

## HISTORY OF OSTEOPOROSIS DISREGARDS OSTEOMALACIA

I read with interest the paper by Stride et al. (*J R Coll Physicians Edinb* 2013; 43:254–61) reviewing the historical ‘milestones’ of osteoporosis. The authors referred to nutritional aspects more than ten times. Nutrition is far more pertinent to osteomalacia (adult rickets) than to osteoporosis.

Calcium plus vitamin D therapies for osteoporosis were introduced more than two decades after Fuller Albright’s pioneer studies on metabolic bone diseases, notably osteoporosis and osteomalacia. Their reported benefits in selected older people were not maintained when trials extended to a large population-based cohort (Witham MD. Enhanced vitamin D intake for all? Why we should say ‘no’. *J R Coll Physicians Edinb* 2011; 41:327–9). One has to suspect that the reported benefits could have resulted from treating an associated osteomalacic component rather than as a response of the osteoporosis itself.

The bone mineral density (BMD) as shown by the dual energy X-ray absorptiometry (DEXA) scan, the main diagnostic tool mentioned in the paper, does not differentiate between osteoporosis and osteomalacia.<sup>1</sup> In other words, a low BMD does not always mean osteoporosis, as the authors appear to have assumed.

The details of fractures, cited from references 25 and 30, do not conform with those characteristic of osteoporosis. Some of the ‘healing fractures’ from reference 25 could well have been healing pseudo fractures of osteomalacia, once designated Looser’s nodes, a term that disappeared recently from some medical dictionaries, similar to the denial of ‘osteomalacia’ by the authors.

Moreover, the mentioned ‘fluctuations’ in bone density with lactation and pregnancy (references 54, 55, 42, 43) are a far better fit for osteomalacia than for osteoporosis. In our region, women with osteomalacia used to present more commonly near the end of an unduly rainy, cloudy and short daytime winter, preceding the availability of the healing effect of an abundance of sunshine on the skin. This evidently contradicts osteoporosis in the pre-bisphosphonate era. Furthermore, the stated ‘short children’ in reference 30 from an English village implies rickets as the cause. In British textbooks of the 1950s, I recall having read that the skeletal imprints of rickets were not uncommon among the elderly in large cities in the UK.

In a recent correspondence<sup>2</sup> concerning another paper that also unjustifiably ignored osteomalacia,<sup>3</sup> I discussed some reasons for the ongoing trend of disregarding osteomalacia.

The recent focus on osteoporosis was partly triggered by the heavy financial burden that its complications

imposed on health budgets, and partly by its increasing prevalence from senescence, physical inactivity so vividly expressed by the authors and the introduction of corticosteroid therapy in the 1950s. These developments overtook the status of osteomalacia but until the 1970s, its comparison to osteoporosis did not fade.<sup>4</sup> Admittedly, it seems that family planning, with the availability of simple and safe contraceptive methods, largely broke the ‘chain’ of repeated pregnancies and lactation; this contributed to the reduction, if not end, of osteomalacia among young adult women.

Such changes appear to have swung the pendulum too far away from osteomalacia, so much so that some researchers gathered more than 15 disorders where vitamin D deficiency could play a role but they ignored the term osteomalacia.<sup>5</sup> The previously cited paper by Witham also failed to mention osteomalacia.

Such ongoing trends might have been used by Dr Stride et al. as an excuse for disregarding the role of osteomalacia in their paper. However, as their study is historical, such a deficit in their evaluations cannot be overlooked; to maintain accuracy, ‘osteoporosis’ must be substituted by ‘osteopenia’. The attractive incorporation of Egyptian mummies within the title of the paper, I guess, would have been designated by the expression of the late Professor JA Strong a ‘red herring’.

Apart from teenage pregnancies, considering the effect of parity and lactation on bones in the cited reports, only one mentioned a harmful effect on bone. Otherwise, none of the remaining reports stated a lasting reduction of BMD; some even showed evidence of improved bone health. We must consider that the report by Li and Zhu is from China, a country where women who give birth to more than one child are subject to heavy monetary fines. Instead of considering the social factors, the authors mentioned the report in their lists on parity and lactation as if to blur the otherwise neutral effect on bones or even improved bone health.

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### Author's reply

We appreciate Professor Al-Dabbagh's interest in our hypothesis. We agree that osteomalacia is often overlooked, and was not addressed in our paper. We certainly need to be alert to the problem of calcium or vitamin D deficiency even in sunny Australia in specific at-risk cultural or religious groups in whom skin exposure to sunlight is minimised below safe and effective doses.<sup>1</sup>

The issue of osteomalacia associated with osteoporosis however is complex, the benefit of either calcium or vitamin D alone on bone integrity remains controversial, and all studies of proven effective therapy for osteoporosis such as the recently published trial of romosozumab<sup>2</sup> include calcium and vitamin D as therapy for active and placebo groups. Diagenesis also invalidates any measurements of bone calcium in skeletons.

The two major points in our paper are that osteoporosis has been detected in archaeological discoveries across five continents including civilisations with abundant food, excluding local nutritional or genetic factors as the major cause, and that the diagnosis of osteoporosis does not depend upon DEXA alone, but also studies using bone histology and magnetic resonance imaging where the diagnosis is more specific.

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## SERUM FERRITIN LEVEL >100 NG/ML DOES NOT VIRTUALLY EXCLUDE IRON DEFICIENCY ANEMIA (IDA)

I read with interest the article 'Interpretation of the full blood count in systemic disease – a guide for the physician' (Leach M. *J R Coll Physicians Edinb* 2014; 44:36–41) and would like to give some comments. The author stated: 'A ferritin level over 100 ng/ml virtually excludes IDA regardless of circumstances.' I am quite concerned with his statement because of the following reasons:

- Guyatt et al. studied 259 elderly patients with anaemia. Bone marrow biopsies were performed. Of 116 patients with serum ferritin >100 ug/L, eight had IDA (6.8%). The authors concluded that ferritin >100 ug/L reduces the probability of IDA to <10%.<sup>1</sup>
- Kalantar-Zadeh et al. studied 25 patients with anaemia and chronic renal failure (CRF). Bone marrow iron stains were graded as follows: 0 no iron; +1 slight iron; +2 patchy iron; +3 patchy to diffuse

staining; +4 diffuse staining; +5 extensive staining. Iron scores of 0 to +1 were considered absolute IDA. Seven patients had a score of +1. Five had ferritin >200 ng/ml. The authors concluded that ferritin < 200 ng/ml was highly predictive of IDA.<sup>[2]</sup>

- Fernandez-Rodriguez et al. studied 63 patients with anaemia and CRF. Bone marrow iron stains were graded as follows: 0 no iron; +1 slight amount of iron or patchy iron stores; +2 diffuse iron staining; +3 extensive iron staining. Iron scores of 0 and +1 were considered IDA. A total of 16 patients had an iron score of 0 and 21 patients had a score of +1. Median ferritin values were 156.6 ± 225.2 ug/L (ng/ml) for score 0 group and 188.2 ± 98.7 ug/L (ng/ml) for score +1. The authors concluded that ferritin of 121 ug/L has sensitivity and specificity of 75% and that ferritin of 121 ug/L may be used as a diagnostic indicator of absolute IDA.<sup>3</sup>

I would like to point out that our understanding and diagnostic approach to patients with IDA and coexisting inflammatory diseases is still not perfect. Although serum ferritin is a useful tool, it is not perfect. Diagnosis of IDA can be missed in a significant number of patients if we dogmatically assume that ferritin >100 ng/ml virtually excludes IDA.

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## CHRONIC KIDNEY DISEASE AND IRON DEFICIENCY

We read with interest the educational article by Leach (Leach M. Interpretation of the full blood count in systemic disease – a guide for the physician. *J R Coll Physicians Edinb* 2014; 44:36–41). We would like to add some further comments on the subject of diagnosing iron deficiency. The author states that a ferritin level of greater than 100 ng/ml virtually excludes iron deficiency regardless of circumstances. This is not necessarily the case in patients with chronic kidney disease (CKD), and particularly those who receive erythropoiesis-stimulation agent (ESA) therapy, who often have a 'normal' serum ferritin levels but may still be iron deficient due to problems with utilisation of the available iron, i.e. functional iron deficiency (FID).

Patients with CKD have impairment of iron homeostasis,<sup>1</sup> thought to be related to raised hepcidin levels which impair iron absorption from duodenum and prevent iron extraction from reticuloendothelial stores via effects on the iron transport protein ferroportin.<sup>2</sup> Therefore the availability of iron, as measured through transferrin saturation (TSat), is often low. Commencing these patients on ESA therapy without first addressing iron availability can exacerbate the problem further and may lead to iron-restricted erythropoiesis. This means that their erythrocyte production is driven by continued stimulation from ESA, yet they cannot incorporate iron fast enough into the developing cells to meet demands.

Functional iron deficiency should be suspected in renal patients with anaemia who have low mean cell haemoglobin (MCH) and low TSat (ferritin is usually >100 ng/ml). This is particularly important in patients on ESA therapy who are at high risk of FID. Monitoring of MCH is useful in assessing trends over a period of weeks or months.<sup>3</sup> Reticulocyte haemoglobin content (CHR), not part of routine full blood count panel, gives a better indication of supply of iron to developing red cells. Another laboratory parameter not widely available, percentage of hypochromic red cells (%HRC), has the best evidence base in assessing for FID and need for parenteral iron therapy, and features in the National Institute for Health and Care Excellence anaemia management guidelines<sup>4</sup> as the preferred method of testing for FID when available. Other markers have been examined and offer future potential.<sup>5</sup>

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## IRON DEFICIENCY ANAEMIA AND ITS CAVEATS

The statement, in Table 1, that mean cell haemoglobin (MCH) is typically low in iron deficiency, even though mean cell volume (MCV) may be occasionally normal (Leach M. Interpretation of the full blood count in systemic disease – a guide for the physician. *J R Coll Physicians Edinb* 2014; 44:36–41), chimes in with the observation made in 201 subjects with serum ferritin <18 mcg/l, where the proportion of subjects with MCH <26 pg (in the presence of MCV 80 fl or more) was significantly ( $p < 0.001$ ) greater than the proportion of subjects with MCV <80 fl in the presence of MCH 26 pg or more.<sup>1</sup>

However, contrary to Leach's statement that 'a ferritin level over 100 ng/ml virtually excludes iron deficiency regardless of circumstances' serum ferritin levels have been known to range from 6–480 mcg/l in anaemic patients with colorectal carcinoma, the latter a powerful risk factor for iron deficiency anaemia.<sup>2</sup> Accordingly, the presence of a serum ferritin >100 mcg/l justifies, instead, the use of a diagnostic trial of iron replacement therapy (end point 2 g/dl increment in haemoglobin) to confirm or refute the diagnosis of iron deficiency anaemia.<sup>3</sup> In one such trial the proportion of patients who experienced correction of anaemia was higher in the intravenous iron group than in the oral iron group.<sup>3</sup>

Finally, a microcytic peripheral blood profile can mask the coexistence of vitamin B12 deficiency with iron deficiency anaemia.<sup>4</sup> In that context, it would be interesting to explore the frequency with which macrocytosis emerges after a diagnostic trial of iron replacement therapy.

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### Author reply

I am grateful for the comments presented in these letters in relation to my article. These comments are mostly directed at my statement that 'a serum ferritin over 100 ng/ml virtually excludes iron deficiency'. Note my use of the word virtually, not always. As noted there are circumstances, particularly in patients with renal disease, where a state of functional iron deficiency exists. In my

experience for the majority of patients this statement holds true and for every exception there will be a dozen patients who have undergone unnecessary endoscopy and colonoscopy for non-iron deficiency anaemias.

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