British Intestinal Failure Alliance (BIFA) Guideline

BIFA Guidelines for the prevention and treatment of metabolic bone disease in patients with chronic intestinal failure

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Summary

Patients with chronic intestinal failure (CIF) are prone to bone fragility, osteoporosis and the risk of fractures. This may be due to the underlying disease (e.g. inflammatory bowel disease), malnutrition, mineral (e.g. calcium and magnesium) and vitamin (e.g. vitamin C, D and K) deficiencies and treatments (e.g. corticosteroids, proton pump inhibitors or heparin). An annual calculation of osteoporosis fracture risk is recommended, and a dual energy x-ray absorptiometry scan should be performed every 3-5 years depending upon fracture risk. Osteopenia is diagnosed if the T-score is between -1 and -2.5, and osteoporosis if a T-score is less than -2.5. Treatment starts with lifestyle changes (e.g. stopping smoking, reduce alcohol and safe sunlight exposure), optimising calcium, magnesium, vitamin D and K intake. Then it is ensured that the parenteral support does not give too much or too little sodium, and that it is not very acidic (acidity may cause a metabolic acidosis). Increasing the acetate/chloride ratio to increase pH in the PS bag may prevent this. Medication may

Aim of the guideline

1. To define metabolic bone disease (MBD).
2. To diagnose MBD.
3. To determine the risk of fractures.
4. To provide a surveillance schedule for patients with chronic intestinal failure (CIF).
5. To review treatment strategies for patients with CIF.

What is metabolic bone disease?

In adults' bone is constantly being remodelled, with the balance of resorption and formation under the influence of mechanical, nutritional, endocrine, environmental and inflammatory factors. There is a carefully controlled balance between osteoblasts (bone formation) and osteoclasts (bone destruction). This process is partly regulated by parathormone (PTH), vitamin D, calcitonin, oestrogens, growth hormone, thyroxine, and corticosteroids. Micronutrients are implicated in bone health including minerals (e.g., calcium, magnesium and sodium), water soluble vitamins (e.g., vitamin C) and fat-soluble vitamins (e.g., vitamin D and K). A high sodium intake may cause calciuria and may enhance bone reabsorption so decreasing bone mineral density (BMD). In addition, a low sodium intake or increased losses may activate the renin-angiotensin-aldosterone system also resulting in reduced BMD [1]. The acid-base status of the patient affects bone mineralisation (acidosis may cause osteoporosis). (Fig 1)

Serum calcium and phosphate are relatively tightly controlled primarily by vitamin D and PTH levels. Changes in bone turnover, growth, or changes in hormones and electrolyte levels can alter the calcium and phosphate concentrations in hydroxyapatite and so result in defective bone density or mineralisation.

MBD encompasses conditions that result from changes in the amount of and/or mineralisation of bone. Osteopenia/osteoporosis reflects a reduction in bone volume. Defects in bone mineralisation includes osteomalacia and renal osteodystrophy. Reductions in both bone volume and mineralisation reduce bone density.

Prior to considering CIF-related factors, risks for osteoporosis needs to be placed in context with other standard predictors of fracture risk such as menopausal status, low body mass index (BMI), smoking, high alcohol intake, previous history of fragility fracture in adulthood and parental history of hip fracture [2] [3] In addition, for patients with CIF, important drivers include underlying conditions (e.g. inflammatory bowel diseases (IBD) or its treatment with corticosteroids). Less common other causes of reduced bone mass include calcium / vitamin D malabsorption, prolonged hypomagnesaemia, vitamin K deficiency and historical concerns of aluminium containing salts in parenteral nutrition (PN) [4].

How is the diagnosis made?

History and Examination

The patient may provide a history of injury or non-injury leading to a fracture (including vertebral collapse) or a complaint of bone pain. A fragility fracture is defined as a fracture resulting from trauma equivalent or less than a fall from standing height or less. Typically fractures of the digits, scaphoid, face and skull are not included. Spine fractures often cause transient back pain that is misdiagnosed, and so most vertebral fractures are missed. A history of height loss of more than 3 cm and/or progressive kyphosis, (measured using wall to occiput distance (cm), known as Flesche test; alternative is using sagittal balance test on radiograph of whole spine and assessing the C7 plumb line) is an indication for imaging of the spine with a lateral Xray or dual-energy x-ray absorptiometry (DEXA) vertebral fracture assessment.

Muscle pain, tenderness and proximal weakness may suggest osteomalacia. A chair rise test for proximal thigh strength is useful. In addition, osteomalacia can result in incomplete fracture of the medial proximal femur, pelvis and scapula resulting in groin pelvic and shoulder pain and localised bony tenderness on examination.

Investigations

Pertinent blood tests include liver function, bone profile including a fasting serum phosphate, vitamin D and PTH levels as well as a 24-hour urine collection for calcium and sodium. The recommended bone turnover marker N-terminal propeptide of type I procollagen (PINP) or a bone specific alkaline phosphatase (ALP) isoenzyme can help differentiate an increased ALP as well as a *gamma*-glutamyl *transferase (GGT) (shows if raised ALP is of liver origin)*. They may be normal (osteoporosis) or may show a raised ALP, low vitamin D and a raised PTH level (osteomalacia).

Radiographic findings compatible with osteoporosis are a loss of bone mass and fractures in common locations, such as forearm, humerus, hip or spine [5]. In children, rickets is suggested with wide growth plates and frayed metaphyses; and osteomalacia may present with radiographic evidence of Looser zones, which are short, transverse lucencies in cortical bone that do not travel the whole way through the bone [5]. In adults, osteomalacia may present with Looser zones in the proximal femur, pelvis and scapula.

Other conditions that may present with radiological changes in patients with CIF, are hand subperiosteal resorption in severe hyperparathyroidism and subperiosteal haemorrhage due to collagen defects in vitamin C deficiency.

Definitive diagnosis of osteopenia/osteoporosis is through DEXA scans that assess BMD in the femoral neck and spine if there is no osteomalacia [6] [7]. International consensus guidelines from the International Society of Clinical Densitometry have determined that osteopenia is diagnosed if the T-score is between -1 and -2.5, and osteoporosis is diagnosed as a T-score <-2.5 using a normative reference database of Caucasian women aged 25-29 for all adults, irrespective of race or gender [8]. Note that a T-score is commonly presented and compares the bone density with that of healthy 30 year old adults allowing a diagnosis of osteoporosis or osteopaenia. A Z-score compares the bone density to that of healthy people

of the same age and sex and can be helpful at alerting to a risk of secondary osteoporosis and are particularly helpful for children, young people, pre-menopausal women and younger men. The diagnosis of osteoporosis has now shifted to fracture risk assessment using FRAX identifying those with low, high and very high fracture risk.

For the diagnosis of bone fragility in children, the diagnosis requires a vertebral compression fracture or a Z-score <2 and either 2 long bone fractures by the age of 10 or 3 long bone fractures by the age of 19 [9]

The negative feature of DEXA is that unfortunately, osteoporosis and osteomalacia cannot be differentiated between purely based on BMD. As a result, it is essential to rule out osteomalacia using blood tests and in some cases a non-de-calcified bone biopsy has a role, particularly after the traditional method of using tetracycline to label bone activity [10].

Risk stratification and surveillance

Calculation of 10-year major osteoporotic fracture risk and hip fracture risk is calculated using a tool, such as the FRAX® tool for those aged from 40 to 90 years [2] [3]. This is a simple scoring tool that should be set to a patients country of assessment, and is based on a number of relevant factors: age (40-90), sex, low body mass index, previous fragility fracture (as defined above), parent having a hip fracture, smoking status, glucocorticoid usage (current oral exposure or has been exposed to oral glucocorticoids for more than 3 months), rheumatoid arthritis, secondary osteoporosis (type I (insulin-dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition or malabsorption, chronic kidney disease (dialysis independent) and chronic liver disease) and an alcohol consumption of 3 or more units per day. This should be undertaken in all adults with a previous fragility fracture and all those aged 50 years and over, those with risk factors for fracture, recent or current long-term oral glucocorticoid therapy, or a BMD T-score ≤ -2.5. If the fracture risk is intermediate, a BMD measurement should be performed using a DEXA and then re-estimate FRAX® score.

A falls assessment to signpost to local frailty/falls pathway should also be undertaken by asking 3 questions: (i) Have you fallen in the past year? (ii) Do you feel unsteady when standing or walking? and (iii) Do you have worries about falling? [11]. In pre-menopausal women and men <50yrs, the following is a non-exhaustive list of parameters that currently fall outside of the FRAX® assessment and may therefore mandate a DEXA assessment to determine treatment thresholds: ≥4cm height loss, kyphosis, type 2 diabetes mellitus, inflammatory conditions, hyperparathyroidism, nutritional deficiencies, and long-term proton pump inhibitor usage.

According to the National Osteoporosis Guideline Group (NOGG), DEXA frequency in UK patients should follow 5 to 10 years of treatment for osteoporosis with oral bisphosphonates and 3 to 6 years for intravenous bisphosphonates [12]. At this time the patient should also be assessed, and a decision made to

either continue treatment for a further 5 years or have a treatment pause. If treatment is paused this should then be reassessed in 2 years with a repeat FRAX score and DEXA [13]. Surveillance with DEXA for CIF is recommended annually by ESPEN [14].

We suggest a baseline DEXA and vertebral fracture assessment (VFA) when home parenteral support (HPS) is started, and a year later to assess the rate and direction of change, and then a yearly FRAX® assessment. If not osteopenic then the DEXA may be repeated at 5 yearly intervals. If the result is in the intermediate risk group, the DEXA may be repeated every 3-5 years. If an initial DEXA is osteoporotic, then commence treatment and follow guidance (e.g. from a metabolic bone clinic) for when to repeat DEXA assessments.

Treatment pathway

Lifestyle changes

Patients should cease smoking and reduce alcohol intake. If they have a low BMI nutritional status should be improved. Increased exposure to sunlight outside of the peak hours of 11:00-15:00 should be considered but is often ineffective. In addition, there needs to be a progressive strength and exercise programme to increase BMD, with exercise pushing loading on the bones, e.g. hopping.

Medication

Potentially causative medication should be reviewed to determine if appropriate to continue or if there is a suitable alternative (e.g., placing on a lower dose or corticosteroid-free regimen; the clinical impact of proton pump inhibitors and anticoagulants remains controversial). In patients requiring parenteral iron treatment, ferric carboxymaltose can cause a renal loss of phosphate resulting in hypophosphataemic osteomalacia [15]. Thus, if this occurs, an alternative iron replacement should be chosen.

Adequate Vitamin D intake is important to facilitate enteral absorption of calcium. Loading with oral vitamin D (if able to absorb it) depends on the level of the deficiency. 300,000 units given as 50,000 units weekly for 6 weeks for severe deficiency (or 800units daily or greater) (BNF). Blood levels of 25-OH vitamin D may guide dosage. Refer to your local Trust guidelines for further advice on oral vitamin D replacement therapies. Sublingual vitamin D therapy may also give adequate absorption. The oral bioavailability (the amount of vitamin D reaching the systemic circulation after an oral dose) of vitamin D supplements may be increased when taken with fats e.g., a glass of milk. In CIF, gut absorption of a fat-soluble vitamin is likely to be poor and so a higher oral dose or commonly an intramuscular (IM) dose of ergocalciferol or cholecalciferol (may be required (300,000 units IM every 3-6 months).

Calcium intake orally is recommended to be 700-1000mg daily, though the oral bioavailability is not clear, but thought to be 10-47% in healthy (non-IF) individuals [16]. Assuming that the aim should be for 30% oral bioavailability, that is 300mg, which is equivalent to 7.5mmol calcium intravenously for normal weight

patients receiving home parenteral nutrition (HPN) and would appear to be an amount that provides enough calcium, though may be assessed by measuring 24hr urine calcium output.

Magnesium replacement (0.1-0.2mmol/kg/day are baseline daily requirements for adults), to achieve serum levels within the normal range, should be given orally or parenterally, with minimisation of medication known to contribute to hypomagnesaemia (e.g., proton pump inhibitors and tacrolimus). It may be necessary to give repeated large doses of 20 mmol (5g) of magnesium sulphate intravenously to correct low serum levels before prescribing a lower oral or intravenous maintenance dose. Organic magnesium salts (e.g., magnesium aspartate and citrate) have a higher bioavailability than inorganic salts (e.g., magnesium sulphate or oxide) [17].

Medication for treatment of metabolic bone disease

Some patients with CIF (not receiving HPS) may have sufficient absorption to take oral medication. In these patients, oral bisphosphonates, which are generally poorly absorbed may be given. They have a short time to maximum blood concentration (e.g., 1 hour for alendronic acid) so after oral administration there is a strong likelihood that even with CIF there will be a moderate degree of drug absorption from the gastrointestinal tract. The administration of oral bisphosphonates requires the patient to take it with a full glass of water (250mL) and remain in the upright position for at least 30 minutes after ingestion and not take any calcium containing supplements for at least 4 hours. Initial response to alendronic acid for osteoporosis occurs after 1 month and the peak response occurs after 3-6 months of treatment. In most patients with CIF (especially if having HPS), parenteral treatment is required (e.g., zoledronate (yearly) or Ibandronate (3 monthly)). A measurement of PINP bone turnover markers before and 3 months after initiation should show adequate suppression unless there is a history of recent fracture [18]. As osteoporosis may be a life-long condition these may need to be used indefinitely, though treatment for >10years needs discussion with the patient about the risks and benefits. Certainly, the aim for patients receiving treatment for secondary osteoporosis should be to at least return them to equivalent density for age/gender-matched individuals. Current recommendations, therefore, are for appraisal by FRAX score and DEXA at 5 years for most bisphosphonates or 3 years for zoledronate. A further 5 years or 3 years respectively may be needed. Treatment beyond this may increase the risk of osteonecrosis of the jaw and atypical femoral fractures, though they are very rare complications: 1 per 100 to 1000 teeth extracted or 1 atypical femoral fracture per 75 hip fractures prevented. Manufacturers advise against their use in women of childbearing age due to theoretical risks (from animal studies) to the developing bones and in causing hypocalcaemia in the newborn. A review of 78 reports found shortened gestational age, low birth weight, and transient hypocalcaemia of the newborn [19].

Alternative parenteral strategies include denosumab, a monoclonal antibody that targets osteoclastic activity to reduce breakdown phase of bone remodelling. If treatment is stopped after 4 doses, BMD rapidly returns to below baseline at time of commencing treatment with a transient increased risk of fractures. Parenteral anabolic treatments include teriparatide and abalaparatide, a subcutaneous parathyroid hormone analogue and romosozumab, an anti-sclerostin antibody. The role of GLP-1 and GLP-2 agonists in treating metabolic bone disease may be purely in the improved enteric absorption of nutrients [20], but may have a direct effect on the bone.

Referral to a metabolic bone disease clinic is indicated if there is deterioration in bone health despite simple measures or if a complex scenario.

Recommendations (see figure 2)

Assessment

1. Assess generic and CIF specific patient factors likely to contribute to lower BMD: age, gender particularly menopausal status, parental history, type 2 diabetes mellitus and hyperparathyroidism.
2. Assess patient life-style factors that may contribute a risk: smoking, alcohol intake, weight-bearing exercise and sunlight exposure.
3. Review medication usage and consider means for reduction of usage: corticosteroids, proton pump inhibitors, heparin containing medication.
4. Undertake a risk score (e.g., using FRAX®) for adults aged 40 to 90 years.
5. Undertake baseline dual energy x-ray absorptiometry (DEXA) with vertebral fracture assessment and then every 3-5yrs if stable or yearly to assess trajectory of change if osteopenic or osteoporotic.
6. Following the BIFA monitoring guidelines regarding:
    a. Electrolytes: serum calcium, magnesium, AM fasting phosphate every 3-4 months.
    b. 25-hydroxy vitamin D, PTH 6 monthly.
    c. Consider serum aluminium levels in discussion with local chemical pathologists.

Treatment of all patients with CIF

7. Encourage lifestyle changes: stop smoking, limit alcohol intake, increase weight if BMI is low and maintain a body mass index of 19-25kg/m², increase weight-bearing exercise and have safe sunlight exposure.
8. Consider hormone replacement therapy (HRT) according to risk and use suitable formulations in the context of a benefit vs. risk assessment.
9. Limitation of medication affecting bone health: corticosteroids, proton pump inhibitors, heparin.
10. If not having HPS optimise calcium intake orally to 1000mg daily (see 14 for parenteral).
11. Treat vitamin D deficiency with oral, sublingual over intramuscular preparations (see 14 for parenteral).
12. Increase vitamin K intake: UK guidelines recommend oral intake of 1 µg/kg/day, whereas in US recommendations are 90-120 µg daily, ESPEN recommends 250-500 µg/week. There are no good

bioassays and whilst using international normalised ratio (INR) as a surrogate marker of vitamin K sufficiency is less than ideal (especially as abnormal in liver disease), it does screen for those who do may benefit from treatment. Oral Vitamin K is absorbed in jejunum and ileum and enhanced with good biliary and pancreatic secretions with fat containing food or drink. Oral replacement with Menadiol sodium phosphate paediatric 2mg in 0.2mL preparation allows 2mg monthly to those regularly deficient to maintain levels of vitamin K. If there is insufficient jejunum, intravenous preparations will be required. See 14e below.

13. Increase magnesium (e.g., Mg oxide/aspartate/glycerophosphate 10-24 mmol/day) intake if tolerated/absorbed to ensure serum concentrations are normal.
14. Optimise HPN composition, in particular:
    a. Reduce excessive sodium intake. Check 24-hour urinary sodium (normal range 40-220 mmol/24 hr).
    b. About 7.5mmol calcium and 15-30mmol phosphate intravenously per day should aid net retention. There is no need for oral calcium if having PN but may be needed if parenteral saline or dextrose only.
    c. Vitamin D is a component of common vitamin supplementation in compounded HPS but if intravenous fluids or multichamber bags, there will be the need to supplement with vitamin preparations added to the bag or infused separately. Vitamin D is contained in Cernevit®, Vitlipid N Adult® and Nutratain® but not in Solvito®.
    d. Additional vitamin K. It is recommended by ESPEN, ASPEN and the FDA that all adult PN preparations should provide 150µg of phylloquinone (vitamin K) per day. Some parenteral multivitamin preparations (e.g., Vitlipid®) require to be given in a lipid emulsion, whilst others (e.g. Nutratain®) can be in an aqueous solution. Be aware that Cernevit® does not contain any vitamin K. Some HPN centres use manual additions of vitamin K (as phytomenadione) to achieve the recommended amount of vitamin K provision.
    e. Prevention and treatment of metabolic acidosis using acetate in place of chloride (acetate:chloride ratio), in compounded PN, should negate the need for supplemental oral bicarbonate (unless having a multi-chamber bag (MCB) or due to stability issues).
15. Treat chronic inflammation.

Treatment of patients with CIF and T score <-2.5 or on >7.5mg oral prednisolone daily for ≥3months

16. Undertake FRAX and decide if treatment needed or treat if on corticosteroids and have had a previous fracture.
17. If oral/enteral absorption is adequate, an oral bisphosphonate (e.g., alendronic acid or risedronate) if tolerated may be given. Alternative strategies include raloxifene hydrochloride and strontium ranelate for post-menopausal women, and tibolone for younger post-menopausal women. Oral bisphosphonates (particularly alendronic acid) can cause significant oesophageal ulceration and so may not be suitable for patients with acid reflux. If absorption is poor, then parenteral bisphosphonates may be used. Risk of osteonecrosis of the jaw and atypical femoral fractures.
18. Parenteral treatment options include denosumab in older adults given concerns about lifelong

therapy if started in younger adults (but beware of treatment cessation and return to pre-treatment osteoporosis levels), zoledronic or Ibandronic acid (risk of osteonecrosis of the jaw and atypical femoral fractures), teriparatide (reserved for post-menopausal women), and romosozumab (for post-menopausal women).

19. Review treatment after 5 years for oral bisphosphonates and 3 years for parenteral bisphosphonate.
20. Involve local metabolic bone disease specialist for support and advice, particularly in complex cases or if not responding to treatment.

Figure 1: Factors that reduce bone mineral density

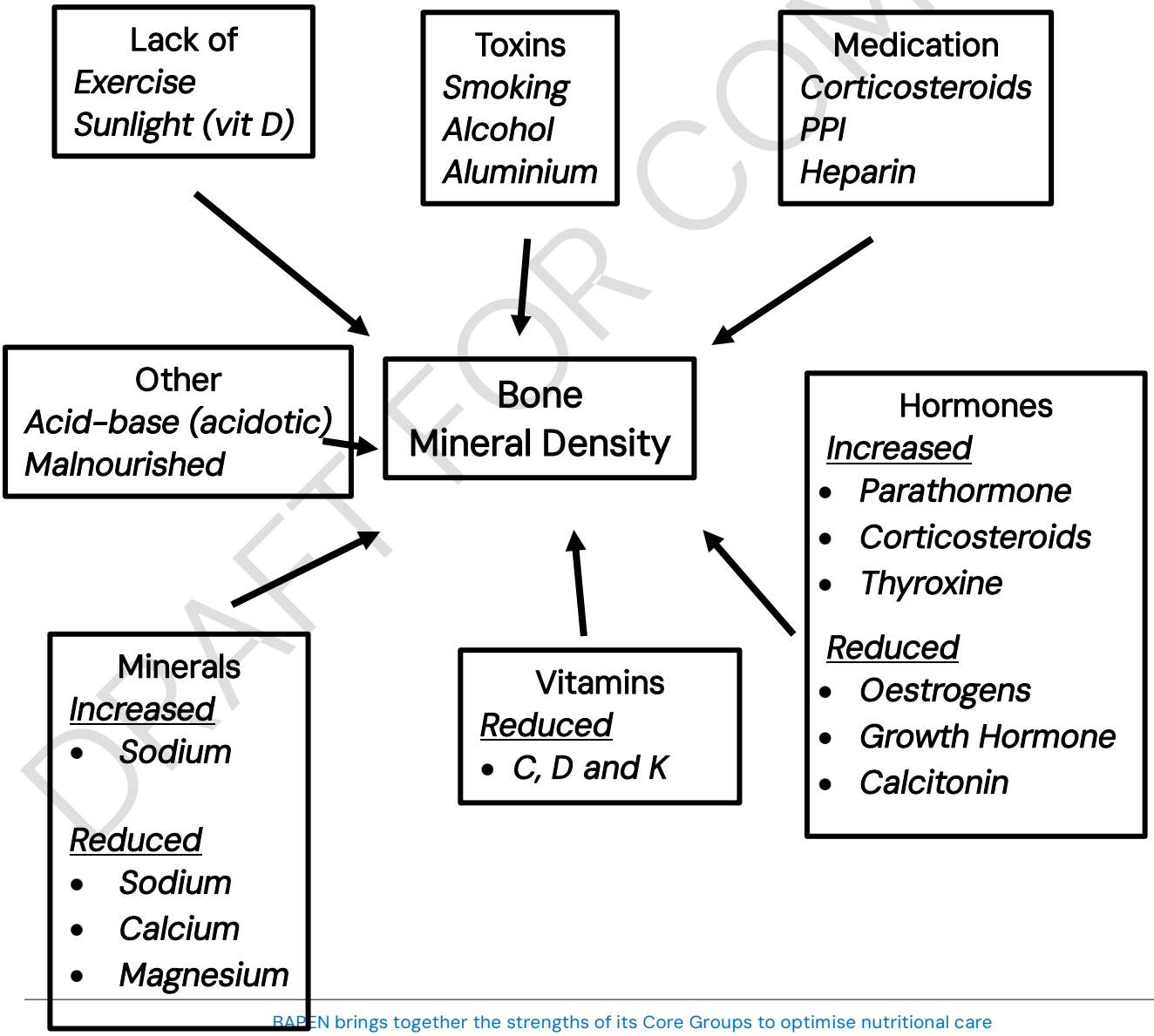
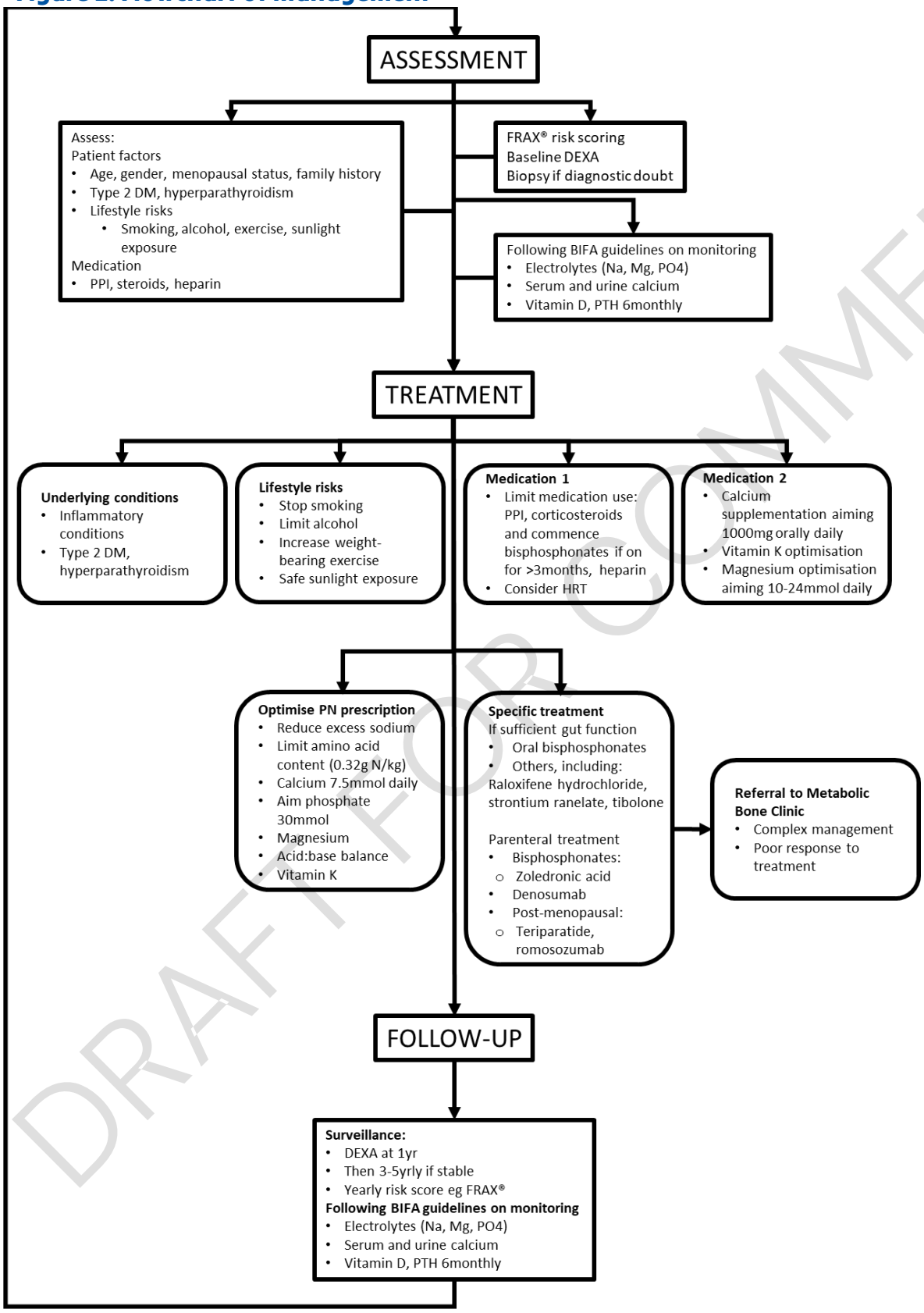


Figure 2: Flowchart of management



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