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Metabolic bone diseases and parenteral nutrition in pediatric patients: clinical and nursing aspects

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ABSTRACT

Total parenteral nutrition is a feeding strategy widely used in children and, particularly, in preterm infants, due to a variety of pathological conditions that hinder enteral feeding. Parenteral feeding has been associated with the development of metabolic bone diseases. These can manifest as rickets and/or pediatric osteoporosis, with a prevalence reaching 40%, while the nutritional limitations of parenteral feeding, along with the increased metabolic needs of the bones at this growth stage, further deteriorate the problem. There are plenty of theories regarding the underlying mechanisms. Deficiency or toxicity of nutrients, such as calcium, phosphorus and vitamin D, and cholestasis have been identified as risk factors. Another contributing factor is the contamination with aluminum, with its numerous deleterious effects, along with the composition of the fatty acid emulsions administered. Appropriate enrichment of parenteral nutrition solutions with specific nutrients plays a key role in managing or preventing the disease. High standards in the use of this method, including the restriction of aluminum contamination, are of high importance. The role of clinicians and nurses is crucial, since a significant level of alert for malnutrition signs is required, as well as high professional standards for applying and maintaining the parenteral nutrition setting.

KEY WORDS: Bone, Metabolic disease, Parenteral nutrition, Pediatric, Nursing

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Introduction

Total Parenteral Nutrition (TPN) constitutes a landmark therapeutic strategy for providing the necessary nutrients and energy, usually through a central vein, to neonates, children and adults, suffering from a condition that hinders normal enteric food intake [1]. While TPN was firstly introduced to the pediatric patient population in the 1960s, it was not until 1980 when the TPN-associated complications were firstly described [2, 3]. Among them lie the TPN-induced Metabolic Bone Diseases (MBD), developed through a variety of speculated mechanisms and manifesting either as rickets (in children) and osteomalacia (in adults) or as osteoporosis [4-8].

Although a significant amount of research has provided valuable knowledge on the clinical manifestations and laboratory findings of these diseases, as well as on the distinct molecular pathways leading to them, the prevalence of MBD in children assisted with TPN is still high, up to 40% [9]. Therefore, exploring these fields at a greater extent, could not only lead the way for a deeper understanding of these conditions, but also for their more effective management. Additionally, it is of paramount importance to enable clinicians and nurses to be informed for the details of these conditions, stay alert for any alarming signs and respond successfully in case needed. Presumably, this study aims, on the one hand, to review the various aspects of TPN-induced MBD, with an emphasis on the speculated mechanisms of development, and, on the other hand, to present a framework for a proper clinical approach by the clinician and the nurse.

Tpn in children

Indications

TPN administered to children differs from that of adults, with respect to the timeframe of the administration, the dosage of various nutrients provided depending on the child's growth needs and the various technical issues associated with the intravenous access [10]. Any gastrointestinal (GI) tract condition that does not permit enteral feeding, such as severe inflammatory bowel disease and GI reflux, generally requires TPN [6-8]. TPN is particularly indicated for preterm and low birth weight infants, immediately after birth, to compensate for the low nutrient reserves, in the face of increased energy consumption due to prematurity diseases and high developmental needs. Since the GI tract is still premature to take up its role, parenteral feeding is usually unavoidable. These issues arise predominantly when birth weight is less than 1.500 kg or the age is lower than 34 weeks [11]. In this cases, TPN is usually applied if it is anticipated that enteral feeding will not be achieved for at least two days [6-8].

Administration regimens

The pattern of TPN usage depends on several factors. Principally, TPN solutions must contain adequate sources of energy (carbohydrates and fats), abundant amino-acids, electrolytes, vitamins, minerals and trace elements. Moreover, solutions might also contain further additives, such as heparin, cysteine and carnitine. In particular, dextrose is used for covering the needs for carbohydrates, while there are specialized amino acid solutions, such as TrophAmine 6% and 10%, Premasol 6% and 10% and Aminosyn-PF 7% and 10%, rich in essential amino-acids and tailored for the needs of infants and children. These solution regimes display a lower pH, permitting the dilution of larger amounts of calcium (Ca^{+2}) and phosphate (P^{+4}) [6-8]. Fats are provided in the form of Intravenous Fat Emulsions (IVFE), which consist either of soybean oil alone or of a combination of soybean with safflower oil. Highly concentrated IVFE are preferred, since they provide abundant calories in relatively small solution volumes. Infants and children must receive at least 0.5–1.0 gr/kg of IVFE per day, while preterm require more than 0.6–0.8 g/kg/day [12].

Frequent electrolyte monitoring to adjust the daily intake is necessary. Preterm and full-term have similar needs in electrolytes, except for Ca^{+2} and P^{+4}, which are higher for preterm, since they lack in the maternal supply of the third gestational trimester, while their growth needs are increased [12]. Despite the ongoing research on optimizing the TPN supplementation strategies, pediatric vitamin products have not evolved and, often, the increased dietary

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needs of malnourished and severe patients are not met [6-8].

Adverse effects

TPN, as a potentially long-term strategy that intervenes with normal physiological procedures, is not exempt from undesired events. Among them, toxicity or deficiency of certain minerals, vitamins and trace elements is a major consideration [6-8, 13]. Cholestasis is another serious complication that requires close attention, as it further obstructs the natural nutrients intake and leads to extended metabolic imbalance [14]. Finally, contamination of TPN fluids with substances, such as aluminum (Al) has also been reported. Al contamination, along with cholestasis and several other distinct causes, have been reported to drive the development MBD in children treated with TPN [15-17].

MBD IN CHILDREN

Classification and clinical manifestations

MBD in neonates and children refers to the reduction of bone mineral content, with respect to the body size or gestational age, presenting with particular radiological and biochemical findings [9]. Rickets and pediatric osteoporosis are the main clinical entities falling under the MBD umbrella term. Osteoporosis in children usually occurs between 1 and 13 years of age and presents with hip and back pain. Long bone and vertebral compression fractures, along with other deformities, can also occur [18]. Osteoporosis is characterized by low net bone mass and normal mineral-to-collagen ratio, leading to microarchitectural lesions that make the bones susceptible to fractures [19].

On the contrary, rickets is characterized by insufficient mineralization of the epiphyseal plates. The deformed open epiphyseal plates lead to architectural changes affecting the bone sized and shape, finally resulting to instability and, possibly, deformities such as chest bone softening, cranial bossing, bowing and craniotabes [20]. After the closure of the epiphyseal plates, the ineffective bone mineralization, once developed, leads to a similar syndrome of "soft" bones called osteomalacia. Osteomalacia, as well as rickets, is characterized by reduced mineral-to-collagen ratio.

Risk factors and disease-causing mechanisms

Osteoporosis can be secondary due to several illnesses and nutritional deficiencies that disrupt the balance between osteoblastic and osteoclastic activity. Inflammatory diseases, such as Crohn's disease, have been found to contribute to the onset of osteoporosis through a cytokine-mediated mechanism. Glucocorticosteroids and hormonal disturbances also have a detrimental effect on the development of bone tissue. Inadequate nutritional intake of Ca^{+2}, P^{+4}, vitamin D and other elements also leads to osteopenia and finally osteoporosis. A predominant cause of rickets/osteomalacia is vitamin D deficiency, leading to diminished intestinal absorption of Ca^{+2} and P^{+4}, and also to their lower usage in bone mineralization. Any disruption in the metabolic pathway of vitamin D up to its bioactive form (1,25-dihydroxycholecalciferol) can result in rickets. Dietary sources provide approximately 20% of the required vitamin D, and the exclusion of these food types can be a cause. The rest amount is produced by the sunlight-mediated transformation of 7-dihydro-cholesterol to cholecalciferol, which is then gradually hydroxylated into its final form in the liver and the kidneys. Abstinence from sun exposure, as well as severe renal diseases can block this pathway, leading the way for the disease [21]. Finally, rare genetic causes have been reported. CYP27B1 and CYP2R1 mutations were shown to cause vitamin D deficiency, as they hinder the hydroxylation process [22].

Premature neonates experience decreased mineralization as a multifactorial disorder. Although several pathways have been described, the reduced placental transfer of Ca^{+2} and P^{+4} in prematurity is the predominant reason. Since most of the mineral accretion happens in the last trimester of pregnancy, preterm infants fail to achieve this critical accumulation [15]. This leads to both decreased bone mass and/or low mineral deposition. Therefore, rickets and osteoporosis can exist in isolation or co-exist. The extended use of TPN constitutes another risk factor in preterms with chronic diseases or prema-

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turity-associated conditions, by promoting MBD through several mechanisms [1, 17, 23].

Laboratory and imaging findings

Diagnosis partly relies on the estimation of certain biochemical markers: Serum Ca^{+2}, P^{+4}, Alkaline Phosphatase (ALP), urinary Ca^{+2} and blood Parathormone (PTH) levels. The earliest finding is the decreased P^{+4} levels. Low P^{+4} levels occur due to nutritional deficiency or/and due to elevated PTH levels, as a response to abnormally low Ca^{+2} levels. In the case of nutritional deficiency, hypophosphatemia can trigger the vitamin D upregulation at such an extent that Ca^{+2} increases and PTH production is suppressed. Cut-off values for estimating ALP vary across studies from 500 IU/L to 1200 IU/L [24-27]. A sharp increase in ALP levels (above 900 IU/L) displays excellent sensitivity and high specificity in diagnosing MBD, since ALP can be 5-fold higher than the normal range [28]. Liver and GI diseases must also be excluded in the face of an abnormally high level of ALP. When PTH is considered together with ALP (over PTH>180 pg/mL or ALP<4.6 mg/dL at 3 weeks) the sensitivity and specificity reach 100% and 94%, respectively [29, 30]. These markers should be monitored weekly or biweekly to estimate the disease progress and achieving normal values should serve as a therapeutic target [31].

Dual Energy X-Ray Absorptiometry (DEXA) is the gold standard technique to reveal even small changes in Bone Mineral Content (BMC) and Bone Mineral Density (BMD), as markers for MBD. In neonates, this method applies ionizing radiation preferably to the lumbar spine, the forearm or the calcaneus. A BMD greater than 0.068 g/cm^2 in preterm infants of <31 weeks, has been associated with low probability of developing MBD [24]. Although a precise method, standardized for the pediatric population, it exposes neonates and older children to radiation and also holds the risk of imprecise measurements due to movement artifacts [32]. A revolutionary novel method employs ultrasounds to estimate the bone speed of sound, usually over the tibia shaft. This method eliminates the risk of radiation, is applicable bedside and has also been standardized for both term and preterm infants at various ages [33]. A study has found that ALP levels are inversely correlated with the ultrasound signal over the tibia, indicating the promising diagnostic value of this method [15].

TPN-induced MBD display the same diagnostic markers as the ones of other causes. In preterm infants, MBD can be diagnosed as early as 2-4 months from birth, as they tend to develop during a 'catch-up' growth period following the recovery from prematurity illnesses [34, 35]. In 40-100% of newborns receiving prolonged TPN, histologic findings of MBD can be found, although the disease usually remains asymptomatic [36].

TPN-INDUCED MBD

Various conditions in neonates and older children, including prematurity with its satellite anomalies, require the use of TPN, which has been associated with the onset of MBD [37]. TPN-associated MBD was initially described with hypercalciuria, normal vitamin D, increased Ca^{+2} and normal P^{+4} levels [38]. Since then, many studies have shown the characteristics of the MBD following the use of TPN and explored the underlying mechanisms [15-17, 23, 39-41]. Lack of nutrients, such as Ca^{+2} and P^{+4}, in the TPN solution, insufficient or excessive amount of exogenously administered vitamin D, altered administration of certain fatty acids, cholestasis and, predominantly, the risk of aluminum (Al) accumulation with its deleterious actions, have been identified as key factors.

Ca^{+2} and P^{+4}

Over 80% of the fetal required amount of Ca^{+2} is accumulated during the last trimester of pregnancy in order to fill 99% of term neonates' stores. Similarly, around 80% of fetal P^{+4} stores are accumulated in the bones by term gestation. Consequently, preterm neonates are deprived of this abundant supply and have an increased need for exogenous compensation [42]. Studies have shown that low intake of Ca^{+2}, P^{+4}, vitamin D and proteins for the first weeks of life, in extremely low weight preterm neonates, is correlated with MBD [43].

It has been reported that TPN solutions often fail

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to achieve adequate concentrations in Ca^{+2} and P^{+4} [44]. This is usually unavoidable due to the limited quantities of Ca^{2+} and P that can be diluted in the small TPN volumes required for pediatric patients and, especially, for preterm neonates [45]. Large amounts of Ca^{+2} and P^{+4} in relatively small TPN volumes hold the risk of precipitation, especially when the amino acid concentration is low, the environmental temperature is high and the pH of the amino acid solution is high [46]. Of note, the available amino acid solutions for children (TrophAmine and Aminosyn-PF) have a relatively low pH to allow the dilution of larger amounts of Ca^{+2} and P^{+4} [47]. Addition of alkaline agents, such as aminophylline, or lipid emulsions in a TPN mixture further increases the risk of precipitation [48]. The Ca^{+2}/P^{+4} weight ratio is crucial for achieving optimal retention and Ca^{+2}/P^{+4} homeostasis in TPN-assisted infants, and has an optimal range from 1.3:1 to 1.7:1 [2, 49, 50].

Vitamin D

Deficiency of the fat-soluble vitamin D has been associated with rickets or osteomalacia in older ages, as its role is to mediate the intra- and extracellular Ca^{+2} concentrations [51]. It stimulates intestinal Ca^{+2} and P^{+4} absorption, as well as bone turnover and, indirectly, mineralization [52]. Due to the underlying illnesses that deter oral vitamin D intake, but also due to the limited exposure to sunlight of patients under TPN, low levels of vitamin D are often observed [53]. On the other hand, excessive administration of vitamin D, especially in the absence of need for Ca^{2+} enteral absorption, might be unneeded or even deleterious for the bones [2]. A study showed that withdrawing vitamin D from TPN in children resulted in normal serum concentrations of the active form of vitamin D (1,25-dihydroxycholecalciferol), Ca^{+2} and P^{+4}, no changes in Ca^{+2} and P^{+4} urine excretion and no significant clinical effects [54]. Another study demonstrated absence of MBD signs in patients receiving extremely small amounts of vitamin D [55]. Even very low amounts of daily administered vitamin D suffice to achieve normal values of serum vitamin D levels in preterm infants [56].

Aluminum

Another crucial risk factor for the development of MBD, associated with the use of TPN, is the contamination of the administered solution with aluminum (Al). Relatively early, an Al-dependent clinical syndrome presenting with hypercalciuria, hypocalcemia and low to normal vitamin D levels was described [2, 57].

A study by Lidor *et al*. (1991) reported a case of Al poisoning with concomitant rickets/osteomalacia and osteopenia, where Al was detected on the bone surface [58]. Another study by Hamilton *et al*. (2004) supported the same theory about the relationship between long-term TPN and MBD [59]. Interestingly, Fewtrell *et al*. (2009) published a study claiming that TPN-associated Al contamination can have a long-term impact on children's bone health. The study showed that, after a 13-to-15-year follow-up, DEXA revealed signs of BMD of the hip and the lumbar spine [60].

The aforementioned findings led the way for many theories attempting to explain the underlying mechanisms of the Al-induced bone lesions. Al comes particularly from the salts of Ca^{+2} and P^{+4}, present in TPN solutions. It is believed that about 20-40 mcg/kg are administered to neonates each day, depending on the mineral content of TPN [61]. Prematurity itself, or any other condition that impairs renal function, deteriorates the Al accumulation in infants [40]. Premature infants on TPN present with negative Ca^{+2} balance and hypercalciuria, which is believed to be a compensatory mechanism, rather than the origin of the condition. High bone Al loading, as well as low bone turnover have been observed, designating the Al-triggered decreased bone uptake of circulating Ca^{+2}, which, in return, leads to hypercalciuria. Moreover, reduced Al levels in PTN solutions were associated with normal levels of vitamin D, while the same result was found in patients with end-stage renal disease treated with the Al-chelation agent deferoxamine. These outcomes suggest the Al contamination as the culprit for the low vitamin D levels of patients on TPN. Finally, the Al accumulation on the mineralization front of the bones indicates that Al has a direct, suppressing impact on bone mineralization [40].

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Cholestasis

PTN typically predisposes infants and older children to cholestasis, which might occur after two to four weeks. PTN-associated cholestasis is a product of reduced or delayed enteral nutrition and leads to decreased enteral absorption of many nutrients, including the fat-soluble vitamin D [62]. However, evidence shows that, despite the adequate replacement of nutrients and vitamin D with TPN, MBD may still persists, suggesting a yet unknown, vitamin D-independent mechanism for its development [63].

Fatty acids

Long-term employment of TPN has been found to induce deficiencies in specific omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), and particularly in docosahexaenoic (DHA) and arachidonic (ARA) acids. It has been shown that these fatty acids are significant modulators of bone formation, with DHA promoting the differentiation of mesenchymal cells into osteoblasts, while ARA enforces the activity of osteoclasts [64]. Animal studies have revealed a beneficial effect of omega-3 PUFA on bone health during the growth period [65]. It has been speculated that there might be a unique window during the first stages of bone formation, when PUFAs exert their effect on osteoblasts/osteoclasts differentiation and activity. More studies evaluating the effect of PUFAs during gestation and lactation are needed [64].

CLINICAL AND NURSING APPROACH

Management of nutritional deficiencies

The first step toward mitigation of the TPN-induced MBD, is to ensure sufficient amounts of all related nutrients, including amino-acids, fatty acids, minerals and vitamin D [6-8]. Specialized amino-acid solutions, highly concentrated in essential amino-acids, are commercially available for infants and children. These include TrophAmine, Premasol and Aminosyn-PF. They are especially designed to display low pH values, appropriate for diluting higher quantities of minerals. Both soybean oil and a mixture of safflower and soybean oil can be used as IVFE, to provide 10 kcal per gram of solution. IVFE not only play a central role in bone metabolism, but also their lower osmolality contributes to the integrity of peripheral lines [6-8].

Unlike the other minerals and electrolytes, the requirements for Ca^{2+} and P differ between preterm and term infants [6-8]. The minimum amounts of Ca^{+2} and P^{+4} to be administered in preterm infants, are 150 mg/kg/d and 75 mg/kg/d, respectively, with a Ca^{+2} to P^{+4} ratio equal to 1.7:1, reflecting the intrauterine mineral accretion in the last gestational trimester [66]. Since the solubility of these substances is severely influenced by temperature, amino-acid concentrations, pH and other factors, close attention must be paid to the proper preparation and storage of these solutions. Adding high amounts of protein in TPN within the first days, along with the earliest possible initiation of enteral feeding, has become the main practice in neonatal care, as it also increases the cellular uptake of P^{+4} [67].

Vitamin D supplementation products for infants and children on TPN have not been drastically reformulated for decades and may lack in covering the augmented needs of these patients [6-8]. Apart from the evidence showing the toxic effect of vitamin D oversupply, it can battle the corticosteroid-induced detrimental effect on osteoblasts and improve the intestinal Ca^{+2} absorption when the enteral feeding is established [68]. The recommended dose by the American Academy of Pediatrics is 400 IU/d, while the European guidelines suggest 800-1000 IU/d for preterm infants [69, 70].

There is also some evidence of the beneficial effect of physical activity on bone mineralization in infants. Particularly, passive range of motion and joint compression performed for 5–15 min/d for 4–8 weeks, improved the ultrasonographic and biochemical markers of bone turnover in preterm infants [71].

Proper use of TPN

TPN is usually administered through a central venous line (CVL), which delivers the TPN content to the superior vena cava or the right atrium of the heart. A CVL offers the ability for a far higher osmolality compared to that of the peripheral ve-

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nous line (PVL), which is limited to 900 mOsm/kg, with a significant concomitant risk of phlebitis and infiltration [72]. Some basic laboratory diagnostics should be made prior to the initiation of a TPN, but also be constantly monitored during its use. These parameters include Ca^{+2}, P^{+4}, magnesium, ALP, hepatic enzymes, total and conjugated/direct bilirubin, albumin and lipid panel. After the initial phase of TPN induction, the monitoring pace can be adjusted according to the stability signs of the patient. Young patients on prolonged TPN call for continuous monitoring to protect the sensitive vitamin and mineral balance [6-8].

It is generally recommended to replace TPN with enteral feeding as soon as possible, not only to eliminate the risk of certain TPN-placement complications, but also to surpass the inherent nutritional limitations of TPN. Weaning from TPN is introduced with human milk, ideally mother's own milk or a pasteurized donor substitute [73]. However, human milk does contain all the required mineral content and, therefore, must be fortified with Ca^{+2}, P^{+4}, vitamin D and other nutrients [74].

Further clinical and nursing considerations

The multilevel risk of MBD in infants (predominantly premature) and children under TPN, requires a constant alert by clinicians and nurses. The weight of the child must be measured daily, under standard conditions, and evaluated against standardized weight velocity charts. In this way, growth, body size and other somatometric parameters are estimated, and nutrient needs are assessed. Clinicians should also be cautious for potential adverse effects of TPN, including infection, hyperglycemia, hypertriglyceridemia, disturbance of acid-base balance, electrolyte abnormalities and phlebitis [6-8]. Osteopenia and vitamin D/mineral deficiency or toxicity are frequent long-term adverse effects and lead to the onset of MBD. Therefore, the corresponding laboratory and radiological markers must be checked and assessed frequently. As for Al contamination, the Food and Drug Administration has set a maximum limit for the tolerable amount of Al to 5 mcg/kg/d [75].

Site infections can be induced by the improper care of the catheter or by its unorthodox use (medication administration, blood draws). Regular skin disinfection and dressing changes are a common practice to prevent these events. Chlorhexidine gluconate is the most widespread disinfectant used in patients older than 7 days. Transparent dressings are replaced every week or when wet or damaged. Moreover, laboratory specimens must be frequently obtained and appropriate flushing performed [6-8].

In 2007, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) published its standards for nutrition support nurses [76]. According to this manual, nurses are recommended to have an active role in the assessment of TPN-assisted patients who are at risk or already diagnosed with TPN-related complications. This includes the identification of signs or markers of imbalanced nutrition, fluid volume deficit/excess, delayed growth and low body weight. This procedure has to be data-driven, relying upon physical examination, interviewing (if possible) and diagnostic procedures. Nurses should also be involved in the development of an individualized nutrition care plan and also monitor its implementation, periodically reassess the route of administration and suggest a plan for transition to enteral feeding. They can also make suggestions on the equipment and supplies needed, as well as on the type of feeding device, the infusion rate and other technical parameters. Moreover, nurses should be alert for signs of complications, such as catheterization site infections, and contribute efficiently to their resolution. The A.S.P.E.N. guidelines emphasize the importance of high quality qualifications and encourage the continuous evaluation of practice skills. They also point out the importance of productive collaboration with colleagues, as well as with the patient, other clinicians and caregivers. Quality and cost-efficiency (efficacy, safety, availability, cost, outcomes) of the nutrition strategies are also considered as important, as well as the focus on research and ethics around this clinical field.

The shift from TPN to breastfeeding can also be aided by specialized nurses. A recent study demonstrates the high awareness of breastfeeding among nurses and their existing efforts in promoting it

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[77]. Psychological support to the family is also of paramount importance and can be, at least partly, provided by the caregiving nurses. High quality education and training, possibly encompassing modern simulation technologies, can accelerate the learning curve and preserve high professional standards [78].

Conclusively, TPN in infants and children is a multidisciplinary field, with the contribution of nurses being of crucial importance. MBD still continue to manifest frequently in these patients, and the high level of alert is necessary for detecting and mitigating them, while ongoing research on the underlying mechanisms, risk factors and successful management strategies is promising.

Conflict of interest

The authors declare no conflicts of interest.

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