0.5	≤ Half of the growth plate affected (as shown for grade 1 in figure)
1	> Half of the growth plate affected

2 bones × 1 multiplier point × 3 grade points = 6 points possible

Total: 10 points possible

*Score the worst knee and the worst wrist.

Thacher TD, Pettifor JM, Tebben PJ, Creo AL, Skrinar A, Mao M, et al. Rickets severity predicts clinical outcomes in children with X-linked hypophosphatemia: Utility of the radiographic Rickets Severity Score. Bone. 2019 May;122:76–81.

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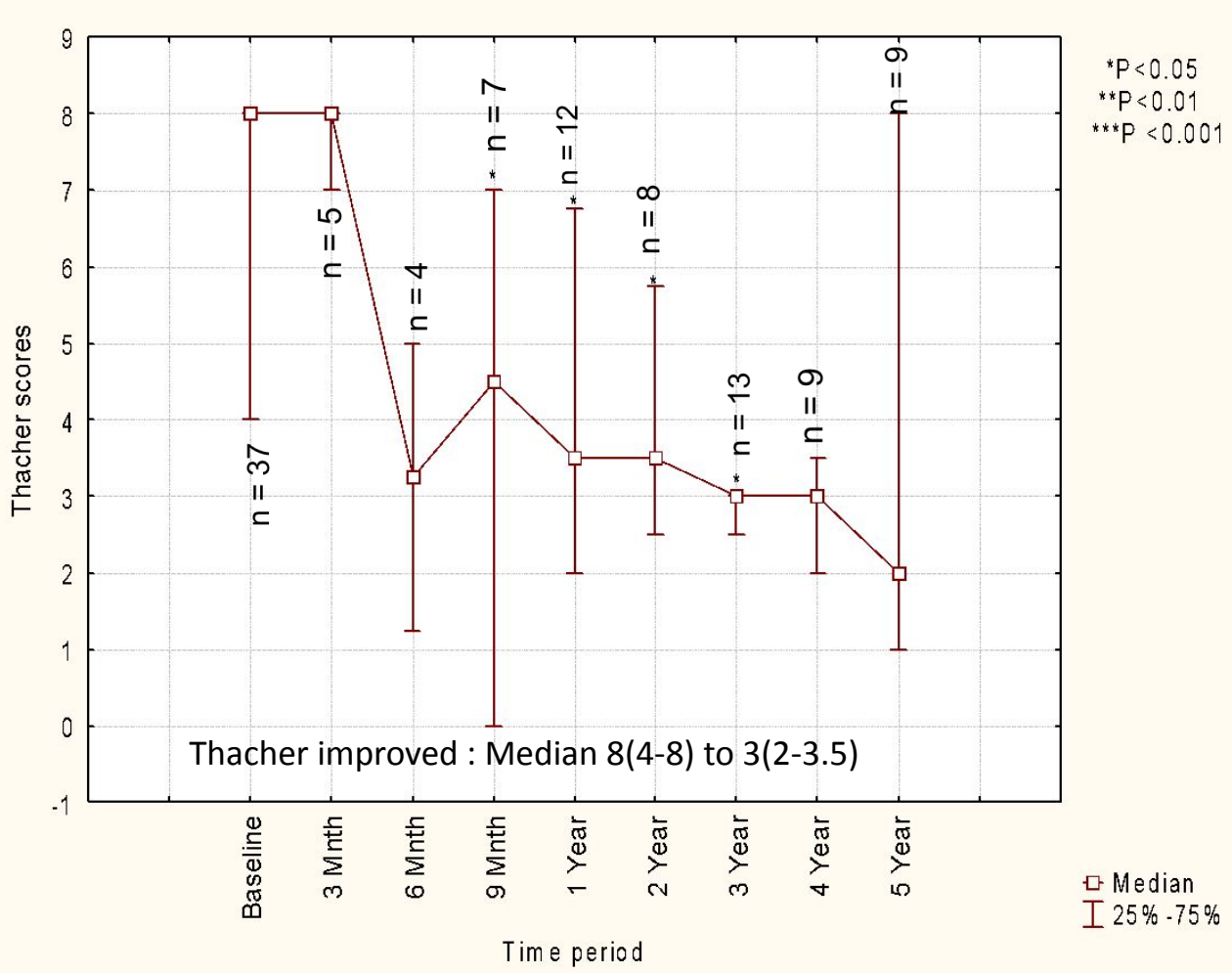
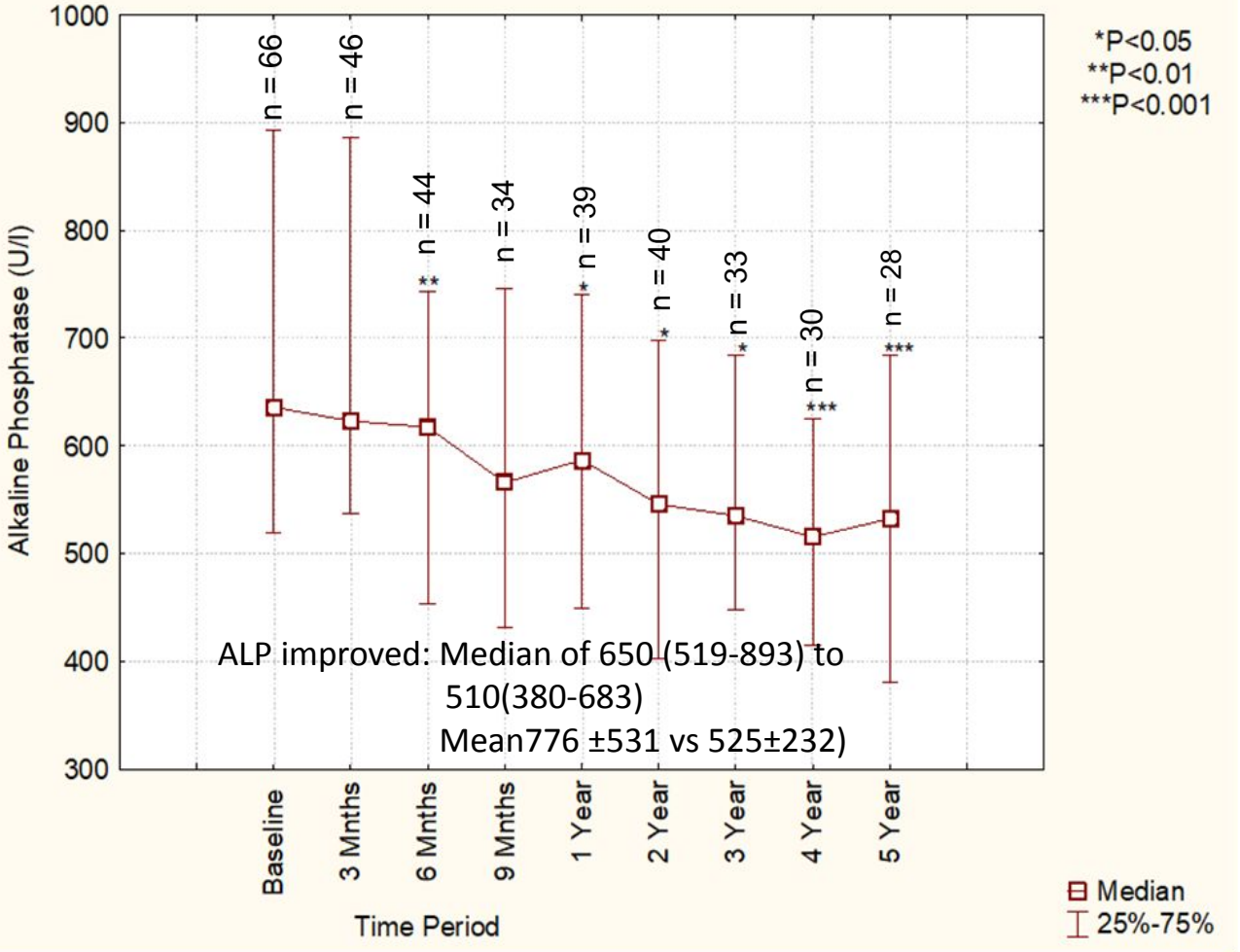
Results

- There were 70 patients were included in the study
- The mean (SD) age of the patients was 59.1 (±44.6) months
- The majority of patients were black South African (n=54 (77%))
- M:F ratio was 1:1.7
- Positive family history in 32 (46%) patients.

Results

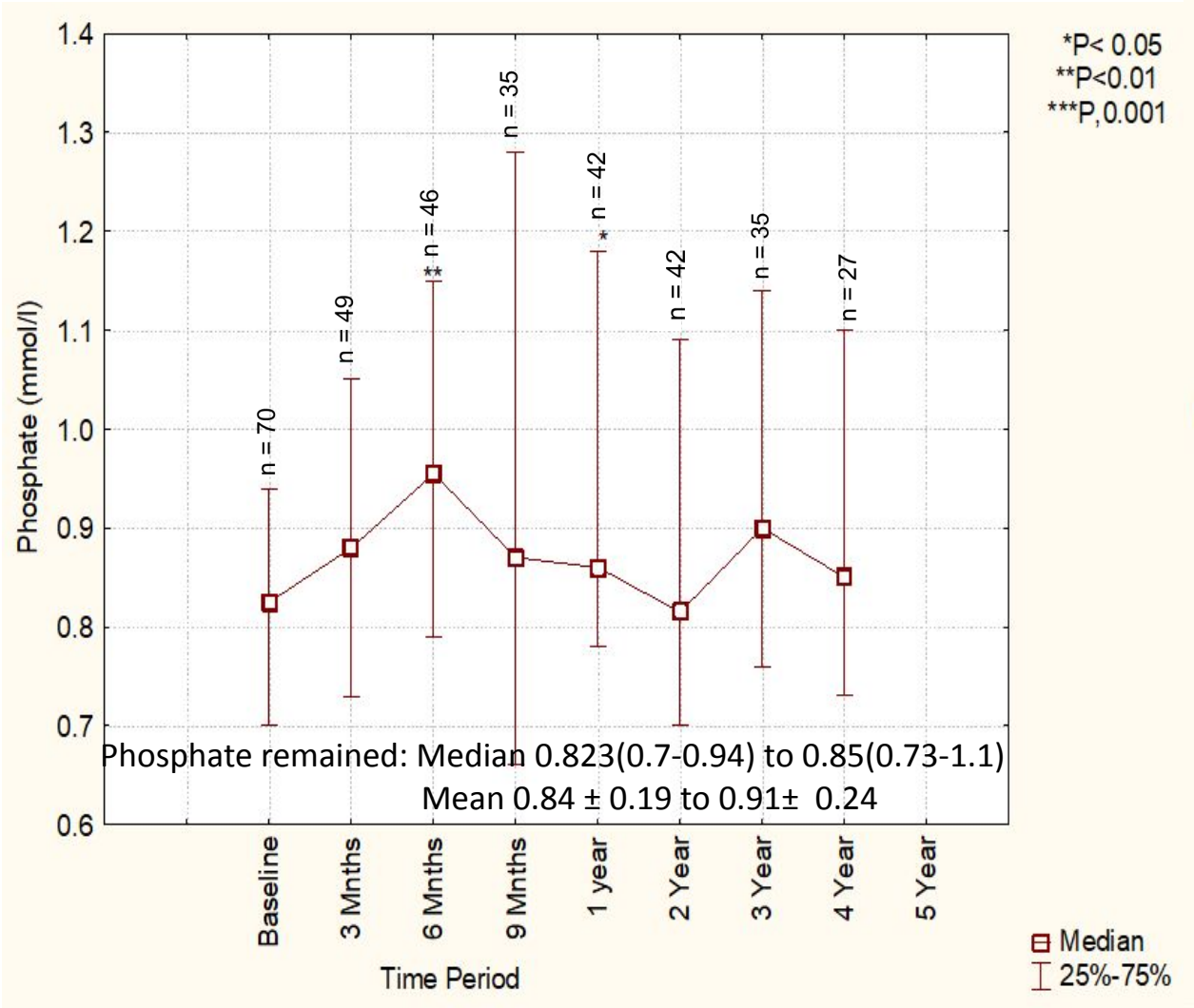




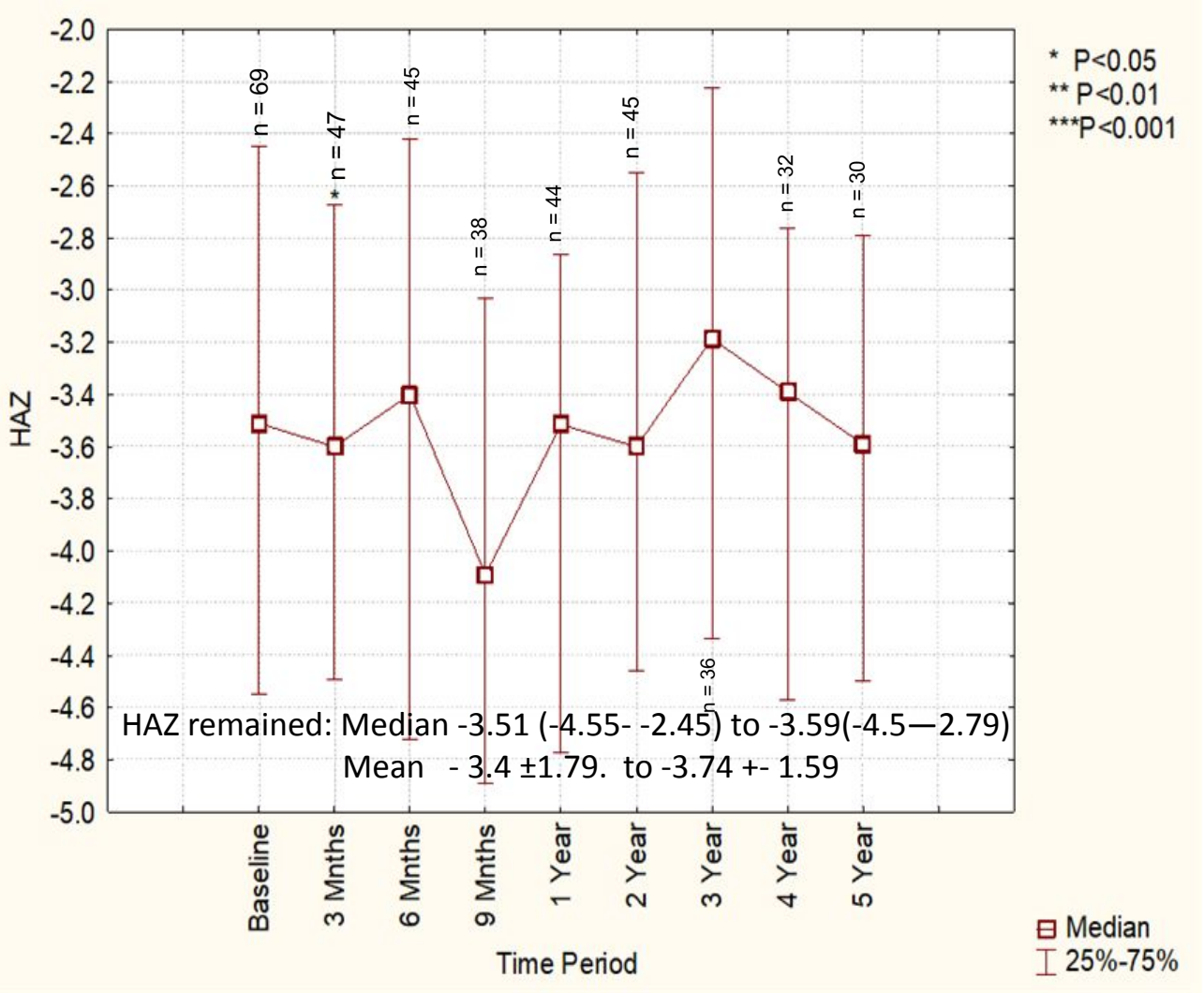
Thacher from baseline till 5 year follow up

ALP from baseline till 5 year follow up

Results



Phosphate remained: Median 0.823(0.7-0.94) to 0.85(0.73-1.1)
Mean 0.84 ± 0.19 to 0.91± 0.24



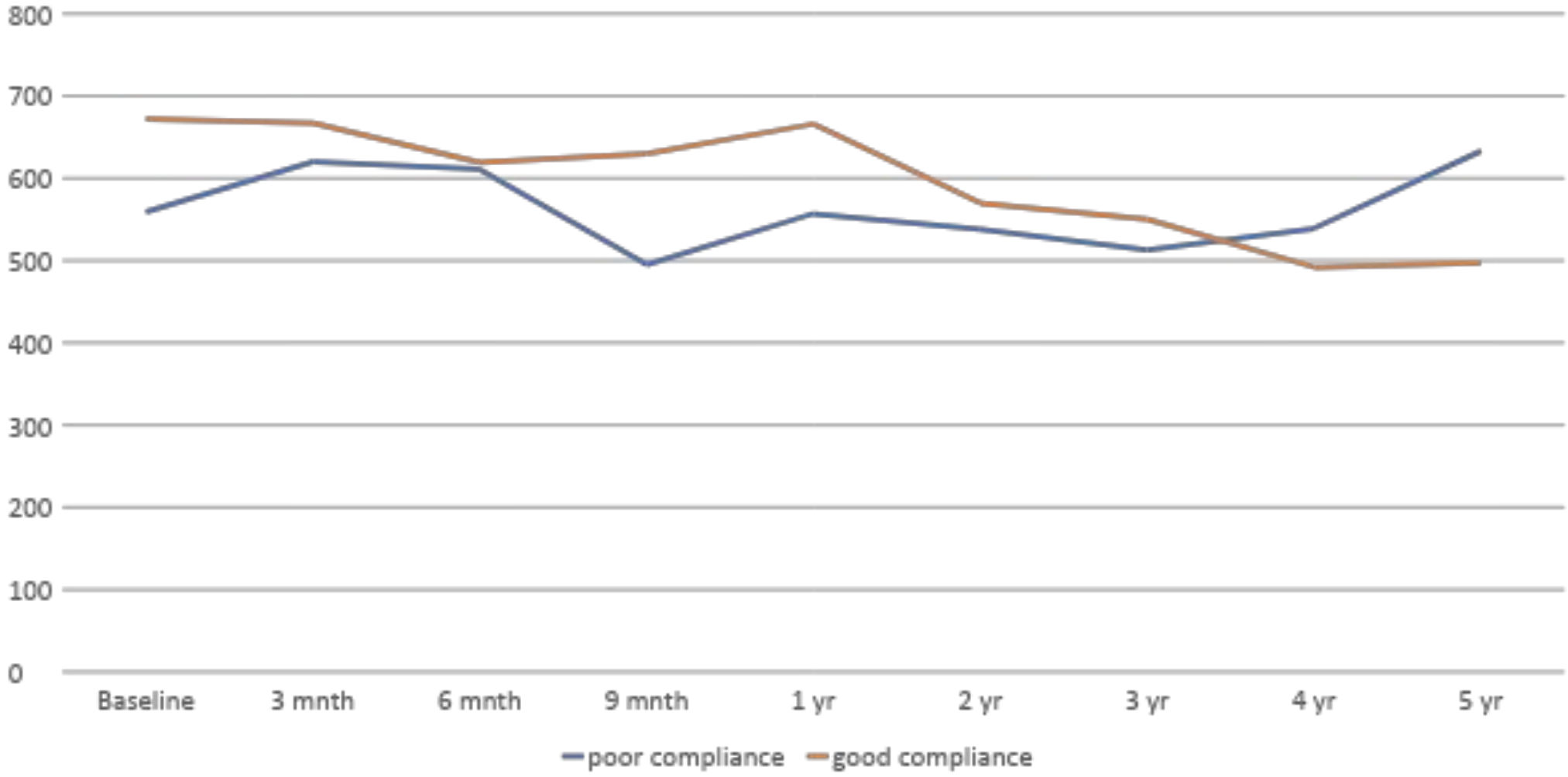
HAZ remained: Median -3.51 (-4.55- -2.45) to -3.59(-4.5—2.79)
Mean - 3.4 ±1.79. to -3.74 +- 1.59

Phosphate from baseline till 4 year follow up

HAZ from baseline till 5 year follow up

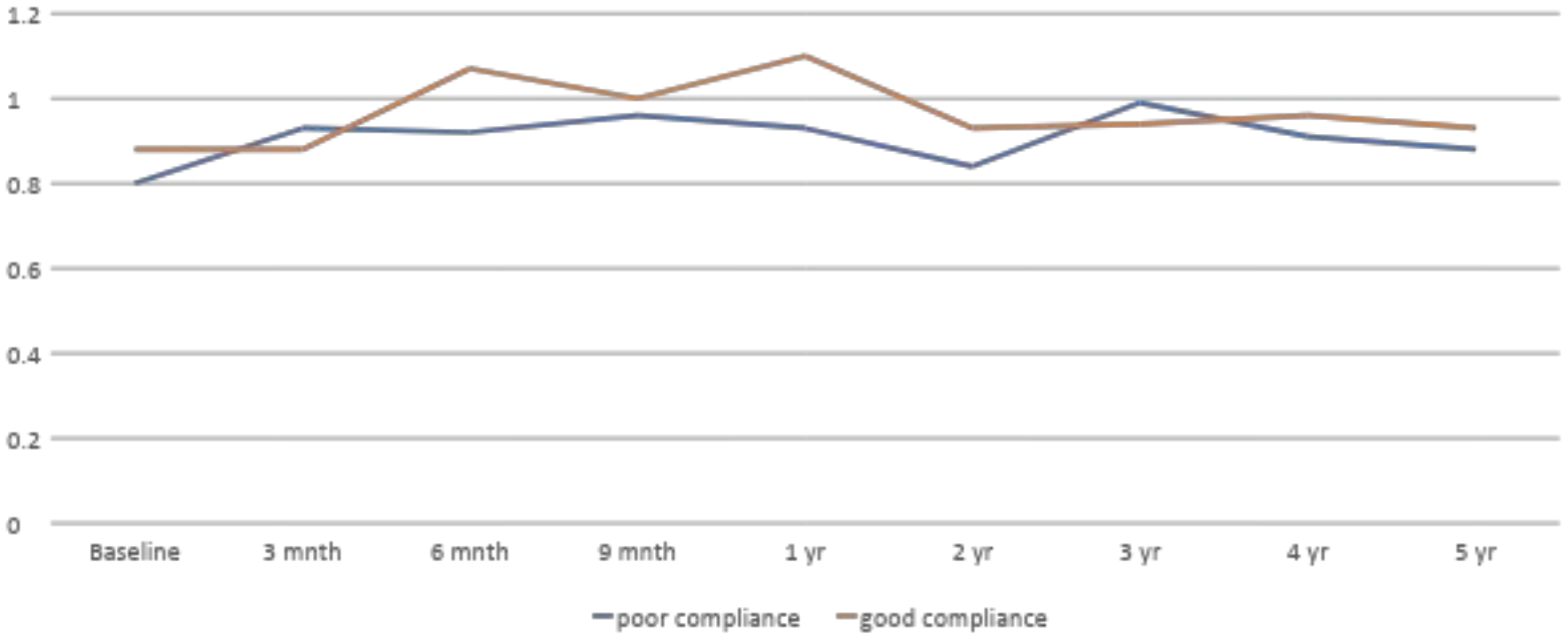
Adherence

Poor compliance 47%
Good compliance 53%



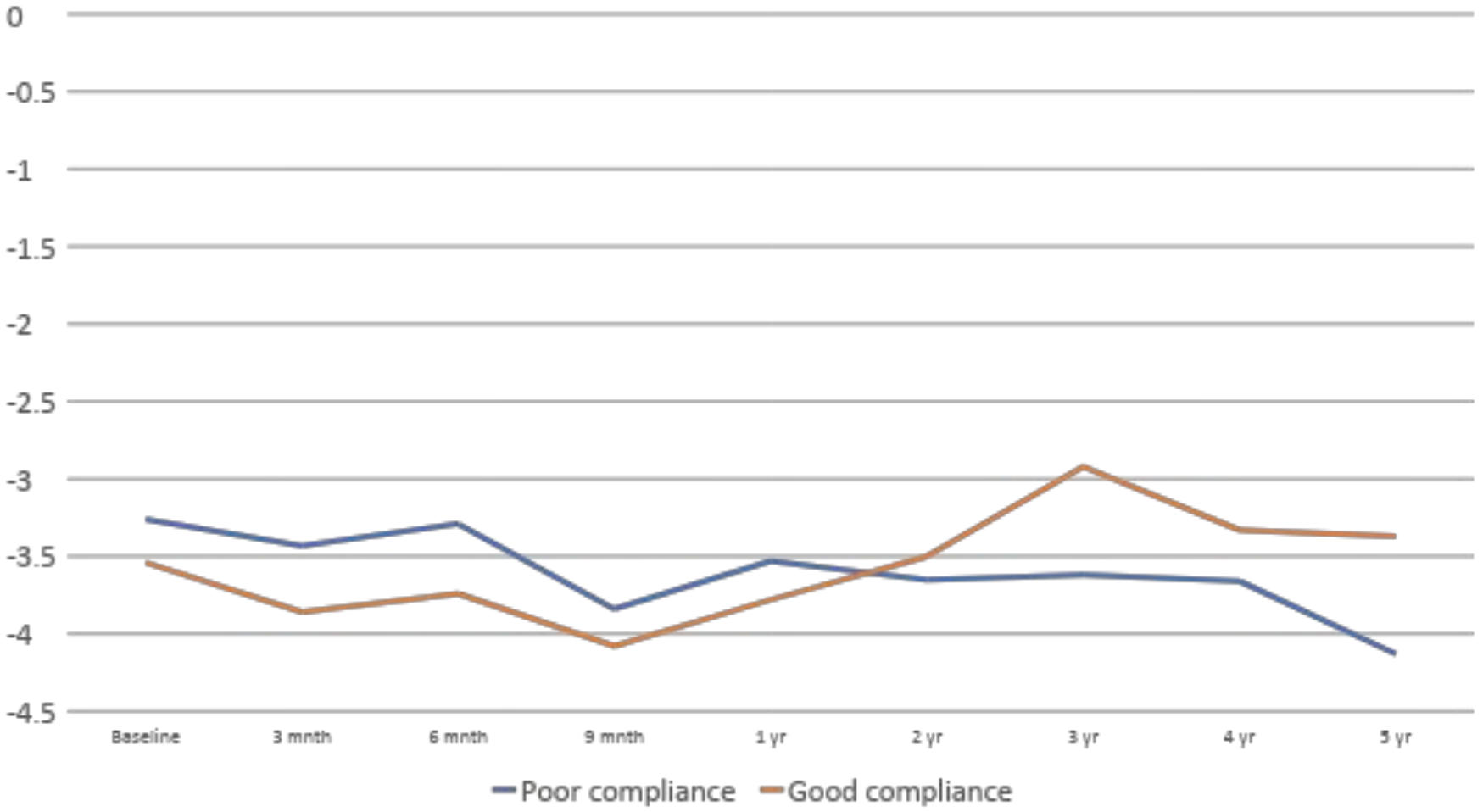
ALP

Adherence



Phosphate

Adherence



HAZ

Limitations

- Retrospective study
- No confirmation of genetics
- The study could have looked into other reasons of poor compliance such as poor accessibility to the hospital and financial constraints

Conclusion

Conventional therapy for the treatment of hypophosphatemic rickets is not associated with an improvement in HAZ or phosphate despite an improvement in radiological features and ALP.

Therefore Burosumab should be made more affordable to the public sector

Adherence to therapy is a challenge for the majority of patients.

Thank you….

Questions ?