
Article:
Lewis, L., Borg, S. orcid.org/0000-0003-4880-9135, Alison, L. et al. (8 more authors) (2022) Parathyroid hormone changes in infants investigated for inflicted injury; an observational retrospective single centre cohort study. Child Abuse & Neglect, 131. 105775. ISSN 0145-2134

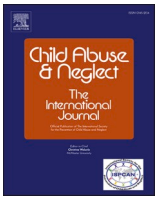
https://doi.org/10.1016/j.chiabu.2022.105775

Child Abuse & Neglect 131 (2022) 105775

Contents lists available at ScienceDirect

Child Abuse & Neglect

journal homepage: www.elsevier.com/locate/chiabuneg



Parathyroid hormone changes in infants investigated for inflicted injury; an observational retrospective single centre cohort study

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ARTICLE INFO

Keywords:
Infant
Fracture
Intracranial injury
Suspected inflicted injury
Parathyroid hormone
Vitamin D

ABSTRACT

Background: Biochemical and haematological testing is recommended in the United Kingdom when inflicted injury is suspected. We examined the associations of test results with radiologically-confirmed fracture(s), and between test results, in a large retrospective observational cohort.

Methods: Infants up to age two years presenting with suspected inflicted injury, without clinically or radiologically apparent bone disease, and where a skeletal survey was undertaken during the period 1st August 2013 to 31st December 2020, were included. Biochemical parameters: corrected calcium (cCa); phosphate (P); alkaline phosphatase (ALP); parathyroid hormone (PTH); 25-hydroxyvitamin D (25D); and haematological parameters: haemoglobin (Hb); mean corpuscular haemoglobin (MCH); mean corpuscular haemoglobin content (MCHC); mean corpuscular volume (MCV); platelet count were collated together with the results of the radiological assessments.

Findings: Of 332 eligible infants (190 male), 142 (84 male) had fracture(s) and/or intracranial injury. Mean PTH in the non-fracture group (n measured 50/190) was 27.3 ng/l; in those with intracranial injury alone (n measured 9/23) was 39.4 ng/l; in those with fracture alone (n measured 62/84) was 45.0 ng/l; and in those with fracture and intracranial injury (n measured 20/35) 51.8 ng/l. F-test of multiple means = 0.0369. There was no difference in 25D between the groups.

Interpretation: PTH was raised in infants who had fracture(s), intracranial injury or both. A single raised PTH may not necessarily be an indicator of prior disturbed skeletal health in these circumstances. The relevance of vitamin D status and interpretation of data from biochemical testing should be informed by the overall presentation in suspected inflicted injury cases. A single raised PTH may be a consequence of the child's injuries rather than prior disturbed bone health.

Abbreviations: cCa, corrected calcium; P, phosphate; ALP, alkaline phosphatase; 25D, 25-hydroxyvitamin D; PTH, parathyroid hormone; Hb, haemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin content; RCPCH, Royal College of Paediatrics and Child Health.

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https://doi.org/10.1016/j.chiabu.2022.105775
Received 5 April 2022; Received in revised form 9 June 2022; Accepted 22 June 2022
Available online 5 July 2022

Panel – research in context

Evidence before this study

Inflicted injury in infants and young children is a common cause of factures up to age one year, and to a lesser degree up to age two years. The relevance of biochemical measures to determine alternative explanations for skeletal fragility has been debated for decades in both medical and legal arenas. Parathyroid hormone (PTH) is known to regulate bone resorption activity; measurement of PTH might help differentiate between those with fragile and normal bones. We searched PubMed for articles from 1987 (when reliable PTH assays became available) up to December 2021, in any language, using the terms: ("parathyroid hormone" OR "PTH" AND "fracture") AND ("child" OR "infant"). We found 3 papers that in total reported on 91 children up to age two years, of whom 51 had had fractures; the relationship of PTH with fracture was inconsistent with lower values at 48 h following clavicular fracture at birth in 36 infants compared with 46 normal infants, as opposed to the raised values in 15 older infants with congenital cardiac disease who had had fractures. Further searching for papers relating prior trauma to PTH using the terms: ("parathyroid hormone" OR "PTH") AND "trauma" provided three papers detailing increased PTH levels following major trauma in adults, one showing subsequent progressive reduction over one week.

Added value of this study

In 332 infants where concerns of occult injury led to skeletal surveys being undertaken, 142 had had fractures and/or intracranial injury. Parathyroid hormone levels progressively increased from those in infants without fracture or intracranial injury; with intracranial injury alone; fracture alone; and intracranial injury with fracture. The highest values were seen in the small group with metaphyseal fractures. There was no similar association of injury with 25-hydroxyvitamin D levels.

Implications of all the available evidence

The data indicate that elevated parathyroid hormone levels are associated with major injury in infants, as in adults, but not necessarily in the causal pathway for fracture. Additional measurements over time might be of value in determining whether a causal relationship can be inferred in individual cases.

1. Introduction

Fractures occur in approximately 80 per 10,000 children under age one year in the UK; a similar number of fractures occur from age one up to age two years (Cooper et al., 2004). Some fractures occur with clearly evident accidental trauma, often at birth, or once independent ambulation is achieved. Fractures can occur as a result of inherited primary bone fragility, usually labelled osteogenesis imperfecta (OI), in 5–24/100,000 births (Folkestad et al., 2016). Bone fragility resulting in fractures occurs in other bone disorders including rickets (17.5 % of ambulant infants and toddlers with radiologically apparent rickets) (Chapman et al., 2010) and in severe hypophosphatasia (approximately 1 in 340,000) (Mornet et al., 2011) as well as other ultra-rare diseases. Bone fragility can be secondary to other disorders such as those that cause immobilisation, and is more common in those born prematurely (Hogberg et al., 2018).

Overall, the rarity of such explanations might suggest that only a small fraction of cases presenting with fracture in infancy have abnormal bones. It is difficult, however, to non-invasively assess bone strength, and hence the obverse - bone fragility - in infancy. Recognised contributors to bone fragility include abnormal bone architecture, low bone mass, abnormal collagen matrix and altered degree of bone mineralisation – too much mineral and the bone becomes brittle as in OI; too little and the bone is insufficiently stiff to resist bending or compressive forces as in rickets. Conventional radiographs can capture gross architecture - bone size and shape - but are relatively insensitive in assessing bone mass, often regarded as a surrogate for bone strength. Other methods of assessing bone mass through imaging, such as dual energy x-ray absorptiometry, have not been found to be helpful in early infancy. The assessment of bone metabolism in infancy is largely limited, except in research studies, to the measurement of calcium (Ca), phosphate (P), alkaline phosphatase (ALP), parathyroid hormone (PTH) and the stable circulating metabolite of vitamin D, 25-hydroxyvitamin D (25D).

The Royal College of Paediatrics and Child Health (RCPCH) has suggested that a bone profile, including PTH and 25D, could aid in determining the likelihood that bone fragility might be present in cases where unexplained fractures in infancy raise the possibility of inflicted injury (Health RCoPaC, 2017). The idea that there is increased bone fragility when serum 25D is low has been debated both in medical journals (Arundel et al., 2012; Arundel et al., 2013) and in civil and criminal Courts. Calcium uptake into bone is rapid in infancy (Abrams, 1998). The active metabolite of vitamin D, 1,25-dihydroxyvitamin D (1,25D), produced in part in response to PTH, enhances the absorption of calcium from the diet, and acts in concert with other factors to increase osteoclastic bone resorption in order to maintain circulating calcium concentrations (Allgrove, 2015). PTH targets both the kidney and osteoblasts in bone, which respond by producing RANK-ligand, a potent activator of osteoclast formation, maturation and activity (Silva et al., 2011). Increased PTH, rather than reduced 25D, drives increased bone destruction. Increased PTH levels might therefore contribute to an increase in susceptibility to fracture. This has been demonstrated in older populations with hyperparathyroidism (Khosla et al., 1999), but has had limited assessment in infancy.

PTH has also been recorded as being elevated after trauma in adults, more so after intracranial injury as well as fracture in road

traffic accidents (Khallaf et al., 2016; Trentz et al., 2005). The reason for this is unclear.

We undertook a retrospective cohort study of infants aged up to two years attending a single centre with suspected inflicted injury requiring a full skeletal survey to be performed. We assessed the results of blood tests in relation to the occurrence of radiologically confirmed fractures and intracranial injury to test the hypothesis that there would be an association of fracture and/or intracranial injury with PTH.

2. Methods

This was a retrospective cohort analysis of infants aged up to two years who attended the Sheffield Children's Hospital and underwent a skeletal survey as part of their investigations into suspected inflicted injury between August 1st 2013 and December 31st 2020. Ethical permission for the study was granted by Health Research Authority and Health and Care Research Wales (REC ref. 21/PR/0013). We lacked prior data on which to base a sample size.

Our local guideline, following the RCPCH and RCR guidelines, states that children under the age of two years with any injury suggestive of inflicted injury should have a skeletal survey (SS), along with ophthalmology, relevant blood tests, a head computed tomography (CT) if under 1 or as indicated if between 1 and 2 years old and magnetic resonance imaging (MRI) scan of the head and spine if clinically indicated. Radiographic procedures were undertaken using standard radiology equipment with age-appropriate settings. The local protocol for follow-up SS changed on the 1st October 2014. Prior to this date, the follow-up was chest radiographs only; after this date, a selective series of radiographs was obtained in accordance with RCR guidelines (https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfcr174_suspected_physical_abuse.pdf). Radiographic images were reviewed by experienced paediatric radiologists, and fractures identified. Number and site of fractures were recorded. Intracranial injury visualised either on head CT or MRI scans was recorded for each infant. Children with radiologically abnormal bones, other than the fractures, were excluded.

We used our electronic laboratory data reporting system to ascertain tests requested and document results. Case notes were reviewed for each patient. The timing of blood sampling in relation to food intake was not recorded. We recorded the time between presentation and when the blood sample for PTH was taken. Where more than one PTH sample was measured, the first measurement was taken.

All blood samples were analysed in the Sheffield Children's Hospital biochemistry and haematology laboratories, except for 25-hydroxyvitamin D (25D), which was analysed at Bristol Royal Infirmary by liquid chromatography tandem mass spectrometry. Serum calcium (Ca) and corrected calcium (cCa), phosphate (P), alkaline phosphatase (ALP) and albumin were measured by dry slide on the Ortho-Clinical Diagnostics Vitros 5.1 analyser and PTH by a CMIA method on the Abbott Architect i1000. Full blood counts were undertaken using a Siemens Advia 2120.

Serum normative data ranges for some of the measured parameters vary with age; for total calcium (mmol/l) the normal range is 2.14–2.74 for neonates and 2.13–2.72 for infants up to age 2 years; corrected calcium is calculated as total calcium − ((albumin − 40) × 0.02) mmol/l. The range of alkaline phosphatase (U/l) for neonates is 73–391; for –-<12 months 59–425; and for 12 months and over 76–308. There are no age-related normative ranges for PTH and 25D.

Infants were excluded from the analysis if there was a clear bony pathology likely to result in increased fracture risk.

Data were analysed using DataDesk 7.0.2. Relationships both between blood-based parameters and fracture and intracranial injury were initially explored graphically. Formal statistical testing was undertaken using F-test of multiple means when comparing more than two groups; Student's *t*-test was used for two sample analyses. A regression model was used to explore the association of PTH with other factors, with and without data transformation to adjust for positive skew for the affected variables. Missing data were not imputed. No sensitivity analysis was undertaken. All available data were used in each analysis; no subgroup analyses were performed.

Table 1
Demographic, biochemical and haematological data.

Parameter	No fracture or intracranial injury n = 190		Intracranial injury only n = 23		Fracture only n = 84		Fracture and intracranial injury n = 35		F test of multiple means
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
Presenting age (days)	190	252 (200)	23	135 (134)	84	272 (177)	35	216 (228)	0.0195
Male sex	106		13		47		24		
Corrected calcium (mmol/l)	91	2.55 (0.11)	19	2.58 (0.16)	77	2.54 (0.09)	32	2.49 (0.15)	0.0258
Phosphate (mmol/l)	95	1.97 (0.25)	19	1.72 (0.44)	77	1.99 (0.25)	32	1.80 (0.40)	0.0002
Alkaline phosphatase (U/l)	99	225 (142)	19	200 (70)	77	225 (129)	32	200 (69)	0.6568
25-Hydoxy vitamin D (nmol/l)	69	76.5 (29.7)	9	86.8 (25.5)	70	70.8 (28.9)	24	75.0 (30.2)	0.3856
Parathyroid hormone ng/l	50	27.3 (11.6)	9	39.4 (26.7)	62	45.0 (46.3)	20	51.8 (45.9)	0.0369
Haemoglobin g/l	145	117 (18)	22	109 (37)	71	114 (21)	32	106 (20)	0.0231
Mean corpuscular volume (fl)	146	85.5 (11.0)	22	90.6 (14.5)	71	83.1 (9.8)	31	87.7 (8.5)	0.0250
Mean corpuscular haemoglobin (g)	145	28.1 (5.9)	22	28.5 (5.1)	71	26.8 (3.3)	31	28.2 (2.8)	0.2756
Mean corpuscular haemoglobin content (g/l)	145	28.1 (5.9)	22	314 (22)	71	322 (11)	31	321 (11)	0.0174
Platelets ($\times 10^9$/l)	146	408 (148)	22	492 (164)	71	384 (119)	31	377 (127)	0.0104

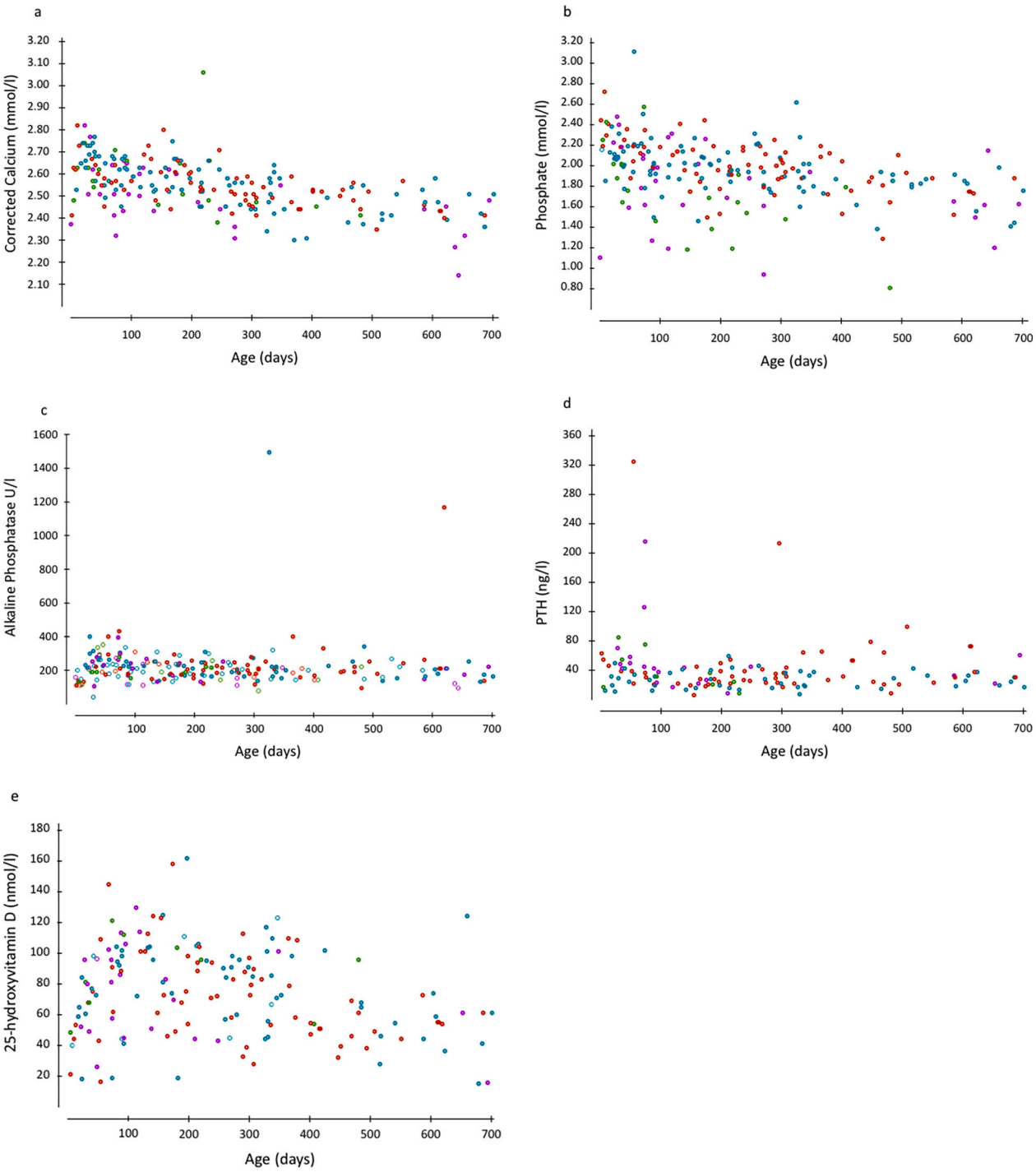

Fig. 1. Biochemical parameters colour coded according to fracture and/or intracranial injury: blue – no fracture or intracranial injury; green - intracranial injury only; red - fracture only; purple - intracranial and fracture.
a) Corrected calcium (mmol/l) by age (days).
b) Phosphate (mmol/l) by age (days).
c) Alkaline Phosphatase (IU/l) by age (days).
d) PTH (ng/l) by age (days).
e) 25D (nmol/l) by age (days). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

332 children (190 male) without apparent underlying bony pathology underwent one or more skeletal surveys during the assessment period; of these, 119 (71 male) had one or more fractures; 58 (37 male) had intracranial injury. A significant number of children did not have a full set of biochemical and haematological investigations performed; the reasons for not performing the tests were not systematically recorded. The numbers of investigations, and their mean (SD), divided into four groups – no fracture or intracranial injury; intracranial injury alone; fracture(s) alone; intracranial injury and fracture(s) - are summarised in Table 1, along with basic demographic data. An F-test of multiple means for each parameter showed significant differences across the groups for age at presentation ($p = 0.0195$); corrected calcium ($p = 0.0258$); phosphate ($p = 0.0002$); PTH ($p = 0.0369$); haemoglobin ($p = 0.0231$); MCV ($p = 0.0250$); MCHC ($p = 0.0174$); and platelet count ($p = 0.0104$). No differences were shown for the other measured parameters, and specifically there were no differences in ALP or 25D.

Scatterplots for each of the biochemical parameters against age are shown in Fig. 1a–e. A number of the parameters measured showed a significant positive skew; these included ALP; PTH; MCH; MCV and platelet count. Natural logarithmic (denoted as "ln" prefix) transformation of these parameters to achieve a more normal distribution and reanalysis increased the significance of the difference between groups for PTH ($p = 0.0050$), but reduced it for MCH ($p = 0.1926$), MCV ($p = 0.0667$) and platelet count ($p = 0.0705$). The difference in lnPTH between those with no fracture or intracranial injury and intracranial injury alone did not reach significance ($p = 0.3916$). The difference in lnPTH between those with no fracture or intracranial injury and fracture alone was significant ($p = 0.0015$). The difference in lnPTH between those with no fracture or intracranial injury and those with both fracture and intracranial injury was significant ($p = 0.0072$). Again, there were no differences in ALP or 25D after transformation.

Whilst there was no relationship between total number of fractures and PTH or lnPTH, there was a significant difference in lnPTH between those with and without metaphyseal fracture, with mean (SD) lnPTH in the metaphyseal fracture group ($n = 10/11$ measured) of 4.27 (0.84) vs 3.38 (0.55) for the rest; $p = 0.009$ 95 % CI for difference 0.28–1.49; back-transforming gives mean values of 71.5 vs 29.4 ng/l. The factors in combination which were associated with PTH were age at presentation; corrected calcium; and presence of metaphyseal fractures, see Table 2. There was no difference in the frequency of multiple fracture occurrence between those with and without intracranial injury.

There was no radiological evidence of rachitic change or bone demineralisation in any child.

4. Discussion

In this retrospective cohort study of 332 children aged up to 2 years and presenting with trauma or injury sufficient to warrant a skeletal survey and without apparent bony pathology, we found that PTH was higher in infants who had fractures with or without intracranial injury. In addition, a small number of infants with metaphyseal fractures had significantly higher lnPTH. In a regression analysis, the factors which in combination best predicted PTH were corrected calcium, age in days at presentation and the presence of metaphyseal fracture(s). There was no difference in 25D levels between any of the groups identified as having altered PTH.

PTH is produced by the parathyroid glands in response to lower circulating ionised calcium levels. It acts on the kidney to enhance calcium reabsorption and increase the production of the active metabolite of vitamin D, as well as on bone tissue to increase the release of calcium from bone mineral. We did not measure ionised calcium, but there was a significant negative relationship between serum corrected calcium and PTH (data not shown) which is consistent with many other reports. We did not find that children with fracture had a lower 25D level.

A number of reports document raised PTH immediately following trauma resulting in fracture and also intracranial injury in adults (Khallaf et al., 2016; Trentz et al., 2005), consistent with this current report on young children and infants. We also found that in infants with metaphyseal fracture, PTH was higher. In the adult reports, the rise in PTH peaks between one and three days following the injury. Osteotomy and surgical procedures e.g. total knee arthroplasty were not so clearly associated with a rise in PTH, however

Table 2
Regression analysis of factors which in combination were most strongly associated with PTH (ng/l).

Response variable is: PTH (ng/l)
332 total cases of which 194 are missing
R squared = 26.7 %; R squared (adjusted) = 25.1 %.
s = 32.54 with 138 − 4 = 134 degrees of freedom.

Source	Sum of squares	df	Mean square	F-ratio
Regression	51,691.9	3	17,230.6	16.3
Residual	141,902	134	1058.97	

Variable	Coefficient	SE (coeff)	t-Ratio	p-Value
Intercept	288.786	82.44	3.50	0.0006
Corrected calcium mmol/l	−95.1924	31.33	−3.04	0.0029
Age (days)	−0.042907	0.0160	−2.55	0.0118
Metaphyseal fracture 1 = yes	56.1943	11.12	5.05	≤0.0001

(Papavasiliou et al., 2012). One older study documented PTH initially within the normal range that fell progressively across the first week following tibial fracture (Hardy et al., 1993).

We studied young children and infants admitted with trauma sufficient to raise concerns about potential occult injury such that a skeletal survey and head CT scan were undertaken. If there is a relationship between trauma and increased PTH, these data suggest that there may be a "trauma threshold" that must be met. There have been no studies of the time course of changes in PTH following fracture in infancy, other than a study following neonates with a fracture of the clavicle to age 48 h at which time PTH was lower in those with fracture compared to a control group (Bagnoli et al., 1984).

At present, the causal pathway relating trauma to PTH is unclear. By contrast, the relationships between the mineral metabolites calcium and phosphate and PTH are much more well understood, with calcium acting through the calcium-sensing receptor to reduce PTH release and phosphate inhibiting that sensing, and thus increasing PTH release (Centeno et al., 2019). The increase in PTH following injury may reflect the movement of calcium into damaged tissue, or the release of phosphate from it. Bone is the largest store of both calcium and phosphate, and release of phosphate occurs both on remodelling surfaces and within the canalicular network (Nango et al., 2016), both of which will be disrupted by a fracture.

There are limited data to inform estimates of "normal" PTH in infancy. Where PTH has been measured in the context of prospective studies, often of vitamin D supplementation, values outside of the immediate perinatal period typically range from 20 to 30 ng/l up to age 12 months. The group mean value for PTH in the children without fracture or intracranial injury (27.3 ng/l) is at the upper end of this range.

In Chandy's study of mother or infant vitamin D supplementation (n = 152 with PTH data), median (IQR) PTH at 3.5 months was 22 ng/l (17–31 ng/l) in breastfed infants of mothers receiving 3000 μg vitamin D within seven days of delivery and then at monthly intervals from 1.5 months; 22 ng/l (18–31 ng/l) in infants receiving 10 μg vitamin D daily; and 28 ng/l (21–49 ng/l) in untreated infants of unsupplemented mothers (Chandy et al., 2016). In Vieth Streym's cohort study of 108 infants, PTH gradually rose from birth to age 9 months; median (IQR) PTH was 2 ng/l (1–3 ng/l) at birth; 20 ng/l (15–25 ng/l) at age 4 months and 29 ng/l (25–38 ng/l) at age 9 months; over 90 % of infants reportedly received vitamin D supplementation (Vieth Streym et al., 2013).

In Valkama's study of vitamin D supplementation in 762 infants, median (IQR) PTH was 24 ng/l (16-33 ng/l) at age 12 months; PTH was >50 ng/l in over 5 %, despite most having "adequate" (≥50 nmol/l) 25OHD levels (Valkama et al., 2017). Atapattu and colleagues described a hospital-based population where, of a subset of 17 with radiologically-proven rickets, 16 had PTH >50 ng/l; age-related PTH values were not given (Atapattu et al., 2013).

PTH rose gradually in all groups of breastfed infants in a randomised dose ranging study of vitamin D supplementation (200-800 IU/d) in Iowa from age 4 months (3 months after starting vitamin D supplementation) to age 12 months, from around 16 ng/l at 4 months, to 23 ng/l at 12 months (Ziegler et al., 2014). Overall, we saw a gradual fall in PTH values with increasing age, but our values, even in the no fracture or intracranial injury group, were at the higher end of the ranges described in the supplementation studies.

PTH and 25D had an inverse relationship over the range of circulating 25D between 0 and 100 nmol/l in the study of apparently healthy children aged one to six years of age reported by Maguire and colleagues (Maguire et al., 2014); the change in PTH was 0.8 pmol/l, equivalent to 8 ng/l using our metrics. We did not find that 25D contributed to prediction of PTH after adjusting for other factors (see Table 2).

A study of apparently healthy North American infants with 25D <20 ng/l (equivalent to <50 nmol/l) found higher values of PTH in two infants with radiologically-apparent bone demineralisation compared to those without; 52 ng/l vs 35 ng/l respectively. Two infants had rachitic changes; none had fractures (Perez-Rossello et al., 2012). In a study of critically ill infants with congenital heart disease where 15 infants had 23 fractures, always associated with radiologically apparent bone demineralisation, "raised" PTH post-fracture (10 of 13 tested had PTH >65 ng/l) was more common than "low" 25D (25D <30 ng/l, equivalent to 75 nmol/l) (Cheng et al., 2016).

We were unable to demonstrate a relationship between number of fractures and PTH, or between time of attendance and time of measurement of PTH; the majority of tests were drawn within 24 h of the skeletal survey having been performed. Accurately estimating time from injury to measurement was not possible for the majority of cases.

The lack of difference between the groups in ALP in our study was surprising. ALP is produced by osteoblasts and is required for the removal of pyrophosphate at bone-forming surfaces (Millan, 2013); when new bone is being formed at a higher rate, ALP should increase. Bone is formed either due to modelling activity – the creation of new bone where none previously existed e.g., at growth plates, on the external cortical surface during growth, and during fracture healing – or remodelling where bone is first removed by osteoclastic bone resorption and then replaced by osteoblastic bone formation at the same site. Studies of total ALP activity in adults following fracture suggest that it rises progressively over several weeks; in one study, bone-specific ALP initially fell, rising after two weeks (Bowles et al., 1996). The apparent lack of increase in ALP in the fracture and/or intracranial injury groups suggests that the overall levels of bone-forming activity were not substantially increased by the fracture healing process (modelling) at the point in time when the measurements were made, possibly because that phase of fracture healing had not yet commenced in most cases.

In common with most retrospective studies there were a few evident limitations. There was inconsistency in the ascertainment of the biochemical data relevant to bone metabolism between groups, whilst haematological data were collected for just over 80 % of patients in each group. Clearly, this could be a source of bias. We were, however, unable to determine any systematic differences (e.g., age or sex) between the cases where biochemistry was or was not checked, within either the fracture or non-fracture groups. Failure to perform those tests seems most likely to reflect the treating clinician's opinion of their relevance in that individual instance; in addition, 15 infants with burns, two who had been poisoned and nine who were siblings of other infants investigated for inflicted injury did not have blood tests undertaken. There was no recording of the timing of blood sampling in relation to recent food intake, which would affect serum phosphate measurements. Other potential factors of interest such as an estimate of dietary calcium intake or type of

feeding were not recorded; if those with fracture and/or intracranial injury had been subjected to abuse, such abuse might also have affected factors relevant to bone health such as nutrition.

The current recommendations by the RCPCH and the British Paediatric and Adolescent Bone Group are that in the context of unexplained fractures in infancy, the level of 25D is not relevant to the causation of the fractures unless there is radiological evidence of rickets using conventional radiological techniques *and* biochemical evidence of rickets. The data from our cohort support these recommendations. It is important to state clearly that these new data do not provide any indication of a threshold for any of the factors measured in relation to prediction of fracture.

5. Conclusions

Although this is the largest such cohort reported, the data we have presented do suggest that further work is required. Whilst we know that an increase in PTH can result in bone loss due to increased bone turnover, we excluded children with radiologically abnormal bones (beyond their fractures). The data as presented are, in fact, consistent with the reports of change in PTH following major trauma in adults. The finding of higher values in those with metaphyseal fractures is intriguing, but unexplained rather than indicative of causation. Relevance of PTH to underlying bone pathology in a specific case might be more readily inferred if PTH was persistently elevated following the initial measurements; we would suggest that those with PTH measurements above the upper limit of the adult normal range for the assay should have repeated measurements undertaken to address such a possibility. Undertaking studies prospectively in larger populations of infants both with and without fracture and intracranial injury could help to guide the timing and need for such repeated measurements.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Funding source

Dr Borg's Clinical Lectureship is funded by the National Institute for Health and Care Research. Professor Bishop's input is supported in part through the Experimental Arthritis Treatment Centre for Children funded by Versus Arthritis, UK.

CRediT authorship contribution statement

Professor Bishop and Dr Alison conceived and designed the study. Professor Offiah was amongst the group of radiologists who reported on imaging findings. Dr Borg, Dr Lewis, Dr Parry-Okeden, Dr Hardisty, Dr Roberts, Dr Kerrin, Dr Chadha, Dr Shabani and Professor Bishop extracted and collated the data. Professor Bishop analysed the data. Dr Lewis wrote the first draft of the manuscript, which was critically reviewed and revised by all the authors. All authors reviewed and approved the final manuscript prior to submission and agree to be accountable for all aspects of the work.

Declaration of competing interest

NB has previously advised Internis on vitamin D supplementation in infancy and children. NB, ACO and LA have appeared as witnesses in Court in child protection cases, ACO has received honoraria and expenses for lecturing on imaging of inflicted injury.

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