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English translation

标准·方案·指南

早产儿代谢性骨病临床管理专家共识（2021年）

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［摘要］早产儿代谢性骨病（metabolic bone disease of prematurity，MBDP）是由于机体钙磷代谢紊乱导致骨矿物质含量减少的全身性骨骼疾病。我国目前对MBDP尚缺乏深入研究和系统认识，在临床管理方面存在很多不规范之处。现基于国内外相关研究，采用证据推荐分级的评估、制定与评价方法（Grading of Recommendations Assessment，Development and Evaluation），制定MBDP临床管理专家共识，从MBDP的高危因素、筛查/诊断、预防、治疗及出院后随访等5个方面提出推荐意见，旨在为相关从业人员提供MBDP临床管理的建议，以减少MBDP的发生及改善其近远期预后。［中国当代儿科杂志，2021，23（8）：761-772］

［关键词］代谢性骨病；专家共识；骨质减少；骨矿化和生长；早产儿

Expert consensus on clinical management of metabolic bone disease of prematurity (2021)

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Abstract: Metabolic bone disease of prematurity (MBDP) is a systemic bone disease with a reduction in bone mineral content due to disorder of calcium and phosphorus metabolism. There is still a lack of in-depth research and systematic understanding of MBDP in China, and there are many irregularities in clinical management of this disease. Based on relevant studies in China and overseas, Grading of Recommendations Assessment, Development and Evaluation was used to develop the expert consensus on the clinical management of MBDP, which provides recommendations from the following five aspects: high-risk factors, screening/diagnosis, prevention, treatment, and post-discharge follow-up of MBDP, so as to provide relevant practitioners with recommendations on the clinical management of MBDP to reduce the incidence rate of MBDP and improve its short- and long-term prognosis.

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Key words: Metabolic bone disease; Expert consensus; Osteopenia; Bone mineralization and growth; Preterm infant

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随着新生儿重症监护技术水平的不断提高，越来越多的极低出生体重（very low birth weight，VLBW）和超低出生体重（extremely low birth weight，ELBW）早产儿得以救治存活，影响其近、远期临床结局的相关合并症如早产儿代谢性骨病（metabolic bone disease of prematurity，MBDP）逐渐引起业界关注。MBDP是指由于早产儿体内钙、磷及有机蛋白质基质含量不足或骨代谢紊乱所致，以骨矿物质含量减少、类骨质不完全矿化为特征的一类骨骼疾病。其本质是早产儿骨矿物质含量不能满足骨骼正常生长发育所需，可伴随血生化和影像学改变，如低磷血症、高碱性磷酸酶血症和骨骼矿化不足的影像学等表现[1]。目前国内外缺乏MBDP筛查、诊断及防治的统一标准，故MBDP的确切发病率尚不清楚[2]。如MBDP未及时诊治，可影响早产儿骨骼健康及生存质量，近期常伴随宫外生长发育迟缓、呼吸机依赖甚至骨折等；远期则可能导致身材矮小、骨量峰值降低、易罹患骨质疏松症等不良后果[3-4]。

2014 年美国对 246 家新生儿重症监护室（neonatal intensive care unit，NICU）的 338 名新生儿科医师开展了一项针对MBDP的诊治问卷调查，结果显示临床实践缺乏同质性，大多医师凭个人临床经验进行相关决策[5]。中国医师协会儿童健康专业委员会新生儿营养与健康管理学组的一项全国早产儿MBDP多中心回顾性调查[6]及另一项国内单中心研究[7]显示，在预防、筛查及诊疗方面普遍存在不规范现象，亟需制订我国MBDP临床管理的专家共识，通过定期监测筛查高危儿，及时采取干预措施，改善MBDP的近、远期预后[8]。

本专家共识由中国医师协会新生儿科医师分会营养专业委员会、中国医师协会儿童健康专业委员会新生儿营养与健康管理学组、中国当代儿科杂志编辑委员会共同发起，已通过厦门大学附属妇女儿童医院/厦门市妇幼保健院人体研究伦理委员会审查批准（批准号：KY-2020-084），并在中国临床试验注册中心注册（http://www.chictr.org.cn），注册号ChiCTR2100042195。由新生儿科、儿童保健科、临床营养科、循证医学、流行病学和医学杂志编辑部等领域的专家组成多学科共识工作组，经过反复多次讨论修改，并经多学科共识工作组审议，最终达成此共识。目标人群是早产儿。计划应用人群为围生医学工作者、新生儿科医师、儿童保健科医师、骨科医师、营养师、社区医疗保健工作者和相关护理人员。本共识旨在为相关从业人员提供MBDP临床管理建议。

本共识通过“bone、neonate、infant”3个关键词检索英文文献，检索数据库包括MEDLINE、PubMed、Web of Science、UpToDate、BMJ Clinical Evidence、National Guideline Clearinghouse、Joanna Briggs Institute Library、Cochrane Library等。通过“钙、磷、代谢性骨病、骨质减少、骨矿化和生长”等关键词检索中文文献，检索数据库包括中国生物医学文献服务系统、中国知网、万方数据库等。所有文献检索截止于2020年12月1日。文献筛选流程见图1。文献证据水平和推荐等级采用证据推荐分级的评估、制定与评价（Grading of Recommendations Assessment，Development and Evaluation，GRADE）的方法，将证据质量分为高（A）、中（B）、低（C）和极低（D）4个等级，推荐强度分为强推荐（1）、弱推荐（2）和高质量临床实践声明（good practice statement，GPS）3个等级（表1）[9-11]。

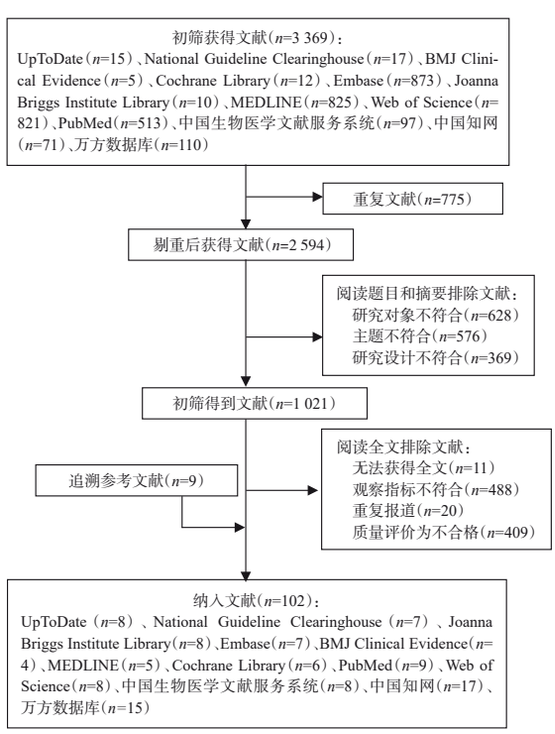

图1　文献筛选流程图

表 1　GRADE 证据质量与推荐强度分级

类别	具体描述
证据质量分级	
高 (A)	非常有把握观察值接近真实值
中 (B)	对观察值有中等把握：观察值有可能接近真实值，但也有可能差别很大
低 (C)	对观察值的把握有限：观察值可能与真实值有很大差别
极低 (D)	对观察值几乎没有把握：观察值与真实值可能有极大差别
推荐强度分级	
强 (1)	明确显示干预措施利大于弊或弊大于利
弱 (2)	利弊不确定或无论质量高低的证据均显示利弊相当
GPS	基于非直接证据或专家意见/经验形成的推荐

注：［GPS］高质量临床实践声明。

1　高危因素

推荐意见一：孕妇维生素 D 水平过低、使用硫酸镁>5 d、胎盘功能不全、绒毛膜羊膜炎、先兆子痫和胎儿宫内生长受限等是 MBDP 的产前高危因素（C 级证据，弱推荐）。

推荐意见二：男婴、胎龄<32 周和/或出生体重<1 500 g 的极/超低出生体重早产儿、钙/磷/维生素 D 补充不足、单纯母乳喂养是 MBDP 的生后高危因素（C 级证据，弱推荐）。

推荐意见三：早产儿合并支气管肺发育不良、坏死性小肠结肠炎、胆汁淤积性肝病等，使用糖皮质激素、甲基黄嘌呤类药物、袢利尿剂、苯巴比妥、苯妥英钠等，延迟建立肠内营养，肠外营养治疗时间>4 周和制动>4 周，这些是 MBDP 的病理性高危因素（B 级证据，弱推荐）。

胎儿宫内 80% 矿物质储备发生在妊娠 24~40 周，高峰期在 34 周；至足月时，矿物质储备量钙约 20 g（沉积率为每日 100~120 mg/kg）、磷约 10 g（沉积率为每日 50~65 mg/kg）[12]。胎儿维生素 D 的储备依赖于母体的 25 羟基维生素 D［25(OH)D］水平，足月时维生素 D 仅达到母体水平的 50%~70%[13]。美国肠内肠外营养协会临床指南[14]指出，孕妇维生素 D 补充不足（<600 IU/d）、妊娠 22 周后每天补充钙剂<2 g 及孕期长期使用硫酸镁（>5~7 d）是 MBDP 的高危因素；胎盘炎症如绒毛膜羊膜炎、胎盘功能不全如宫内生长受限和先兆子痫等使胎盘功能受损，胎儿骨量减少，导致生后 MBDP 发生风险增加。

宫内较高的雌激素、降钙素及较低的甲状旁腺激素（parathyroid hormone，PTH）环境，可促进胎儿高血钙状态，有利于骨构造和皮质下骨的形成，使骨矿物质密度持续高效增加。由于早产儿提前出生，矿物质转运突然中断，激素水平骤然变化，生后早期肠内外营养中钙、磷和维生素 D 的补充不足或钙磷比例不当，以及各种并发症影响钙、磷和维生素 D 的代谢等，胎龄<32 周早产儿的骨矿物质含量比足月儿低 25%~70%，且胎龄越小，出生体重越低，MBDP 发病率及严重程度越高[6, 15]。国内外相关研究显示，ELBW 早产儿的 MBDP 患病率为 50% 左右；VLBW 早产儿的 MBDP 患病率为 20%~30%，其中 17%~34% 可发生自发性肋骨或长骨骨折[6, 15-17]。此外，男婴肾脏发育相对不成熟和雌激素水平相对低下，肾小管磷排泄增加和重吸收减少，更易罹患 MBDP[17-18]。

母乳中维生素 D 含量仅 25~50 IU/L，未经强化的足量母乳喂养（每日 180~200 mL/kg）只能提供同胎龄胎儿钙磷宫内获得量的 1/3，母乳中钙磷含量不能满足早产儿骨矿化需求。研究显示，有强化营养指征的早产儿给予持续纯母乳喂养者 MBDP 发生率为 40%，而早产儿配方奶喂养者 MBDP 发生率仅为 16%[5, 19]。国内多中心调查结果显示，胎龄<32 周早产儿纯母乳、强化母乳、早产儿配方奶、混合喂养组 MBDP 发生率分别为 27.8%、19.4%、13.4%、21.8%[6]。使用足月儿配方奶或其他未强化钙、磷和维生素 D 的特殊配方奶喂养等均会增加 MBDP 的发生率[8, 20]。

早产儿罹患胆汁淤积性肝病、坏死性小肠结肠炎尤其是术后、支气管肺发育不良等均会造成钙、磷和维生素 D 的吸收不良和消耗增加；在实施肠外营养过程中，由于受钙磷溶解度低、温度不稳定、配制方法的不同及液体限制等多种因素的影响，钙磷的生物利用度难以维持充足的骨矿化需要量；玻璃瓶包装的葡萄糖酸钙存在铝污染问

题[21]。研究显示，接受肠外营养治疗>4周的早产儿骨骼内铝含量是对照组的10倍，铝过多沉积于骨骺表面，影响成骨细胞活性，可降低青春期脊柱骨矿物质含量和骨小梁面积[14]。一些药物如糖皮质激素、甲基黄嘌呤类药物和袢利尿剂等可增加破骨细胞活性，抑制成骨细胞增殖，减少胃肠道对钙的吸收，促进肾小管对钙的排泄；苯巴比妥、苯妥英钠可增加25(OH)D的分解代谢，从而增加MBDP的发生风险[20]。

研究显示，NICU中的早产儿制动>4周，且由于早产儿失去了在宫内对抗子宫壁的主动运动刺激，从而抑制成骨细胞增殖，增加破骨细胞活性，导致骨质吸收和尿钙排泄增加，骨矿物质含量和密度分别减少11%（P=0.06）和14%（P=0.02），使MBDP发生风险增加[22]。

2 诊断和筛查

推荐意见一：血碱性磷酸酶（alkaline phosphatase，ALP）>900 IU/L，伴有血磷<1.8 mmol/L高度提示MBDP。出生3周后血PTH>180 pg/mL，伴有血磷<1.5 mmol/L，提示严重MBDP（C级证据，弱推荐）。

推荐意见二：不推荐将25(OH)D作为MBDP的诊断依据（GPS）。

推荐意见三：不推荐使用双能X线吸收法（dual energy X-ray absorptiometry，DEXA）作为MBDP常规筛查的检查（A级证据，强推荐）。

推荐意见四：具有MBDP高危因素的早产儿建议进行MBDP筛查（GPS）。

MBDP的诊断需要综合病史、临床表现、生化指标和影像学检查。目前MBDP的确诊多基于典型的临床表现和X线片发现，但此时骨矿物质密度已显著下降。MBDP早期症状隐匿，无统一明确的诊断方法，因此早期发现和诊断较为困难。为减少MBDP所带来的不良预后，对具有高危因素的早产儿进行筛查并早期干预意义重大。新生儿骨质状况评价方法包括生化指标和影像学检查。

2.1 血生化指标

临床常用的血生化指标为血清钙、磷、ALP、PTH和25(OH)D。

体内血钙水平受降钙素和PTH共同调节。血钙降低时，机体在PTH调节下通过动员骨钙维持血钙水平，当机体缺钙时血钙可正常或偏高，MBDP晚期骨钙储备耗竭时才出现血钙降低，所以血钙对MBDP早期诊断无价值。血磷浓度可较好反映骨磷储备状况，血磷持续降低提示磷摄入不足和骨质疏松的风险增加[23]，血磷<1.8 mmol/L提示低骨密度的特异度为96%，但灵敏度仅为50%，不适用于早期诊断[24]。

ALP是由多种组织分泌的糖蛋白酶，至少有4种同工酶。新生儿体内90%的ALP来源于骨骼，作为一种成骨细胞成熟的活性标志物，能较好反映骨骼代谢状况。ALP在生后2~3周呈生理性轻度升高；当体内矿物质缺乏伴ALP进一步升高才考虑MBDP的诊断。需要指出的是胆汁淤积症、感染和铜缺乏等因素也会导致ALP增高，而锌缺乏或应用糖皮质激素可导致ALP反应性下降，从而干扰临床判断。关于ALP是否适用于MBDP的诊断及阈值范围，各研究结果不同。Hung等[25]研究发现，在胎龄<34周早产儿中，采用前臂X线诊断MBDP，血ALP>700 IU/L的诊断敏感度为73%，特异度为74%。Viswanathan等[26]在一项纳入230例胎龄<30周的ELBW早产儿的回顾性分析中发现，ALP>500 IU/L与MBDP相关。Figueras-Aloy等[27]对336例VLBW早产儿进行了DEXA检查，以及血ALP、钙和磷指标的检测，也发现ALP>500 IU/L与低骨矿物质密度相关。Backström等[24]发现，根据DEXA检查结果，ALP>900 IU/L伴有血磷<1.8 mmol/L诊断MBDP的灵敏度和特异度分别达100%和71%。ALP水平的增高与MBDP的发生相关，可早于临床症状的出现[28]。

PTH的分泌主要受血浆钙离子浓度调节，通过动员骨质溶解、促进肾小管对钙的重吸收和磷酸盐的排泄，维持血钙水平。新生儿尤其是早产儿尚无统一的PTH正常值范围。Matejek等[29]连续检测了134例VLBW早产儿的血PTH后得出其参考范围约15.1~87.7 pg/mL，接近成人参考值。Moreira等[30]通过回顾分析发现出生体重<1 250 g的早产儿出生后3周时PTH>180 pg/mL诊断重度MBDP的灵敏度为71%，特异度为88%，联合血磷<1.5 mmol/L的诊断灵敏度和特异度分别上升至100%和94%。

25(OH)D是维生素D在血液中的主要运输形式，正常的维生素D水平是确保钙和磷吸收的前提，美国内分泌协会建议婴儿血清25(OH)D水平保持在50 nmol/L（20 ng/mL）以上[31]。我国儿童（0~14岁）血清25(OH)D水平参考值范围为37.5~

250.0 nmol/L（15~100 ng/mL）[32]。MBDP 的主要病因是钙磷缺乏，血清 25(OH)D 可正常、降低甚至升高，因此 25(OH)D 不作为 MBDP 的诊断指标。

2.2 尿生化指标

尿生化指标包括尿钙、尿磷、尿钙/肌酐、尿磷/肌酐和肾小管磷重吸收率（tubular reabsorption of phosphorus，TRP）。尿钙、尿磷排泄与新生儿成熟程度、喂养方式和药物（利尿剂、激素）使用等有关，变异很大。由于 ELBW 早产儿肾磷阈值很低，即使体内血磷偏低，仍可从尿中排泄磷。TRP 的计算公式为：TRP（%）=［1-（尿磷/尿肌酐）×（血肌酐/血磷）］×100。通过检测经肾脏滤过后重吸收磷来反映机体磷储备状况，正常值约为 85%~95%。TRP>95% 伴血磷下降提示机体磷缺乏；TRP 正常或降低伴 PTH 增高可能提示机体钙缺乏 [2]。关于尿生化指标对 MBDP 诊断价值的研究结果还存在争议，目前不推荐单独将尿生化指标用于诊断 MBDP [33]。

2.3 影像学

影像学检查是基于骨矿物质密度的测定，主要包括 X 线检查法、DEXA、定量 CT 和定量超声法（quantitative ultrasound，QUS）。

MBDP 的 X 线片可表现为长骨末端骨质稀疏、干骺端杯口样或毛刺样改变，肋骨末端膨大，骨膜下新骨形成或骨折。X 线仅适合诊断有明显骨质疏松或骨折的严重 MBDP，对骨量减少<20%~40% 的骨质疏松并不敏感 [23]，因此尽管 X 线片用于诊断 MBDP 的特异度很高，但不适用于早期诊断。DEXA 是诊断骨质疏松的金指标，反映骨骼二维面积密度，但不能反映骨骼立体密度。将 DEXA 常规用于 MBDP 的筛查存在技术困难，包括操作可行性、具有放射性、初始扫描的时机选择、重复频率、不同胎龄新生儿的正常值、干预切点及干预方式等，均有待进一步研究 [3, 34]。定量 CT 的优点是可测量骨立体密度，但具有与 DEXA 同样的局限性。

QUS 是上世纪八十年代初研发的一种新型诊断技术，不仅反映骨矿物质密度，也可反映骨微结构及骨弹性和强度等特性。该方法无辐射、无创、可床旁简便操作，在 MBDP 临床诊断中具有很大优势。体外研究证实前臂 QUS 参数与骨强度显著相关，儿童研究中显示这些参数与 DEXA 评估的骨矿物情况一致 [35]。常用 QUS 参数是超声传播速度（speed of sound，SOS）。2018 年关于早产儿应用 QUS 诊断的系统综述指出，SOS 与胎龄、出生体重呈正相关；SOS 随日龄增加而呈下降趋势，下降幅度与胎龄呈负相关；SOS 与血磷、血钙和维生素 D 水平呈正相关，与 ALP 呈负相关。SOS 测量能够反映新生儿的骨骼状态，与骨矿物质密度有高度相关性 [36]。目前早产儿 SOS 缺乏统一的标准参考范围，因此 QUS 在筛查和诊断 MBDP 的阈值尚未确定，影响因素较多。但 QUS 在早产儿中的应用极具优势，有良好的临床应用前景。

目前缺乏统一标准的早产儿 MBDP 筛查流程。Rayannavar 等 [2] 建议所有早产儿从生后 4~6 周开始每 1~2 周检测血钙、磷和 ALP；对于 ELBW 和/或 VLBW 早产儿等 MBDP 高危人群，建议同时行 X 线片检查。如果 ALP>800 IU/L，或 ALP>500 IU/L 且呈上升趋势，并伴低磷血症，需进行 PTH 和 TRP 检测，根据高危因素选择性检测血 25(OH)D 水平。Chacham 等 [4] 建议对具有高危因素的新生儿生后每 4 周检测血钙、磷和 ALP，直至 6 月龄；筛查异常者进一步行血 PTH、25(OH)D 和 QUS 检测。本共识建议对具有高危因素的早产儿进行 MBDP 筛查（图 2）。

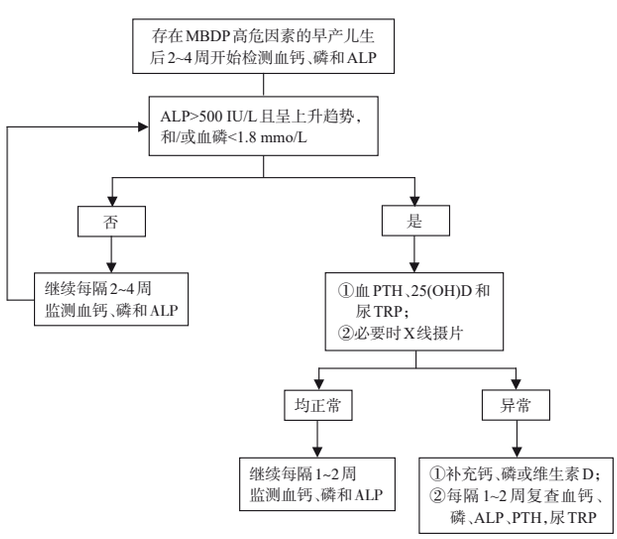

图 2 MBDP 筛查流程图 ［MBDP］早产儿代谢性骨病；［ALP］碱性磷酸酶；［PTH］甲状旁腺激素；［25(OH)D］25 羟基维生素 D；［TRP］肾小管磷重吸收率。

3 预防

推荐意见一：MBDP 高危儿生后早期部分肠外营养（parenteral nutrition，PN）期间，每日元素钙 24~40 mg/kg，元素磷 18~30 mg/kg，钙磷比 1~1.3：

1（质量比）；当PN达全量后，元素钙目标量65~100 mg/kg，元素磷目标量50~80 mg/kg，钙磷比可至1.7∶1（C级证据，强推荐）。

推荐意见二：MBDP高危儿达全肠内喂养后，每日钙摄入量100~160 mg/kg，磷摄入量60~90 mg/kg，钙磷比1.6∶1~1.8∶1（B级证据，强推荐）；通过强化母乳或早产儿配方奶补充钙磷摄入量（C级证据，强推荐）。

推荐意见三：MBDP高危儿出院后应持续强化营养配方奶喂养到矫正足月或直至定期临床监测无合并MBDP的证据（C级证据，强推荐）。

推荐意见四：早产儿每日维生素D摄入量400~1 000 IU，生后1~2周开始通过添加母乳强化剂、早产儿配方奶或维生素D制剂补充，需定期监测血清25(OH)D的浓度以维持其水平>50 nmol/L（C级证据，强推荐）。

推荐意见五：MBDP高危儿达到全肠内喂养后可进行日常被动操训练以预防MBDP（B级证据，强推荐）。

早产儿骨骼健康管理的重点在于提供充足的钙和磷摄入，促进骨骼正常生长。研究显示，早产儿生后钙磷的吸收率与日龄、钙、磷、乳糖和脂肪摄入量呈正相关，同时受维生素D水平影响。VLBW或ELBW早产儿生后应尽快通过PN补充钙和磷，推荐剂量见表2[37-39]。2项随机对照研究均显示早期PN中每日补充钙、磷高剂量组（元素钙75 mg/kg，元素磷44.1 mg/kg）与低剂量组（元素钙45 mg/kg，元素磷26.5 mg/kg）相比，能有效预防早产儿MBDP的发生[40-41]。美国肠外肠内营养协会和2005年欧洲儿科肠外营养指南均推荐早产儿PN液中最佳钙磷比为1.7∶1（质量比）[14, 38]。2018年欧洲儿科肠外营养指南强调了早产儿生后1周内PN液中钙磷比1~1.3∶1（质量比）为宜，以避免高钙血症和低磷血症的发生[21]。国内PN中钙磷制剂常选10%葡萄糖酸钙和10%甘油磷酸钠。基于妊娠晚期胎儿体内钙磷的蓄积速率和钙磷肠道吸收率，早产儿达到全肠内喂养时每日钙推荐量为100~160 mg/kg，每日磷推荐量为60~90 mg/kg，可以满足体重增长所需要的矿物质，并减少MBDP发生率[42-43]。部分VLBW/ELBW早产儿对钙磷的需求可能更高，有关早产儿肠内营养相关指南中VLBW早产儿达到全肠内喂养时钙磷的推荐摄入量见表3[12, 43-47]。钙磷比值也会影响骨矿化程度，美国学者的研究推荐肠内喂养时钙磷比为1.6∶1~1.8∶1（质量比），磷的体内保留率更高[43]。

表2　VLBW早产儿肠外营养时钙和磷的推荐剂量[37-39]

项目	TPN初始	TPN液体量达每日140~150 mL/kg
钙 (每日 mg/kg)	24~40	65~100
磷 (每日 mg/kg)	18~30	50~80
钙磷比值 (质量比)	(1~1.3)∶1	1.7∶1

注：［VLBW］极低出生体重；［TPN］全肠外营养。

表3　相关指南中VLBW早产儿达全肠内喂养时钙、磷、维生素D的推荐剂量[12, 43-47]

项目	Klein 2002[44]	Tsang 2005[45]	Rigo 2007[12]	Agostoni 2010[46]	Abrams 2013[43]	Koletzko 2014[47]
钙 (每日 mg/kg)	150~220	120~200	100~160	120~140	150~220	120~200
磷 (每日 mg/kg)	100~130	70~120	60~90	60~90	75~140	60~140
维生素D (IU/d)	90~225	200~1 000	800~1 000	800~1 000	200~400	400~1 000

注：［VLBW］极低出生体重；钙元素mg换算成mmol时需除以40；磷元素mg换算成mmol时需除以31。

母乳强化剂中的钙磷可满足早产儿的骨矿化需求[48]。MBDP高危儿的母乳喂养量达每日50~80 mL/kg时，应开始添加母乳强化剂[49]。如无法获取母乳，应使用早产儿强化营养配方奶，可有效促进骨的生长及矿化过程，预防MBDP的发生，见表4[43, 47, 50]。

表4　母乳及不同营养配方奶中钙、磷的含量（肠内喂养量达每日160 mL/kg）[43, 47, 50]

项目	母乳	普通配方	早产儿配方	早产儿出院后配方	标准强化母乳
钙 (每日 mg/kg)	37	50	210~234	125~144	192~197
磷 (每日 mg/kg)	21	28	117~129	74~80	103~110
维生素D (IU/d)	2.4	400	194~384	125~127	189~253

研究显示，出院后继续使用强化营养策略至足月对早产儿生长和骨健康有利[51]。但针对小胎龄的早产儿使用强化营养的持续时间并无充分依据。目前建议MBDP高危儿在住院期间和出院后至少持续强化营养至矫正足月，一般到矫正3~4月龄，直至定期监测婴儿生长情况良好、临床监测无合并MBDP的证据。

一项小样本前瞻性随机对照研究显示，50%体重<1 250 g的MBDP早产儿在生后6周时，血清25(OH)D水平显著低于非MBDP组婴儿[52]。国内外指南均推荐早产儿在生后1~2周且肠内喂养可耐受的情况下即开始补充维生素D，推荐摄入量400~1 000 IU/d，需要定期监测血清维生素D水平，以保证血清25(OH)D浓度达50 nmol/L以上[43, 53]。早产儿维生素D的每日需求量可通过强化母乳、早产儿配方奶及维生素D制剂来补充。美国儿科学会建议，所有母乳喂养、混合喂养和使用强化维生素D配方奶每日喂养量不足800~1 000 mL/d时，应补充维生素D至少400 IU/d预防MBDP的发生[43, 54]。

骨关节处的机械牵拉刺激可促进骨生长和骨矿化过程。Moyer-Mileur等[55]开发了以四肢关节为中心被动伸展和屈曲运动的一种被动操训练项目，当早产儿达到每日肠内营养能量≥110 kcal/kg时开始进行，每次进行腕、肘、肩、膝、踝和髋关节被动伸展和屈曲5次，整个过程持续约5~10 min，每天1次，每周锻炼5 d。2014年一项系统综述纳入单中心研究11项，共纳入胎龄26~34周的早产儿324例，通过在住院期间进行关节被动操运动持续3~8周，可促进早产儿骨矿物质含量、骨矿物质密度和骨面积的增长[56]。

4 治疗

推荐意见一：在强化营养配方奶喂养基础上，需要额外补充钙、磷及维生素D制剂（C级证据，强推荐）。

推荐意见二：元素磷起始剂量为每日10~20 mg/kg，最大剂量为每日40~50 mg/kg；元素钙起始剂量为每日20 mg/kg，最大剂量为每日70~80 mg/kg；维生素D摄入量为每日400~1 000 IU（C级证据，强推荐）。

推荐意见三：当血磷恢复正常，血清ALP<500 IU/L且有降低趋势时，可考虑停止钙磷治疗（C级证据，强推荐）。

MBDP患儿需采取综合性营养管理措施。治疗关键是在强化营养配方奶喂养的基础上补充钙、磷及维生素D制剂，以保证钙、磷、维生素D的每日摄入量达到目标量，尽快纠正低磷血症、继发性甲状旁腺功能亢进、维生素D缺乏等异常代谢状态。

MBDP患儿的血生化改变最早以低磷血症为特征性改变。当低磷血症持续存在时，骨质吸收增加，经肾脏的钙排泄持续增加，进而出现钙耗竭状态[42]。单纯补充磷制剂，可加重体内钙磷失衡，导致继发性甲状旁腺功能亢进，加重骨骼病变。因此强调，对于MBDP患儿，应在给予强化营养配方奶喂养基础上，额外补充钙磷制剂[21, 43]。元素磷起始剂量为每日10~20 mg/kg，根据耐受情况增至最大剂量（每日40~50 mg/kg），可选择磷酸钠或磷酸钾的静脉剂型或口服磷酸盐复合制剂；元素钙起始剂量为每日20 mg/kg，根据耐受情况增至最大剂量（每日70~80 mg/kg）；可选用无机钙盐制剂或液体有机钙等。

MBDP患儿需同时补充维生素D，剂量为每日400~1 000 IU，以促进肠道对钙磷的吸收。当临床监测存在维生素D缺乏的证据且合并肝肾等慢性疾病时，可考虑给予维生素D活性形式即1,25-$(OH)_2D_3$，治疗期间需定期监测血磷、血钙、25(OH)D、PTH及尿钙和尿磷，及时调整治疗方案，避免出现钙磷负荷过多等不良反应[21, 43]。经过充足的钙、磷、维生素D治疗后，如低磷血症无改善，且ALP水平继续升高，还需鉴别是否存在其他原因所致的骨代谢疾病。

MBDP患儿通过增加肠内或肠外矿物质补充，数周后可见影像学改善。治疗达6~8周时，可通过影像学检查评估疗效。一旦生化指标改善且影像学显示骨折愈合或骨量增加征象，可在2~4周内逐渐减少钙和磷补充量，当血磷恢复正常，血清ALP<500 IU/L且有降低趋势时，可考虑停止治疗[43]。

5 出院后随访

推荐意见一：应根据MBDP高危因素的风险程度及MBDP严重程度制订随访监测计划，监测时间/频率为：出院时；出院后至纠正1月龄内每2周1次；纠正1~6月龄内每月1次；纠正7~12月龄内每2个月1次；纠正13~24月龄内每3个月1次；纠正24月龄后每半年1次（GPS）。

推荐意见二：定期（可选择在出院时、纠正1月龄、3月龄及6月龄）监测骨代谢生化指标并评估治疗效果，必要时可结合QUS和DEXA等进行骨密度测定（GPS）。

推荐意见三：MBDP出院后定期监测体重、身长、头围等体格生长指标并进行专业的营养评估和指导（GPS）。

通过早期筛查和诊断MBDP并及时补充足够的钙、磷和维生素D，多数MBDP病例在2岁时恢复或自行消退[4]，预后良好。由于ELBW或VLBW早产儿的骨量减少大多出现于纠正胎龄40周左右，易被忽视，可导致以下并发症。

（1）骨折[4]：发生率为17%~34%，多见于生后第6~12周，通常发生在长骨或肋骨。（2）撤机困难[4]：因为肋骨软化和/或自发性肋骨骨折造成胸廓不稳定及骨折后疼痛引起呼吸窘迫，可导致撤机困难；还可能增加吸氧及住院时间，增加呼吸暂停、感染及支气管肺发育不良等风险，甚至增加病死率等[56]。（3）佝偻病或骨骼畸形[21, 56]：可出现佝偻病临床表现及一种或多种继发性骨骼畸形。（4）近视[57]：伴或不伴视网膜病，其机制可能是骨矿物质含量减少引起颅骨长头畸形、短额轴畸形和眼球椭圆畸形而导致近视。（5）生长发育落后[56]：虽然ELBW或VLBW早产儿在出院后出现追赶生长，但MBDP可导致早产儿生长速率受阻，部分MBDP患儿在纠正月龄18~24个月或更晚可出现神经运动发育异常或落后。导致身材矮小的风险效应可持续至12岁，甚至到青春期部分早产儿的身高仍未赶上足月儿。（6）骨质疏松：母乳喂养的早产儿直到2岁的骨矿化尚未达标，而早产儿配方奶喂养也需要到6岁左右才能达到与相应年龄足月儿的骨骼矿化度[58]。Tinnion等[59]发现早产儿的腰椎、脊柱、前臂和髋关节等部位骨矿物质含量和密度较足月儿低，甚至影响成年后的骨密度及老年时的骨骼稳态，更易罹患骨质疏松。

MBDP预后受多种因素影响，如胎龄、出生体重、并发症、药物和营养等，为减少MBDP并发症，改善其近远期预后和线性生长，对存在MBDP高危因素的早产儿强调定期随访与监测，管理目标是保持正常的血钙和血磷，并避免过度的尿钙排泄；以保持理想的身长、体重和头围等指标增长。

（1）定期监测骨代谢生化指标，如钙、磷、ALP、TRP、PTH等，若2次ALP>800 IU/L，应进一步选择QUS、DEXA或定量CT等进行骨密度测定[4, 57-58]。

（2）营养评估与监测：MBDP可出现生长缓慢，特别是身高增长落后，并且这种阻碍生长的效应可持续至8~12岁[4, 56, 58]。但目前并没有针对MBDP个性化的营养评估方法，根据早产儿出院时营养风险程度分类[60]，大部分MBDP患儿与早产儿支气管肺发育不良一样，均属于高危早产儿，故对MBDP患儿在出院后的营养评估内容和频率可参照早产儿支气管肺发育不良营养管理专家共识及《早产儿保健工作规范》[61-62]，定期进行体格生长评估、生化评估、临床表现及膳食分析。体格指标评估标准可选择Fenton曲线（纠正胎龄40~50周前）、2016 WHO儿童生长标准（http://www.who.int/childgrowth/standards/en/）或2018中国九市标准（纠正胎龄40周后）[63]。

（3）随访与监测时间/频率：出院时；出院后至纠正1月龄内每2周1次；纠正1~6月龄内每月1次；纠正7~12月龄内每2个月1次；纠正13~24月龄内每3个月1次；纠正24月龄后每半年1次[21]。营养评估可持续至成年。随访与监测流程见图3。

（4）出院后干预措施：诊断为MBDP的早产儿在出院后随访过程中，一旦评估与监测发现异常，应及时补充维生素D、钙和磷；加强户外活动，结合被动运动和抚触；并给予个体化的营养/喂养指导（参考早产、低出生体重儿出院后喂养建议[60]）。

6 结语

随着临床医师对MBDP认识的逐渐深入，需要对MBDP进行同质化的规范管理。本共识基于目前国内外能获取的最佳证据，根据GRADE方法进行证据分级，并经多学科共识工作组专家认真讨论后形成。本共识共有19条推荐意见，其中A级1条，B级3条，C级10条，GPS 5条，具体汇总见表5。本共识存在以下局限：（1）由于高质量的临床研究较少，因此，推荐意见等级较低；（2）制订过程中缺乏儿科代谢内分泌专家的参与，也缺乏患儿家长和社会工作者的意见。本共识拟5年更新一次，在检索新的证据后咨询专家意见，收集使用人群及目标人群的意见，形成更新决策证据表，遵循卫生保健实践指南的报告条目进行更新。

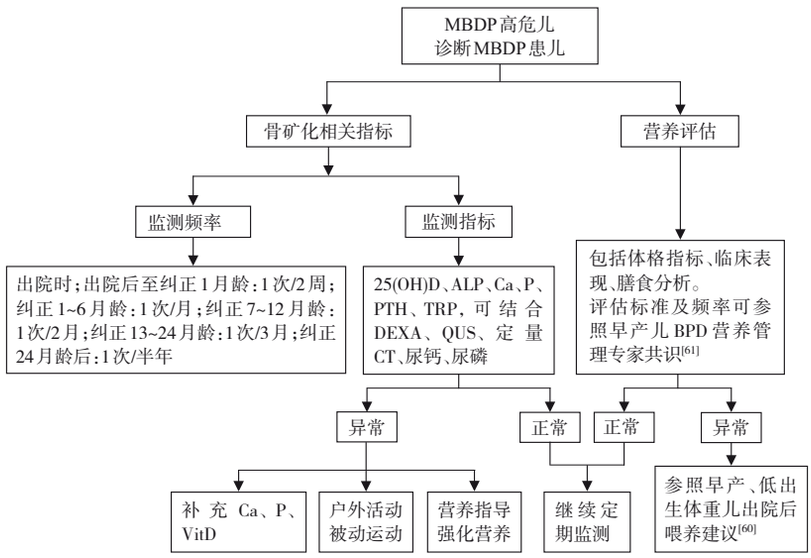

图3　随访与监测流程图　［25(OH)D］25羟基维生素D；［VitD］维生素D；［ALP］碱性磷酸酶；［Ca］钙；［P］磷；［PTH］甲状旁腺激素；［TRP］肾小管磷重吸收率；［DEXA］双能X线吸收法；［QUS］定量超声法。

表5　MBD临床管理专家共识推荐意见

项目	推荐意见	证据等级及推荐强度#
高危因素	①孕妇维生素D水平过低、使用硫酸镁>5 d、胎盘功能不全、绒毛膜羊膜炎、先兆子痫和胎儿宫内生长受限等是MBDP的产前高危因素	2C
	②男婴、胎龄<32周和/或出生体重<1 500 g、钙磷及维生素D补充不足、单纯母乳喂养是MBDP的生后高危因素	2C
	③早产儿合并支气管肺发育不良、坏死性小肠结肠炎、胆汁淤积性肝病等，使用糖皮质激素、甲基黄嘌呤类药物、袢利尿剂、苯巴比妥、苯妥英钠等，延迟建立肠内营养，肠外营养治疗时间>4周和制动>4周是MBDP的病理性高危因素	2B
诊断和筛查	①血ALP>900 IU/L，伴有血磷<1.8 mmol/L高度提示MBDP。出生3周后血PTH>180 pg/mL，伴有血磷<1.5 mmol/L，提示严重MBDP	2C
	②不推荐将25(OH)D作为MBDP的诊断依据	GPS
	③不推荐使用DEXA作为MBDP常规筛查检查	1A
	④具有MBDP高危因素的早产儿建议进行MBDP筛查	GPS
预防	①MBDP高危儿生后早期部分PN期间，每日元素钙24~40 mg/kg，元素磷18~30 mg/kg，钙磷比(1~1.3)∶1(质量比)；当PN达全量后，元素钙目标量65~100 mg/kg，元素磷目标量50~80 mg/kg，钙磷比可至1.7∶1	1C
	②MBDP高危儿达全肠内喂养后，每日钙摄入量100~160 mg/kg，磷摄入量60~90 mg/kg，钙磷比1.6∶1~1.8∶1(1B)；通过强化母乳或早产儿配方奶补充钙磷摄入量(1C)	1B; 1C
	③MBDP高危儿出院后应持续强化营养配方奶喂养至矫正足月或直至定期临床监测无合并MBDP的证据	1C
	④早产儿每日维生素D摄入量400~1 000 IU，生后1~2周开始通过添加母乳强化剂、早产儿配方奶或维生素D制剂补充，需定期监测血清25(OH)D的浓度以维持其水平>50 nmol/L	1C
	⑤MBDP高危儿达到全肠内喂养后可进行日常被动操训练以预防MBDP	1B
治疗	①在强化营养配方奶喂养基础上，需要额外补充钙、磷及维生素D制剂	1C
	②元素磷起始剂量为每日10~20 mg/kg，最大剂量为每日40~50 mg/kg；元素钙起始剂量为每日20 mg/kg，最大剂量为每日70~80 mg/kg；维生素D摄入量为每日400~1 000 IU	1C
	③当血磷恢复正常，血清ALP<500 IU/L且有降低趋势时，可考虑停止钙磷治疗	1C
出院后随访	①应根据MBDP高危因素的风险程度及MBDP严重程度制定随访监测计划，监测时间/频率为：出院时；出院后至纠正1月龄内每2周1次；纠正1~6月龄内每月1次；纠正7~12月龄内每2个月1次；纠正13~24月龄内每3个月1次；纠正24月龄后每半年1次	GPS
	②定期监测骨代谢生化指标并评估治疗效果，必要时可结合QUS和DEXA等进行骨密度测定	GPS
	③MBDP出院后定期监测体重、身长、头围等体格生长指标并进行专业的营养评估和指导	GPS

注：#A、B、C、D分别表示推荐质量等级为高、中、低、极低；1、2分别表示强推荐和弱推荐；GPS表示高质量临床实践声明。［MBDP］早产儿代谢性骨病；［ALP］碱性磷酸酶；［PTH］甲状旁腺激素；［DEXA］双能X线吸收法；［PN］肠外营养；［QUS］定量超声法。

参与共同讨论的专家（按单位名称拼音排序）：

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Expert consensus on clinical management of metabolic bone disease of prematurity (2021)*

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Abstract: Metabolic bone disease of prematurity (MBDP) is a systemic bone disease with a reduction in bone mineral content due to disorder of calcium and phosphorus metabolism. There is still a lack of in-depth research and systematic understanding of MBDP in China, and there are many irregularities in clinical management of this disease. Based on relevant studies in China and overseas, Grading of Recommendations Assessment, Development and Evaluation was used to develop the expert consensus on the clinical management of MBDP. This consensus provides recommendations from the following five aspects: high-risk factors, screening/diagnosis, prevention, treatment, and post-discharge follow-up of MBDP, so as to provide relevant practitioners with recommendations on the clinical management of MBDP to reduce the incidence rate of MBDP and improve its short- and long-term prognosis.

Key words: Metabolic bone disease; Expert consensus; Osteopenia; Bone mineralization and growth; Preterm infant

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With the continuous development of neonatal intensive care technology, more and more very low birth weight (VLBW) and extremely low birth weight (ELBW) preterm infants have been treated and surviving. Promising strides have been taken to improve their short and long-term outcomes, such as those involving complications like metabolic bone disease of prematurity (MBDP). MBDP is a type of bone disease characterized by reduced bone mineral content (BMC) and incomplete mineralization of osteoid material due to insufficient calcium, phosphorus and organic protein substrates or disturbances in bone metabolism in preterm infants. The essence of the disease is that the BMC of preterm infants cannot meet the requirements of normal bone growth and development, which may be accompanied by imaging of skeletal mineralization deficiency and biochemical changes in blood, such as hypophosphatemia and hyperalkaline phosphatasia[1]. The exact prevalence of MBDP is unknown because of the lack of uniform criteria for screening, diagnosis, prevention and treatment of the disease in China and other countries[2]. MBDP can affect the skeleton health and quality of life of preterm infants. Complications include extrauterine growth retardation, ventilator dependence and even fractures in the near term. In the long term, MBDP may lead to more adverse outcomes such as short stature, reduced peak bone mass, and susceptibility to osteoporosis[3-4].

A survey on the diagnosis and treatment of MBDP among 338 neonatologists in 246 neonatal intensive care units (NICUs) in the United States in 2014 showed a lack of homogeneity in clinical practice, with most doctors making decisions related to MBDP based on their personal clinical experience[5]. A national multicenter retrospective survey of MBDP in preterm infants by the Neonatal Nutrition and Health Management Group of Professional Committee of Child Health of Chinese Medical Doctor Association and a single-center study showed that there were widespread irregularities in prevention, screening, diagnosis and treatment[6-7], and there is an urgent

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need to develop an expert consensus on the clinical management of MBDP in China. Regular monitoring, screening for high-risk infants, and providing timely interventions are vital to improve the overall prognosis of MBDP[8].

This expert consensus is co-sponsored by the Nutritional Committee of Neonatology Branch of Chinese Medical Doctor Association, Neonatal Nutrition and Health Management Group of Professional Committee of Child Health of Chinese Medical Doctor Association, and Editorial Committee of Chinese Journal of Contemporary Pediatrics. It is registered with the Chinese Clinical Trials Registry (http://www.chictr.org.cn) with registration number ChiCTR2100042195, and it has been reviewed and approved by the Human Research Ethics Committee of the Women and Children's Hospital Affiliated to Xiamen University /Xiamen Maternal and Child Health Hospital (approval number: KY-2020-084). Experts in the fields of neonatology, child health, clinical nutrition, evidence-based medicine, and epidemiology, accompanied by editors of medical journals, have formed a multidisciplinary consensus working group, and this consensus was finally reached after several rounds of discussion, revision, and consideration by the team. The target population is preterm infants, while the planned application is for perinatal medicine practitioners, neonatologists, child health practitioners, orthopedists, dietitians, community health care workers, and related caregivers. It is intended to provide recommendations on the clinical management of MBDP.

For this consensus, the literature in English was assessed via the three keywords, "bone and neonate or infant", in academic platforms such as UpToDate, BMJ Clinical Evidence, National Guideline Clearinghouse (NGC), Joanna Briggs Institute Library (JBI), Cochrane Library, and the like. Chinese literature was also assessed by searching the five keywords "calcium, phosphorus, metabolic bone disease, osteopenia, and bone mineralization and growth", in SinoMed, CNKI, Wanfang Online, and others. The search for literature was concluded on December 1, 2020. The flowchart of literature screening is shown in Figure 1. The level of evidence and recommendation grade of the literature were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method, which classified the quality of evidence as high (A), medium (B), low (C) and very low (D). Moreover, the strength of recommendation was classified into three levels: strong recommendation (1), weak recommendation (2) and good practice statement (GPS) (Table 1)[9-11].

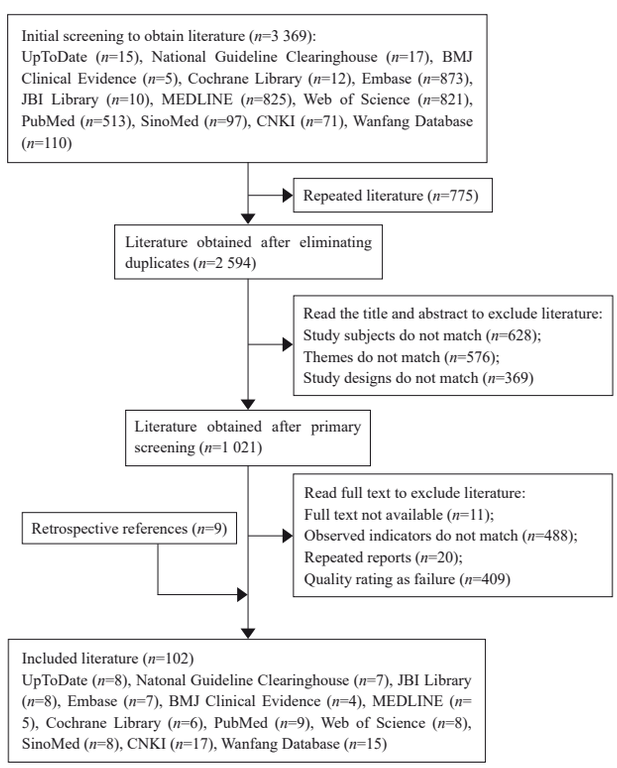

Figure 1 Flow chart of literature screening

Table 1 Grading quality of evidence and strength of recommendations

Rank	Definition
Quality of evidence	
High (A)	Very confident that the observed value is close to the true value
Moderate (B)	Medium confidence in the observed value: the observed value may be close to the real value, but it may also be very different
Low (C)	Limited confidence in the observed value: the observed value may be very different from the real value
Very low (D)	Little confidence in the observed value: there may be a great difference between the observed value and the real value
Strength of Rrecommendation	
Strong (1)	To do (or not to do) where the benefits clearly outweight the risk (or vice versa) for most, if not all patients
Weak (2)	Where benefits and risk are more closely balanced or are more certain
GPS	Point Not backed by sufficient evidence; however, a consensus reached by working group, based on clinical experience and expertise

Note: GPS, good practice statement.

1 High-risk factors

Recommendation 1: The Pregnant women with low vitamin D levels, use of magnesium sulfate >5 d, placental insufficiency, chorioamnionitis, pre-eclampsia, and fetal intrauterine growth restriction are high prenatal risk factors for MBDP (level C evidence, weak recommendation).

Recommendation 2: Male infants, infants born with less than 32 weeks of gestation, VLBW and ELBW infants, inadequate supplementation of calcium, phosphorus, and vitamin D, and exclusive breastfeeding are postnatal high risk factors for MBDP (level C evidence, weak recommendation).

Recommendation 3: The preterm infants complicated by bronchopulmonary dysplasia, necrotizing enterocolitis, cholestatic liver disease, treated with glucocorticoids, methylxanthines, loop diuretics, phenobarbital, phenytoin sodium, delayed establishment of enteral nutrition, the duration of parenteral nutrition therapy >4 weeks, and immobilization >4 weeks are pathologically high risk factors for MBDP (level B evidence, weak recommendation).

The 80% of mineral deposits in the fetus occurs from 24 to 40 weeks, with a peak at 34 weeks. By full term, the mineral reserves are approximately 20g of calcium (deposition rate of 100-120 mg/kg per day) and 10 g of phosphorus (deposition rate of 50-65 mg/kg per day)[12]. Fetal vitamin D reserves are dependent on maternal 25(OH)D levels, with vitamin D reaching only 50% to 70% of the maternal level at full term[13]. The American Society for Parenteral and Enteral Nutrition Clinical Guidelines [14] stated that inadequate maternal vitamin D supplementation (less than 600 IU/d), calcium supplementation with less than 2 g per day after 22 weeks of gestation, and long-term use of magnesium sulfate during pregnancy (more than 5-7 d) are high risk factors for MBDP. Placental inflammation, such as chorioamnionitis, placental insufficiency such as intrauterine growth restriction and pre-eclampsia also impair placental function and reduce fetal bone mass, leading to an increased risk of MBDP after birth.

An intrauterine environment with the higher level of estrogen and calcitonin and the lower of parathyroid hormone (PTH) promotes a high fetal blood calcium state, which facilitates bone structure and subcortical bone formation, and consequently leads to a sustained and efficient increase in bone mineral density (BMD). The bone mineral density of preterm infants born with less than 32 weeks of gestation is 25%-70% lower than that of term infants. This is because of the sudden interruption of mineral transport, the abrupt changes in hormone levels, the complications affecting metabolism of calcium, phosphorus, and vitamin D, and the inadequate supplementation of these minerals through parenteral and enteral nutrition or inappropriate calcium-phosphorus ratios. Additionally, the shorter the gestational age and the lower the birth weight, the higher the incidence and the more severity of MBDP[6,15]. According to studies in China and other countries, the prevalence of MBDP in ELBW infants is about 50% and in very low birth weight (VLBW) infants it is 20%-30%. 17%-34% of them may procure spontaneous rib or long bone fractures[6,15-17]. Furthermore, male infants with relatively immature kidney development and low estrogen levels are more susceptible to MBDP due to increased renal tubular phosphorus excretion and reduced reabsorption[17-18].

The vitamin D content of breast milk is only 25-50 IU/L. Unfortified adequate breastfeeding (180-200 mL/kg/day) provides only a third of the intrauterine acquisition of calcium and phosphorus in fetuses at the same gestational age, so the calcium and phosphorus contents of breast milk do not meet the bone mineralization requirements of preterm infants. Studies have shown that the incidence of MBDP in preterm infants, who should be indications by fortification, is 40% because of exclusive breastfeeding, while the incidence of MBDP in preterm infants fed with preterm formula is only 16%[5,19]. The results of a multicenter survey in China showed that the incidences of MBDP in preterm infants(less than 32 weeks gestational age) were 27.8%, 19.4%, 13.4%, and 21.8% in the exclusive breastfeeding, fortified breast milk, preterm formula, and mixed feeding groups, respectively[6]. The incidence of MBDP was increased with the use of formula for full-term infants or other specially formulated milk, which are not fortified with calcium, phosphorus, and vitamin D[8,20].

Preterm infants suffering from cholestatic liver disease, necrotizing enterocolitis especially after surgery, and bronchopulmonary dysplasia can encounter malabsorption and increased consumption of calcium, phosphorus and vitamin D. During the implementation of parenteral nutrition, the bioavailability of calcium and phosphorus is insufficient to maintain adequate bone mineralization requirements due to various factors such as low solubility of calcium and phosphorus, unstable temperature, different preparation methods and fluid restriction. Calcium gluconate packaged in glass bottles is also subject to aluminum contamination[21]. In relation, a study showed that preterm infants treated with parenteral nutrition for more than 4 weeks, had aluminum in their bones10 times more than the controls. Moreover, it was found that excessive aluminum deposition on the epiphyseal surface affected osteoblast activity and could reduce adolescent spinal bone mineral content and trabecular bone area[14]. A number of drugs such as glucocorticoids, methylxanthines, and loop diuretics can increase osteoclast activity, inhibit osteoblast proliferation, reduce calcium absorption from the gastrointestinal tract, and promote calcium excretion from the renal tubules. Phenobarbital and phenytoin sodium can also increase the catabolism of 25(OH)D, thus rised the risk of MBDP[20].

Another study showed that preterm infants in the NICU who are immobilized for more than 4 weeks and are more likely to develop MBDP due to the loss of active motor stimulation in utero against the uterine wall, which inhibits osteoblast proliferation and increases osteoclast activity. The factors lead to a

higher risk of MBDP linked to increased bone resorption and urinary calcium excretion, with 11% (P=0.06) and 14% (P=0.02) reduction in BMC and BMD, respectively[22].

2 Diagnosis and screening

Recommendation 1: The serum alkaline phosphatase (ALP) >900 IU/L with serum phosphorus <1.8 mmol/L is highly suggestive of MBDP. Serum PTH >180 pg/mL at 3 weeks after birth with serum phosphorus <1.5 mmol/L is suggestive of severe MBDP (Level C evidence, weak recommendation).

Recommendation 2: The serum level of 25 (OH) D is not recommended as a diagnostic basis for MBDP (GPS).

Recommendation 3: Dual energy X-ray absorptiometry (DEXA) is not recommended as a routine screening test for MBDP (Level A evidence, strong recommendation).

Recommendation 4: Screening for MBDP is recommended for preterm infants with high risk factors for MBDP (GPS).

The diagnosis of MBDP requires a comprehensive assessment of medical history, clinical manifestations, biochemical indicators and imaging tests. At present, the diagnosis of MBDP is mostly based on typical clinical manifestations and radiographic findings, but at this point, BMD has already significantly decreased. Early symptoms of MBDP are insidious and there is still no clear and uniform diagnostic method, so preliminary detection and diagnosis are difficult. To reduce the poor prognosis associated with MBDP, it is important to screen and manage preterm infants with high-risk factors at earlier stages. The ideal methods for evaluating the bone quality status of newborns include biochemical indicators and imaging tests.

2.1 Blood biochemical indicators

Commonly the used clinical blood biochemical indicators are serum calcium, phosphorus, ALP, PTH and 25(OH)D.

Serum calcium in the body is regulated by both calcitonin and PTH. When serum calcium is reduced, the body maintains blood calcium levels by mobilizing bone calcium under the regulation of PTH. Serum calcium can be normal or high when the body is calcium-deficient, and only when bone calcium reserves are depleted at the late stage of MBDP will serum calcium decrease. In light of this, serum calcium is not valuable for the early diagnosis of MBDP. In relation, serum phosphorus concentration can better reflect the status of bone phosphorus reserves, and a persistent decrease in serum phosphorus suggests inadequate phosphorus intake and an increased risk of osteoporosis[23]. When the serum phosphorus is lower than 1.8 mmol/L, it suggests the low BMD with a specificity of 96%, but a sensitivity of only 50%, which is not suitable for early diagnosis[24].

ALP is a glycoproteinase secreted by a variety of tissues and has at least four isozymes. 90% of ALP in neonates comes from bones, which can reflect bone metabolism well as an active marker of osteoblast maturation. ALP is physiologically mildly elevated in the first 2 to 3 weeks after birth; the diagnosis of MBDP is only considered when mineral deficiency is accompanied by further elevation of ALP. It should be noted that cholestasis, infections, copper deficiency, and other related factors can also lead to increased ALP, while zinc deficiency or glucocorticoid application can result to decreased ALP responsiveness. The amalgamation of these factors can all interfere with clinical judgement. Numerous studies have varying results regarding the applicability of ALP to the diagnosis of MBDP and the threshold range. Hung et al.[25] determined a diagnostic sensitivity of 73% and specificity of 74% for serum ALP higher than 700 IU/L in the diagnosis of MBDP in preterm infants less than 34 weeks gestational age using a forearm X-ray. Viswanathan et al[26]. found that the serum ALP, higher than 500 IU/L , is associated with MBDP in a retrospective analysis, which included 230 cases of ELBW with gestational age less than 30 weeks. Figueroas-Aloy et al[27]. tested and evaluated DEXA, serum ALP, calcium and phosphorus indicators in 336 cases of VLBW and also found the serum ALP, higher than 500 IU/L, to be associated with low BMD. Backström et al[24]. found a sensitivity and specificity of 100% and 71% for the diagnosis of MBDP based on DEXA findings when the serum ALP higher than 900 IU/L with serum phosphorus lower than 1.8 mmol/L. Overall, increased serum ALP levels can precede the onset of clinical symptoms and influence the development of MBDP[28].

Regulated by serum calcium ion concentration, the normal secretion of PTH maintains serum calcium levels by mobilizing osteolysis, which promotes calcium reabsorption by renal tubules and phosphate excretion. Research has shown that PTH is more sensitive than ALP in the diagnosis of MBDP. However, it must be noted that there is no uniform range of normal values for PTH in neonates, especially in preterm infants. Matejek et al.[29] tested serum PTH in 134 consecutive cases of VLBW and came up with a reference range of about 15.1 to 87.7 pg/mL, which is close to adult reference values. Moreira et al[30]. found by retrospective analysis that in preterm infants with birth weight <1 250 g, the serum PTH higher than 180 pg/mL at 3 weeks after birth had a sensitivity of 71% and a specificity of 88% for the diagnosis of severe MBDP. Additionally, the sensitivity and specificity increased to 100% and 94% when combined with serum phosphorus lower than 1.5 mmol/L.

Finally, 25(OH)D is the primary form of vitamin D transported in the blood, and normal vitamin D levels are a prerequisite for ensuring proper calcium and phosphorus absorption. The American Endocrine Society recommends serum 25(OH)D levels >50 nmol/L (20 ng/mL) in infants[31]. In relation, the reference range of serum 25(OH)D levels for children (0-14 years) in China is 37.5-250.0 nmol/L (15-100 ng/mL)[32]. The main etiology of MBDP is calcium and phosphorus deficiency, and serum 25(OH)D can be normal, decreased or even increased, 25 (OH)D is not used as a diagnostic indicator of MBDP.

2.2 Urinary biochemical indicators

Urinary biochemical indicators include urinary calcium and phosphorus, urinary calcium/creatinine, urinary phosphorus/creatinine, and tubular reabsorption of phosphorus (TRP). The urinary excretion of calcium and phosphorus is highly variable in relation to neonatal maturation, feeding practices, and medications involving diuretics and hormones. Due to the low renal phosphorus threshold of ELBW, phosphorus can still be excreted through urine in spite of decreased blood phosphorus in the body. TRP (%)=[1-(urinary phosphorus/urinary creatinine) × (blood creatinine/blood phosphorus)] ×100, which reflects the phosphorus reserve status of the body by detecting the reabsorption of phosphorus after filtration by the kidneys, has a normal value of about 85%-95%. TRP>95% with blood phosphorus decline suggests phosphorus deficiency in the body, while normal or reduced TRP with increased PTH may indicate calcium deficiency[2]. The results of various studies on the diagnostic value of urinary biochemical indices for MBDP are controversial, and the use of urinary biochemical indices alone for the diagnosis of MBDP is not recommended at present[33].

2.3 Imaging

Imaging is based on the measurement of BMD and mainly includes methods such as X-ray, DEXA, quantitative CT and quantitative ultrasound (QUS).

The characteristic changes of X-rays in infants with MBDP may show thinning at the end of the long bones, cupping or burr-like changes at the metaphysis, swelling of the rib ends, and subperiosteal new bone formation or fracture. The X-ray is only to the diagnosis of severe MBDP with significant osteoporosis or fractures since it is not sensitive to osteoporosis as the bone loss less than 20% to 40%[23]. Therefore, although an X-ray is highly specific for the diagnosis of MBDP, it is not suitable for early diagnosis. DEXA is the gold standard for the diagnosis of osteoporosis. However, it can only reflect the two-dimensional area density of the bone, not the three-dimensional density of the bone. There are also technical difficulties involved in the routine use of DEXA for screening of MBDP, including operational feasibility, radioactivity, timing of the initial scan, frequency of repetition, normal values for newborns of different gestational ages, intervention cut points, intervention modalities, and more similar factors which require further study[3,34]. Quantitative CT has the advantage of measuring bone stereoscopic density, but has the same limitations as DEXA.

QUS is a new diagnostic technique developed in the early 1980s that reflects not only BMD, but also bone microstructure, bone elasticity, and strength properties. This method offers a lot of practical advantages in terms of clinically diagnosing MBDP since it is non-radioactive, non-invasive, and easily performed at the bedside. In vitro research, it has confirmed that forearm QUS parameters correlate significantly with bone strength, and these parameters have been shown to be consistent with bone mineral conditions assessed by DEXA in pediatric researches[35]. The commonly used QUS parameter is the speed of sound propagation (SOS). A systematic review, conducted in 2018 on the application of QUS diagnosis in preterm infants, stated that SOS was positively correlated with the gestational age and the birth weight. SOS tended to decrease with the age to increase, and the decrease was negatively correlated with the gestational age. Moreover, SOS is positively correlated with serum phosphorus, serum calcium and vitamin D levels and negatively correlated with the level of serum ALP. Generally, SOS measurements could reflect the skeletal status of newborns and are highly correlated with BMD[36]. At present, there is a lack of a standard reference range for SOS in preterm infants due to many influencing factors, so the threshold of QUS in screening and diagnosing MBDP has not been determined. However, the application of QUS in preterm infants is highly advantageous and has good clinical application prospects.

Currently, there is not a standardized screening procedures for MBDP in preterm infants. Rayannavar et al[2]. recommended testing serum calcium, phosphorus, and ALP every 1 to 2 weeks starting at 4 to 6 weeks postnatally in all preterm infants. For those with high risk of MBDP, such as ELBW or VLBW, X-rays are recommended. If the serum ALP is higher than 800 IU/L or higher than 500 IU/L with an increasing trend, accompanied by hypophosphatemia, serum PTH and TRP need to be examined. At the same time, the serum 25(OH)D also have to be tested selectively in view of risk factors. Chacham et al[4]. recommended testing the serum blood calcium, phosphorus, and ALP every 4 weeks until 6 months after birth in newborns with high risk of MBDP. It is also encouraged to further evaluate serum PTH, 25(OH)D, and QUS for infants with abnormalities during the initial screening. This consensus recommends screening for MBDP in preterm infants with high risk factors (Figure 2).

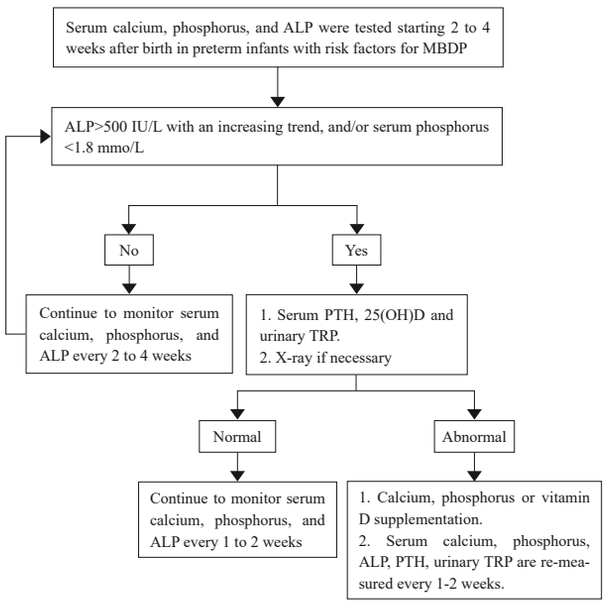

Figure 2 Flow chart for the screening of MBDP
MBDP, metabolic bone disease of prematurity; ALP, alkaline phosphatase; PTH,parathyroid hormone; 25(OH)D,25 hydroxyvitamin D;TRP, tubular reabsorption of phosphorus.

3 Prevention

Recommendation 1: In the early postnatal period, partial parenteral nutrition (PN) in infants with high risk of MBDP, the recommended doses of elemental calcium is 24-40 mg/kg and the elemental phosphorus is 18-30 mg/kg per day, with a calcium-phosphorus ratio of 1-1.3∶1 (mass ratio); In the stage of using TPN, the target recommended doses of elemental calcium is 65-100 mg/kg and elemental phosphorus is 50-80 mg/kg, and the calcium-phosphorus ratio can be upped to 1.7∶1 (Level C evidence, strong recommendation).

Recommendation 2: When the infants with high risk of MBDP achieve total enteral feeding, the recommended daily calcium intake is 100-160 mg/kg and phosphorus intake is 60-90 mg/kg, with a calcium to phosphorus ratio of 1.6∶1 to 1.8∶1 (Level B evidence, strong recommendation). For preterm infants, supplementary calcium and phosphorus intake through fortified breast milk or formula are recommended (Level C evidence, strong recommendation).

Recommendation 3: Infants with high risk of MBDP should continue fortified formula feeding after discharge until corrected full term or until regular clinical monitoring is free of evidence of MBDP (Level C evidence, strong recommendation).

Recommendation 4: Preterm infants should receive 400-1 000 IU of vitamin D daily, supplemented with breast milk fortification, preterm formula, or vitamin D preparations beginning at 1-2 weeks after birth, with regular monitoring of serum 25(OH)D concentrations to maintain it higher than 50 nmol/L (Level C evidence, strong recommendation).

Recommendation 5: Infants with high risk of MBDP can be trained through daily passive exercises to prevent MBDP after achieving full enteral feeding (Level B evidence, strong recommendation).

The management of bone health in preterm infants focuses on providing adequate calcium and phosphorus intake to promote normal bone growth. Studies have shown that postnatal calcium and phosphorus absorption rates in preterm infants are positively correlated with age, calcium, phosphorus, lactose, and fat intake. They are also influenced by vitamin D levels. ELBW and VLBW preterm infants should be supplemented with calcium and phosphorus by PN as soon as possible after birth, and the recommended doses are shown in Table 2[37-39]. Two randomized controlled studies have both shown that daily calcium and phosphorus supplementation in early PN in the high-dose group (elemental calcium 75 mg/kg, elemental phosphorus elemental phosphorus 44.1 mg/kg) was effective in preventing MBDP in preterm infants compared to the low-dose group (elemental calcium 45 mg/kg, elemental phosphorus 26.5 mg/kg)[40-41]. Both the A. S. P. E. N clinical guidelines and the guidelines on Paediatric Parenteral Nutrition of ESPGHAN in 2005 recommend an optimal calcium-to-phosphorus ratio of 1.7:1 (mass ratio) in PN fluid for preterm infants[14,38]. The ESPGHAN guidelines in 2018 emphasize that a calcium-to-phosphorus ratio of 1 to 1.3:1 (mass ratio) in PN fluid for 1 week after birth is appropriate for preterm infants to avoid hypercalcemia and hypophosphatemia[21]. In China, 10% calcium gluconate and 10% sodium glycerophosphate are often chosen as calcium and phosphorus preparations in PN. Based on the accumulation rates of calcium and phosphorus in the fetus during late gestation, along with the intestinal absorption rates of calcium and phosphorus in preterm infants who reach the recommended daily calcium dose of 100-160 mg/kg and the recommended daily phosphorus dose of 60-90 mg/kg under total enteral feeding, it is possible to meet the minerals required for weight gain and reduce the incidence of MBDP[42-43]. Some ELBW and VLBW infants may have higher calcium and phosphorus requirements, and the recommended calcium and phosphorus intakes for VLBW infants reaching total enteral feeding are shown in Table 3[12,43-47]. The calcium-to-phosphorus ratio also affects the degree of bone mineralization, and a study by American authors recommended a calcium-to-phosphorus ratio of 1.6:1 to 1.8:1 (mass ratio) for enteral feeding, with higher in vivo retention of phosphorus[43].

The calcium and phosphorus in breast milk fortification can meet the bone mineralization needs of preterm infants[48]. Breast milk fortification should be initiated when breastfeeding reaches 50-80 mL/kg per day in infants with high risk for MBDP[49]. If breast milk is not available, a fortified nutritional formula for preterm infants should be used, which can effectively promote bone growth and mineralization processes and prevent MBDP (Table 4[43,47,50]).

Table 2 Recommendations for TPN on the daily intake of calcium and phosphorus for VLBW infants[37-39]

Indicator	TPN (Initial quantity)	TPN (The liquid volume reaches 140-150 mL / kg per day)
Calcium (mg/kg)	24-40	65-100
Phosphorus (mg/kg)	18-30	50-80
Calcium/Phosphorus ratio (mass ratio)	(1-1.3):1	1.7:1

Note:VLBW, very low birth weight; TPN, total parenteral nutrition.

Table 3 Recommendations for enteral nutrition on the daily intake of calcium, phosphorus and vitamin D for VLBW infants[12,43-47]

Indicator	Klein 2002[44]	Atkinson 2005[45]	Rigo 2007[12]	Agostoni 2010[46]	Abrams 2013[43]	Koletzko 2014[47]
Calcium (mg/kg)	150-220	120-200	100-160	120-140	150-220	120-200
Phosphorus (mg/kg)	100-130	70-120	60-90	60-90	75-140	60-140
Vitamin D (IU)	90-225	200-1 000	800-1 000	800-1 000	200-400	400-1 000

Note:VLBW, very low birth weight; Ca mg to mmol needs to be divided by 40, P mg to mmol needs to be divided by 31.

Table 4 Intakes of calcium, phosphorus, and vitamin D from various enteral nutrition feedings at 160 mL/kg per day[43,47,50]

Indicator	Unfortified human milk	Normal infant formula	Preterm Formula	Transitional Formula	Fortified Human Milk
Calcium (mg/kg)	37	50	210-234	125-144	192-197
Phosphorus (mg/kg)	21	28	117-129	74-80	103-110
Vitamin D (IU)	2.4	400	194-384	125-127	189-253

A study showed that continued use of fortification strategies after hospital discharge to full term is beneficial for growth and bone health[51]. However, there is no sufficient basis to determine the ideal duration of fortification for preterm infants with small for gestational age. It is currently recommended that infants at high risk of MBDP continue fortification during hospitalization and after discharge at least until corrected full term, typically until 3 to 4 months of corrected age. This should last until clinical monitoring shows improved infant growth, along with no evidence of complicated MBDP.

A small-sample prospective randomized controlled study showed that 50% of MBDP preterm infants weighing <1 250 g had significantly lower serum 25(OH)D levels than infants in the non-MBDP group at 6 weeks postnatally[52]. Both national and international guidelines recommend starting vitamin D supplementation in preterm infants at 1 to 2 weeks postnatally and when enteral feeding is tolerated, with a recommended intake of 400-1 000 IU/d. Additionally, serum vitamin D levels need to be monitored regularly to ensure that serum 25(OH)D concentrations reach 50 nmol/L or higher[43,53]. The daily demand of vitamin D in preterm infants can be supplemented with fortified breast milk, preterm formula, and vitamin D preparations. The American Academy of Pediatrics recommends that all breastfeeding, mixed feeding, and use of fortified vitamin D formula at less than 800-1 000 mL/d should be supplemented with at least 400 IU/d of vitamin D for the prevention of MBDP[43,54].

Mechanical pulling stimulation at the bone joints has also been found to promote bone growth and bone mineralization processes. Moyer-Mileur et al[55]. developed a passive exercise training program centered on passive extension and flexion exercises of the extremity joints. This regimen was started once preterm infants reached a daily enteral nutritional energy more than 110 kcal/kg, with five rounds of passive extension and flexion of the wrists, elbows, shoulders, knees, ankles, and hip joints per session. The entire procedure lasted about 5-10 min, and the series of exercises was performed once a day, 5 days per week. A systematic review in 2014 included 11 single-center studies with a total of 324 preterm infants between 26 and 34 weeks of gestational age, and the growth of BMC, BMD and bone area (BA) in preterm infants was promoted by performing joint passive gymnastic exercises for 3-8 weeks during hospitalization[56].

4 Treatment

Recommendation 1: Additional calcium, phosphorus and vitamin D preparations are needed on the base of fortified nutritional formula feeding (Level C evidence, strong recommendation).

Recommendation 2: The starting dose of elemental phosphorus is 10-20 mg/kg per day and the maximum dose is 40-50 mg/kg per day. The starting dose of elemental calcium is 20 mg/kg per day and the maximum dose is 70-80 mg/kg per day. Vitamin D intake is 400-1 000 IU per day (Level C evidence, strong recommendation).

Recommendation 3: Consider discontinuing calcium and

phosphorus therapy when the serum phosphorus level returns to normal and serum ALP is <500 IU/L with a trend toward reduction (Level C evidence, strong recommendation).

Infants with MBDP require comprehensive nutritional management measures. The key to treatment is supplementation with calcium, phosphorus, and vitamin D preparations based on fortified nutritional formula feeding to guarantee that the daily intake of these substances reaches the target amounts. This also ensures that abnormal metabolic states such as hypophosphatemia, secondary hyperparathyroidism and vitamin D deficiency are corrected as soon as possible.

Biochemical alterations in the blood of children with MBDP are first characterized by hypophosphatemia. When hypophosphatemia persists, both bone resorption and calcium excretion via the kidneys increase, resulting in a state of calcium depletion[42]. Supplementation with phosphorus preparations alone can exacerbate the imbalance of calcium and phosphorus in the body (manifested as hyperphosphatemia and hypocalcemia), leading to secondary hyperparathyroidism and exacerbating skeletal lesions. Therefore, it is encouraged that infants with MBDP should be given additional supplementation with calcium and phosphorus preparations on the basis of fortified nutritional formula feeding[21,43]. The starting dose of elemental phosphorus is 10-20 mg/kg per day, which can be increased to a maximum dose of 40-50 mg/kg per day as tolerated, either in the intravenous form of sodium or potassium phosphate or in the oral phosphate complex. The starting dose of elemental calcium is 20 mg/kg per day, which can be increased to a maximum dose of 70-80 mg/kg per day as tolerated. Inorganic calcium salt preparations or liquid organic calcium can also be used.

Infants with MBDP require concomitant vitamin D supplementation of 400-1 000 IU daily to promote intestinal absorption of calcium and phosphorus. When there is evidence of vitamin D deficiency upon clinical monitoring in cases of chronic conditions such as liver and kidney diseases, the active form of vitamin D, i.e., $1,25(OH)_2$ vitamin D, can be considered. Serum phosphorus, serum calcium, 25(OH)D, PTH, and urinary calcium and phosphorus indicators also need to be monitored regularly during treatment to efficiently adjust the therapeutic regimen and avoid adverse effects such as calcium and phosphorus overload[21,43]. After adequate calcium, phosphorus, and vitamin D therapy, if hypophosphatemia does not improve and ALP levels continue to rise, the presence of other factors causing metabolic diseases of the bone must be identified.

In infants with MBDP, improvement in imaging can be observed after several weeks of increased enteral or parenteral mineral supplementation. The efficacy of treatment can usually be determined by imaging after 6 to 8 weeks. Once biochemical parameters improve and imaging shows signs of fracture healing or increased bone mass, calcium and phosphorus supplementation can be gradually reduced over 2 to 4 weeks. Overall, discontinuation of treatment can be considered once serum phosphorus returns to normal and serum ALP is <500 IU/L with a reducing trend[43].

5 Follow-up

Recommendation 1: Based on the degree of high-risk factors and the severity of MBDP, a follow-up monitoring plan should be developed with the following timeline: at discharge, once every 2 weeks from discharge to 1 month old, once every month from 1 to 6 months old, and once every 2 months from 7 to 12 months old; once every 3 months from 13 to 24 months of age; once every six months after correction at 24 months of age (GPS).

Recommendation 2: Regularly monitoring (optional at discharge, correction at 1 month, 3 months and 6 months) biochemical indicators of bone metabolism and assessing the effect of treatment of MBDP. The detection of bone densitometry in combination with QUS and DEXA is necessary (GPS).

Recommendation 3: Regularly monitoring physical growth indicators such as weight, body length, head circumference, and MBDP infants should be given professional nutritional assessment and guidance after discharge (GPS).

With early screening and diagnosis of MBDP, combined with timely and adequate calcium, phosphorus and vitamin D supplementation, most infants with MBDP recover or resolve on their own by the age of 2 years old[4]. Since most of the bone loss in preterm infants with ELBW and VLBW occurs around 40 weeks of corrected gestational age, it can be easily overlooked and leaded to the following complications.

(1) Fractures[4]: There is 17% to 34% incidence, most often in the 6th to 12th postnatal week, usually in the long bones or ribs. (2) Difficulty in ventilator weaning[4]: thoracic instability due to rib osteomalacia and/or spontaneous rib fractures, as well as respiratory distress due to post-fracture pain, can lead to difficulty in ventilator weaning. It may also increase the number of days of oxygen inhalation and hospitalization and heighten the increase the risk of apnea, infections, bronchopulmonary dysplasia, and even mortality[56]. (3) Rickets or skeletal deformities[21,56]: clinical manifestations of rickets and one or more secondary skeletal deformities may be present. (4) Myopia[57]: with or without retinopathy, the mechanism underlying myopia may be due to reduced bone mineral content causing long head deformity of the skull, short frontal axis deformity, and ocular ellipsoidal deformity. (5) Growth and development retardation[56]: although catch-up growth occurs after discharge in cases of ELBW or VLBW, MBDP can lead to impaired growth rates in preterm infants. Some infants with MBDP may have abnormal or lagging neuromotor development at the age of 18 to 24 months of corrected age or later. The risk of short stature can persist up to 12 years of age, and some preterm infants still do not catch up to full-term infants in height even until adolescence. (6) Osteoporosis: preterm infants with breast feeding had not reached the standard of bone mineralization until 2 years of age, and formula feeding of preterm in-

fants also took until about 6 years of age to achieve bone mineralization comparable to that of full-term infants at the corresponding age[58]. Tinnion et al[59]. found that preterm infants had lower BMC and BMD in different parts such as the lumbar spines, forearms, and hips compared to those of full-term infants, thus even affecting BMD in adulthood and skeletal homeostasis in old age. The increased susceptibility to osteoporosis is apparent.

MBDP prognosis is influenced by a myriad of factors, such as gestational age, birth weight, complications, medications, and nutrition. To reduce MBDP complications and improve the near- and long-term prognosis and linear growth of affected individuals, regular follow-up and monitoring is emphasized for preterm infants with risk factors for MBDP. The management goals include maintaining normal serum calcium and phosphorus, as well as avoiding excessive urinary calcium excretion, so as to maintain ideal growth in indicators such as length, weight, and head circumference.

(1) Regularly monitoring biochemical indicators of bone metabolism, such as Ca, P, ALP, TRP, and PTH. If ALP >800 IU/L occurs 2 times, further bone densitometry such as QUS, DEXA and quantitative CT should be selected[4,57-58].

(2) Nutritional assessment and monitoring: MBDP can present with slow growth (typically lagging height increase), and this growth-impeding effect can persist until 8 to 12 years of age[4,56,58]. However, there is no individualized nutritional assessment method for MBDP, and most infants with MBDP are high-risk preterm infants, as is bronchopulmonary dysplasia in preterm infants, according to the classification of nutritional risk level at discharge[60]. In light of this, the expert consensus on nutritional management of bronchopulmonary dysplasia in preterm infants and health care for premature infants can be used as references[61-62] for the content and frequency of nutritional assessment for infants with MBDP after discharge. Regular physical growth assessment, biochemical assessment, clinical manifestations, and dietary analysis should also be carried out. The criteria for assessment of physical indicators can be selected from the Fenton curve (before age corrected 40-50 weeks), 2016 WHO Child Growth Standards (http://www.who.int/childgrowth/standards/en/) (40 weeks after correction) or the 2018 China Nine Cities Standards[63].

(3) Frequency of follow-up and monitoring: Based on the degree of high-risk factors and the severity of MBDP, a follow-up mornitoring plan should be developed with the following timeline: at discharge, once every 2 weeks from discharge to 1 month old, once every month from 1 to 6 months old, and once every 2 months from 7 to 12 months old; once every 3 months from 13 to 24 months of age; once every six months after correction at 24 months of age, respectively[21]. Nutritional assessment can continue into adulthood. The flow chart for follow-up and monitoring is shown in Figure 3.

(4) Post-discharge interventions: The preterm infants with MBDP should receive vitamin D, calcium, and phosphorus supplementation during post-discharge follow-up once abnormalities are identified by assessment and monitoring. Enhanced outdoor activity combined with passive movement and touch are also recommended. Individualized nutrition and feeding instructions may be utilized as well (refer to the post-discharge feeding recommendations for preterm, low birth weight infants[60]).

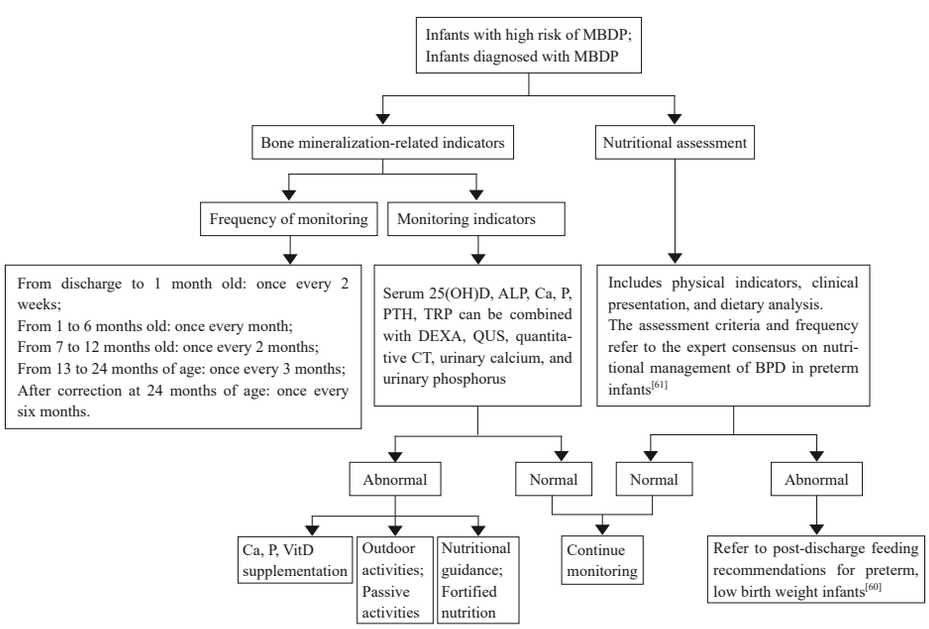

Figure 3 Chart of follow-up and monitoring 25(OH)D,25 hydroxyvitamin D; VitD, vitamin D; ALP, alkaline phosphatase; PTH, parathyroid hormone; TRP, tubular reabsorption of phosphorus; DEXA, Dual energy X-ray absorptiometry; QUS, quantitative ultrasound.

6 Concluding remarks

With the continuously deepened understanding of MBDP among clinicians, it grows more and more evident that there is a need for the homogenized and standardized management of MBDP. These guidelines are based on the best evidence that can be obtained in China and other counties so far, according to the GRADE method. Moreover, the guidelines were formed after careful discussion by experts in the multidisciplinary consensus working group, in the hopes of providing a solid foundation for clinical practitioners. There are 19 recommendations in this set of guidelines, including 1 grade A, 3 grade B, 10 grade C, and 5 GPS recommendations. The specific summary is shown in Table 5.

One of the limitations is that these guidelines had a low level of recommendations because of the scarce number of high-quality clinical studies. In addition, the consensus development process lacked the participation of pediatric metabolic endocrinologists and the opinions of the infants' parents and social workers. This consensus is proposed to be updated once every five years by consulting with experts after retrieving new evidence, collecting opinions from the affected populations and stakeholders. Finally, a consensus update decision evidence table is formed, which followed the reporting entries of the health care practice guidelines.

Table 5 Clinical management expert consensus recommendation on MBDP

Category	Recommendations	Quality of evidence and strength of recommendations[#]
High-risk factors	①The pregnant women with low vitamin D levels, use of magnesium sulfate >5d, placental insufficiency, chorioamnionitis, pre-eclampsia, and fetal intrauterine growth restriction are high prenatal risk factors for MBDP.	2C
	②Male infants, infants born with less than 32 weeks of gestation, VLBW and ELBW infants, inadequate supplementation of calcium, phosphorus, and vitamin D, and exclusive breastfeeding are postnatal high risk factors for MBDP.	2C
	③The preterm infants complicated by bronchopulmonary dysplasia, necrotizing enterocolitis, cholestatic liver disease, treated with glucocorticoids, methylxanthines, loop diuretics, phenobarbital, phenytoin sodium, delayed establishment of enteral nutrition, the duration of parenteral nutrition therapy >4 weeks, and immobilization >4 weeks are pathologically high risk factors for MBDP .	2B
Diagnosis and screening	①The serum ALP >900 IU/L with serum phosphorus <1.8 mmol/L is highly suggestive of MBDP. Serum PTH >180 pg/mL at 3 weeks after birth with serum phosphorus <1.5 mmol/L is suggestive of severe MBDP.	2C
	②The serum level of 25 (OH) D is not recommended as a diagnostic basis for MBDP.	GPS
	③DEXA is not recommended as a routine screening test for MBDP.	1A
	④Screening for MBDP is recommended for preterm infants with high risk factors for MBDP.	GPS
Prevention	①In the early postnatal period, PN in infants with high risk of MBDP, the recommended doses of elemental calcium is 24-40 mg/kg and the elemental phosphorus is 18-30 mg/kg per day, with a calcium-phosphorus ratio of 1-1.3:1 (mass ratio); In the stage of using TPN , the target recommended doses of elemental calcium is 65-100 mg/kg and elemental phosphorus is 50-80 mg/kg, and the calcium-phosphorus ratio can be upped to 1.7:1.	1C
	②When the infants with high risk of MBDP achieve total enteral feeding, the recommended daily calcium intake is 100-160 mg/kg and phosphorus intake is 60-90 mg/kg, with a calcium to phosphorus ratio of 1.6:1 to 1.8:1 (1B). For preterm infants, supplementary calcium and phosphorus intake through fortified breast milk or formula are recommended (1C).	1B; 1C
	③Infants with high risk of MBDP should continue fortified formula feeding after discharge until corrected full term or until regular clinical monitoring is free of evidence of complicated MBDP.	1C
	④Preterm infants should receive 400-1000 IU of vitamin D daily, supplemented with breast milk fortification, preterm formula, or vitamin D preparations beginning at 1-2 weeks after birth, with regular monitoring of serum 25 (OH) D concentrations to maintain it higher than 50 nmol/L.	1C
	⑤Infants with high risk of MBDP can be trained through daily passive exercises to prevent MBDP after achieving full enteral feeding.	1B
Treatment	①Additional calcium, phosphorus and vitamin D preparations are needed on the base of fortified nutritional formula feeding.	1C
	②The starting dose of elemental phosphorus is 10-20 mg/kg per day and the maximum dose is 40-50 mg/kg per day. The starting dose of elemental calcium is 20 mg/kg per day and the maximum dose is 70-80 mg/kg per day. Vitamin D intake is 400-1 000 IU per day.	1C
	③Consider discontinuing calcium and phosphorus therapy when the serum phosphorus level returns to normal and serum ALP is <500 IU/L with a trend toward reduction.	1C

Continued to Table 5

Category	Recommendations	Quality of evidence and strength of recommendations[#]
Follow-up	①Based on the degree of high-risk factors and the severity of MBDP, a follow-up monitoring plan should be developed with the following timeline: at discharge, once every 2 weeks from discharge to 1 month old, once every month from 1 to 6 months old, and once every 2 months from 7 to 12 months old; Once every 3 months from 13 to 24 months of age; once every six months after correction at 24 months of age.	GPS
	②Regularly monitoring biochemical indicators of bone metabolism and assessing the effect of treatment ofMBDP. The detection of bone densitometry in combination with QUS and DEXA is necessary.	GPS
	③Regularly monitoring physical growth indicators such as weight, body length, head circumference, and MBDP infants should be given professional nutritional assessment and guidance after discharge.	GPS

Note:[#]A, B, C and D refer to high, medium, low and very low recommended quality grades respectively; 1 and 2 refer to strong and weak recommendation respectively; GPS, good practice statement; MBDP, metabolic bone disease of prematurity; ALP, alkaline phosphatase; PTH, parathyroid hormone; DEXA, dual energy X-ray absorptiometry; PN, parenteral nutrition; QUS, quantitative ultrasound.

Conflict of interest: All authors of this article declare that there is no conflict of interest.

Experts participating in the consensus: (Order by Pinyin of the name of the expert's institution)

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