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Joint Compression Therapy in the Prevention of Osteopenia of Prematurity:Current Research and Future Considerations

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Abstract

Osteopenia of prematurity is a metabolic bone disease affecting neonates born during the second trimester of pregnancy and classified as very low birth weight, or less than 1500 grams at birth. Improvements in neonatal nutrition have reduced osteopenia of prematurity by increasing available calcium, phosphorus, magnesium and vitamin D for bone mineralization. Ossification also requires the presence of adequate bone matrix for mineralization to be completed. Passive mechanical stimulation such as joint compression replicates the resistance and weight bearing movements of the fetus in utero. Fetal osteoprogenitor cells are signaled to develop into osteoblasts, thus creating bone matrix which can then be mineralized. Research into the effects of passive physical exercise with joint compression on the prevention of osteopenia of prematurity are compared and discussed to ascertain recommendations for future implementation and considerations.

Almost 65,000 neonates are born each year with birth weights less than 1500 grams, qualifying them as very low birth weight (VLBW) infants. In the vast majority of cases, VLBW designation also corresponds to a gestational birth age of less than 32 weeks (Hamilton, Martin, & Ventura, 2010). Among the many potential consequences is osteopenia of prematurity (OOP), which affects approximately 30% of premature, VLBW neonates (Cross & Vasquez, 2009).

OOP is described as a loss of bone density resulting from suboptimal bone mineralization (Lam, So, & Ng, 2007). OOP should not be considered expected sequelae of VLBW birth, nor is it without its own consequences. OOP can produce soft, unstable bones unsuitable for maintaining normal physical structure. In particular, a neonate with severe chronic lung disease may not have the structural strength of the ribs to keep the chest wall from pressing down onto the lungs, making it even more difficult to wean off a ventilator (Williford, Pare, & Carlson, 2008). An osteopenic neonate is susceptible to fractures with normal handling during routine care. The neonate can sustain loss of function and pain from the fractures (Williford, Pare, & Carlson, 2008). OOP negatively impacts neonatal growth rate (Mitchell, Rogers, Hicks, Hawthorne, Parker, & Abrams, 2009). Severe OOP with alkaline phosphotase levels $\geq$ 1200 IU/ml have been associated with reduced linear growth at 18 months of age (Demarini, 2005).

Normal Physiology Related to Term Gestation

Fetal ossification of strong, stable bones is strongly influenced by movement (Lam, So, & Ng, 2007). Bone structure follows function, and a variety of stressors from joint impact (weight bearing) to mechanical pull increases both length and cortical thickness (So & Ng, 2005). By the end of the second trimester (approximately 28 weeks gestation), the fetus can move up to thirty times per hour (Nihira, 2009). The muscular walls of the uterus acts as resistance to provide

weight-bearing experiences for the fetus as the arms and legs extend, then recoil back to flexed positions. In addition, the mother moves and changes positions throughout the day. This activity changes the plane of movement for the fetus, creating differing mechanical strains on muscles (Land & Schoenau, 2008).

Physical activity and weight bearing/resistance movement signals bone-forming cells called osteoblasts to secrete bone matrix according to areas being stressed by function. Once surrounded by matrix, osteoblasts are considered mature bone cells, or osteocytes. The final step of stable bone formation is mineralization via deposition of calcium, phosphorus and magnesium (Rauch & Schoenau, 2002). Mineralization depends on proper nutritional intake, gastrointestinal absorption into the bloodstream, and presence of vitamin D to assist the regulation of these processes (Demarini, 2005).

The fetus is dependent upon the mother for all nutrients throughout the pregnancy. Beginning in the second trimester, an increasing amount of calcium crosses the placenta and enters fetal circulation (Rauch & Schoenau, 2002). However, the vast majority of mineral exchange occurs in the third trimester, peaking at 36-38 weeks gestation (Williford, Pare, & Carlson, 2008). At this point, large amounts of calcium are flowing into the fetus creating fetal serum calcium levels approximately five times higher than maternal serum calcium levels.

Fetal serum phosphorus levels also increase in the third trimester (Cross & Vasquez, 2009). During this time, the fetus is actively mineralizing strong, stable bones as well as storing extra calcium and phosphorus in the bones. This is necessary biologically as the maternal-to-fetal hypercalcemic circulation is abruptly halted at delivery when the umbilical cord is cut (Land & Schoenau, 2008).

After birth the term newborn ingests very little at breast for the first two or three days. Thereafter, maternal breastmilk contains much less calcium than the rich blood supply in utero. It is during this time the extra mineral stores are slowly released from the bones to maintain adequate serum levels (Williford, Pare, & Carlson, 2008). Specifically, low serum calcium levels trigger the release of parathyroid hormone (PTH). PTH signals another type of bone cell, the osteoclast, to release calcium into the bloodstream by breaking down or "remodeling" areas of bone (Land & Schoenau, 2008).

Pathophysiology Related to Preterm, VLBW Neonates

The greatest risk of OOP for the VLBW neonate results from the lack of mineral store deposition during the third trimester (Eliakim & Nemet, 2005). Lacking exposure to the calcium-rich maternal/placental circulation, the premature infant begins life at a distinct disadvantage: Though typical for gestational age, the VLBW neonate has relatively unstable bones. In addition, the neonate has little in the way of extra calcium and phosphorus stores from which to draw in order to meet the needs of bone mineralization (So & Ng, 2005).

A preterm, VLBW neonate faces a host of other contributing factors which can increase the risk and severity of OOP. The VLBW neonate is not likely to tolerate full enteral feedings within the first week of life. Intravenous nutrition in the form of total parenteral nutrition (TPN) is minimally capable of supplying optimal daily intake of calcium and phosphorus (So & Ng, 2005). Even centrally infusing TPN cannot deliver the daily recommended amounts of minerals for VLBW neonates. Reasons vary and include limits on calcium:phosphorus solubility (Lam, So, & Ng, 2007).

Almost all VLBW neonates are treated with fluid restrictions which further limit the mineral inclusion in the TPN recipe (So & Ng, 2005). This factor becomes more pronounced if IV access is peripheral only. Many NICUs do not infuse calcium peripherally. An NICU which opts to infuse calcium peripherally should do so in small amounts to minimize risk of infiltration-associated tissue sloughing (Abrams, 2008). A provider would still be unable to administer enough to meet the neonate's daily needs.

A VLBW neonate is at higher risk to remain on TPN for a prolonged period of time. Reasons include feeding intolerance of unknown etiology, intestinal dysmotility, septicemia requiring a hold on enteral feeds, and/or necrotizing enterocolitis (So & Ng, 2005). The optimal solution is a transition to enteral feedings as soon as possible (Cross & Vasquez, 2009). Appropriate enteral feedings consist of breastmilk fortified with a powder additive delivering additional calcium, phosphorus and calories equally 24 calories per ounce. A formula alternative would be a specialized premature infant formula containing higher levels of calcium and phosphorus, also providing 24 calories per ounce (Eliakim & Nemet, 2005). Unfortunately, some VLBW neonates do not initially tolerate fortified, higher-calorie feedings. Unfortified breastmilk and premature formula do not provide the requisite amount of mineral intake (So & Ng, 2008).

Routinely prescribed medications can negatively affect the neonate's ability to properly mineralize bone matrix. Furosemide is known to cause hypercalcuria and nephrocalcinosis. Furosemide signals the kidneys to filter calcium out of the bloodstream and excrete it (Cross & Vasquez, 2009). As the serum calcium level drops, PTH rises and osteoclasts begin to remodel bone to maintain serum calcium levels. Methylxanthines and glucocorticoids are also implicated as risk factors for the development of OOP (So & Ng, 2005).

One of the most overlooked contributing factors of OOP is physical movement. As part of neonatal developmental care, a significant effort has been made to promote flexion-predominant positioning, boundaries, and a "hands-off" approach towards neonatal care (Eliakim & Nemet, 2005). In reality, neonates in utero are exposed to muffled noises, shades of light, exterior movement from the mother, and self-movement within a tactile environment.

After birth, the VLBW neonate is no longer able to move freely within a buoyant environment, experiencing positional changes as the mother goes about daily life. The VLBW neonate is subjected to the forces of gravity in the NICU (Demarini, 2005). Instead of free-floating, weight-bearing extension/flexion, the neonate experiences restricted movement via gravitational pull (Rauch & Schoenau, 2002). Indeed, this difference between in utero and ex utero movement diminishes the VLBW neonate's ability to engage the body's system of function/structure ossification (Land & Schoenau, 2008). A decrease in function decreases osteoblast activity, thus creating less osteiod structure to mineralize even if optimal calcium, phosphorus, magnesium and vitamin D intake are provided (Rauch & Schoenau, 2002). Physical exercise programs including joint compression are specifically designed to re-engage the function/structure ossification process of VLBW neonates.

Diagnosis of OOP

Among the difficulties in treating OOP is the lack of a single accepted definition. In general, OOP is diagnosed by lab values including serum phosphorus of $\leq$ 3.5-4 (Cross & Vasquez, 2009) and elevated alkaline phosphotase (alk phos) at five times the normal adult levels (Rauch & Schoenau, 2002), or $\geq$ 650-800, depending on sources. Interestingly, high alk phos levels correlate poorly to high degrees of hypo-mineralization (So & Ng, 2005; Mitchell et al, 2009). Much

controversy surrounds typical lab values currently utilized to measure nutrition status and degree, or risk of OOP. For example, some sources quote a serum phosphorus < 4.5 mg/dL as diagnostic (Land & Schoenau, 2008).

Many NICU guidelines suggest following serum calcium levels, although these results actually have little value. Activation of PTH assures normal serum calcium in all but the most severe hypocalcemic states (Cross & Vasquez, 2009). More telling are ionized calcium (iCa) levels, as iCa reflects the biologically available calcium in the blood. Concerning iCa levels would be < 1 mmol/L (Abrams, 2008).

Standard radiographs are also used in the detection of OOP. Bone demineralization can be visualized as a haziness or milky quality of the long bones and ribs on x-ray. Unfortunately this is a late sign of OOP. A neonate has to lose 30-40% of bone mineralization before it is apparent on standard radiographs (Lam, So, & Ng, 2007; Eliakim & Nemet, 2005). Often the first radiographical sign is a fracture; a hairline fracture of a rib or long bone, or a cross-sectional fracture. This represents advanced OOP.

Literature Review

Much of the current knowledge and protocols are based on the seminal research report published by Moyer-Mileur, Luetkemeier, Boomer, and Chan in the October 1995 issue of *The Journal of Pediatrics*. Moyer-Mileur set the stage for subsequent research into physical exercise routines for VLBW neonates. The Moyer-Mileur protocol consists of passive range-of-motion and gentle joint compression movements to the six large joints of the extremities for the experimental or exercise (EX) groups. This encompasses the shoulder, elbow, wrist, hip, knee, and ankle. The control groups (C) receive a commensurate amount of time being held and stroked but not

exercised. The purpose is to neutralize any advantage of positive touch by assuring all neonates receive soothing touch during the entirety of the study.

Eligibility for the original Moyer-Mileur study included 1) corrected gestational age (CGA) of 26-34 weeks, 2) body size and weight deemed appropriate for gestational age (AGA), 3) enteral feedings at ≥ 110 kcal/kg/day, 4) intake of no medications other than vitamin supplements, and 5) parental consent. Each group of neonates received the prescribed treatment activity for 5-10 minutes per day for four weeks. All neonates were fed either breastmilk with Enfamil Human Milk Fortifier 24 cal/oz, or Enfamil Premature Formula 24 cal/oz. A total of 13 neonates completed the study in each group (exercise and control). Groups were matched for birth weight, gender, and gestational age, and were randomly placed in either the exercise or control group. Baseline and 4-week assessments were collected for the study.

Standard growth parameters such as weight, length and head circumference (OFC) were collected. Lab studies included routine nutritional levels (calcium, phosphate, alk phos) in addition to PTH and vitamin D levels. Bone characteristics were measured via single-beam photon absorptiometry. Data was analyzed using descriptive statistics, independent *t*-Test, ANOVA, and correlation and linear regression. A synopsis of the original Moyer-Mileur results includes:

1. Similar nutritional intakes between groups appropriate for gestational age
2. Statistically significant greater daily weight gain by the EX group as compared to the C group (17.8 vs. 13.4 gr/kg/day, $p = 0.01$)
3. EX group: 12% gain in bone width, 18% gain in bone mineral density, 34% gain in bone mineral content over the course of the study

4. C group: 2% gain in bone width, 17% loss in bone mineral density, 11% loss in bone mineral content over the course of the study
5. Biochemical markers similar except for alkaline phosphotase which was lower in EX group vs. C group at the end of the study (72 $\pm$ 21 vs. 122 $\pm$ 29 U/L; $p = <0.001$); results for all groups within normal ranges
6. Negative association between bone mineral content and PTH values; $r = -0.83$, $p = 0.01$
7. Conclusions: exercise program for healthy preterm infants may promote positive weight gain and increased bone mass

Since the original study, Moyer-Mileur and others have repeated studies in the effort to replicate, support, and expand on the original findings.

Joint compression and range-of-motion as exercise therapies (Table 1)

Moyer-Mileur, Brunstetter, McNaught, Gill, and Chan (2000) studied 32 neonates comparing range-of-motion (ROM) and joint compression (JC) as exercise regimens against positive touch and the effects of each intervention on bone mineralization and growth. Aly et al (2004) took a somewhat different approach in adding short periods of massage therapy to the exercise group, and removing the purposeful positive touch from the control group.

Moyer-Mileur et al (2000) was the first to utilize a DEXA scanner to determine bone mineral density and content in premature neonates. With 16 neonates in each group matched for gestational age and birth weight, each randomly assigned to either the EX and to the C group. In addition to the standard measurements of growth parameters, other indices of bone mass were collected. The biomarker of bone formation for this study was serum type I collagen C-terminal

propeptide (PICP): The biomarker for bone resorption was urine pyridinoline cross-links of collagen (Pyd). Additionally, standard nutritional lab values for VLBW neonates were obtained as well as PTH levels. All measurements were made at the beginning of the study and again when each neonate reached two kilograms (2 kg) in weight. Study eligibility included 1) birth weight 800-1600 grams, 2) GA 26-32 weeks, 3) AGA, 4) tolerating enteral feeds of $\geq$110 kcal/kg/day, 5) no medications other than vitamin supplements, and 5) parental consent. All neonates were fed either breastmilk with Enfamil Human Milk Fortifier 24 cal/oz or Enfamil Premature Formula 24 cal/oz.

Data analysis utilized descriptive statistics, independent t-Test, ANCOVA, and correlation and linear regression. Ad hoc data comparison was analyzed in four stages including birth to study entry, study entry to 1.5 kg, 1.5-1.8 kg, and 1.8-2 kg. The purpose was to delineate if other factors such as catch-up growth were the main reasons behind weight increases as opposed to the study exercise regimens. A synopsis of the study results includes:

1. Similar body measurement throughout the study.
2. The EX group demonstrated greater daily weight gain from study entry to 2 kg compare to C group (16.3 ± 2.6 vs. 14.6 ± 2 gr/kg/d, $p < 0.02$).
3. EX group had greater forearm length, bone area, and bone mineral content at 2 kg ($p = \leq 0.05$, *t*-test).
4. Serum chemistry results were comparable. Pyd levels did not change in either group.
5. EX group experienced a stable PICP while the C group experienced a significant decrease in PICP (between-groups $p = 0.05$, ANCOVA).
6. Conclusions suggest a lower rate of bone mineralization in the C group, thus supporting neonatal physical exercise programs for VLBW neonates who are stable on excellent nutrition.

Aly et al (2004) also considered physical exercise with the combination of JC/ROM to be superior. In addition, his study added five minutes of massage to the EX group. The C group did not receive anything specific for this study. This double-blinded randomized trial included 30 neonates, 15 in each group. Inclusion criteria were 1) GA $\leq$ 35 weeks, 2) post-natal age < 2 weeks, 3) tolerating full enteral feeds, 4) no medications other than vitamin supplements, and 5) parental consent. Exclusion criteria included congenital malformations, asphyxia, or musculoskeletal, liver, or renal diseases. The EX group received five repetitions of JC/ROM on each extremity per the Moyer-Mileur design plus another five minutes of massage. The intervention routine was performed once each day by the same physician from study entry until attainment of 1.8 kg.

Growth parameters, standard nutritional labs, and PTH levels were followed. Bone biomarkers included serum PICP and urine Pyd. All information was documented at study entry and at 1.8 kg. Data analysis methods included *t*-Test, ANOVA, and linear regression. A synopsis of the study results includes:

1. No difference in GA or birth weight between groups
2. Over time, urine Pyd increased for both groups with the results having no statistical significance.
3. EX group serum PICP increased while C group serum PICP decreased (statistically significantly, $p = 0.0001$).
4. Serum alk phos levels did not change significantly between the groups.
5. Conclusions indicate increased bone mineralization among EX group neonates receiving JC, ROM, and massage compared to C group neonates receiving no specified touch.

Range-of-motion only as exercise (Table 2)

ROM-only has been utilized as the basis for two studies whose purpose was to test the effect of length of treatment. Litmanovitz et al (2003) researched the effects of ROM vs. positive touch on bone strength of VLBW neonates. The study compared extremity ROM five days per week for four weeks vs. positive touch of the same duration. Each group consisted of 12 neonates meeting the eligibility criteria of 1) birth weight < 1500 grams, 2) AGA, 3) postnatal age < 1week, and 4) parental consent. This study excluded neonate with major congenital anomalies, severe central nervous system disorders, or intrauterine growth retardation. Of note, this is one of the first studies to consider exercise in the first week of life regardless of enteral feeding status or medications prescribed.

Participant information was tracked for age, weight, feeding status, and oxygen needs. Specific markers of bone strength for this study included bone-specific alkaline phosphates (BSAP, same as BALP). Bone resorption was tested with serum carboxy terminal cross-links telopeptide of type-I collagen (ICTP), which reflects osteoclast activity. Lastly, bone mineralization was measured using Quantitative Ultrasound (QUS) to assess the Speed of Sound (SOS) through the left tibia. Statistical analysis was completed utilizing unpaired *t*-Test and 2-way repeated measures ANOVA with level of significance set at $P < 0.05$. A synopsis of the study results includes:

1. No difference in birth weight, GA, gender, ethnicity, morbidities, or days to full enteral feedings.
2. No significant differences at the beginning of the study in the body measurements or tibial SOS.

3. Differences in bone growth of both groups during the study were not statistically significant.
4. Tibial SOS remained steady in the EX group but decreased in the C group significantly ($p < 0.006$).
5. Both groups experienced increases in BSAP with concurrent decreases in ICTP; intergroup differences were not significant.
6. Conclusions suggest an attenuation of decreased bone SOS in VLBW neonates.

This study did not demonstrate increased bone health benefits of previous studies. Possible rationale include the use of a newer bone measuring device (QUS-SOS) which considers factors such as bone elasticity in its calculations. Another difference was the inclusion of VLBW neonates who were not yet on enteral feeds or who were still receiving medications which potentially interfered with calcium deposition in the bones. Lastly, joint compression was not utilized as an intervention.

As a follow-up, Litmanovitz, Dolfin, Arnon, Regev, Nemet, and Eliakim (2006) replicated the Litmanovitz et al (2003) study in its entirety with the exception of lengthening the intervention to eight weeks in duration. The purpose was to determine an optimal duration of an exercise program. Inclusion/exclusion criteria, statistical analysis, and measurements of bone strength/turnover were unchanged from the previous study. The EX and C groups had eight participants each. Characteristics of the participants in each group were matched and without statistical differences. A synopsis of the study results includes:

1. Increase in EX group tibial SOS with corresponding decrease in C group tibial SOS (between-group difference $P = 0.01$)
2. Most of the tibial SOS change in both groups occurred in the first four weeks

3. Less dramatic changes in tibial SOS continued to occur throughout the second four weeks
4. Unable to document positive effects on weight gain when exercise regimen is started early in life
5. Tibial SOS stability in EX group occurred without significant gains in weight.
6. Conclusions suggest a positive outcome from early exercise intervention, in this case stability of bone without growth gains.

Possible rationale for lack of growth gains in this study includes the participation of VLBW neonates within the first week of life. During this time, the VLBW neonate can be expected to lose 10-15% of birth weight via extracellular water contraction. Furthermore, VLBW neonates are usually under a fluid restriction, and must work up to full enteral feedings gradually (Cunningham, 2009). These factors may mask exercise-related weight gains during the first several weeks when VLBW neonates begin an exercise program during the first week of life. Again, JC was not utilized.

Range-of-motion only as exercise with maternal involvement (Table 3)

The final study took a different approach to testing neonatal exercise. Moyer-Mileur, Ball, Brunstetter, and Chan (2008) tested the effects between EX participants with ROM delivered by the mother (MOM group), EX participants with ROM delivered by an occupational therapist (OT group), and C group participants receiving positive touch. The purpose of the study was to determine if neonatal exercise could be safely and effectively provided by a parent. Eligibility criteria included 1) gestational age 26-31 weeks, 2) AGA, 3), tolerant of feedings of fortified breastmilk > 110 kcal/kg/day, 4) no medications other than vitamin supplements, and 5) parental

consent. EX group neonates received extremity (six joint) ROM from either the mother or an OT. C group neonates received five minutes per day of dedicated positive touch. Eligible neonates were randomized into groups until there were 11 participants in each group. Each participant was studied from entry into the study until attaining a body weight of 2 kg.

Data collection included the usual birth information and growth parameters along with nutritional data including serum lab studies of nutrition. Biochemical bone markers included serum BSAP for bone formation and urine Pyd for bone resorption. Bone strength measures were obtained utilizing a portable DEXA scanning of the right radius and ulna. Mothers involved in the study were taught ROM by the OT's and also received weekly reviews. Mothers maintained diaries to document the ROM sessions. Data analysis included descriptive statistics, ANOVA, linear regressions, and the use of one-tailed significance of 0.05. Data was collected at study entry and upon reaching 2 kg in weight.

All groups were matched for age, birth weight, ethnicity and growth measurements. Energy and dietary intake were similar, and number of exercise/touch session was equal among all groups. A synopsis of the study results includes:

1. No difference in growth rate (gr/kg/d), head, or length measurements before or during the study period.
2. BSAP remained constant for MOM and OT groups but was significantly lower in the C group by 2 kg of weight ($P = 0.04$) although all results were within normal limits.
3. No differences in Pyd levels among groups.

4. At 2 kg, bone area of right forearm was greater in MOM and OT groups (P = 0.03). Size-adjusted gains for bone area and bone mineral content from baseline to 2 kg were significantly greater in the MOM and OT neonates ($P \leq 0.001$) vs. the C group neonates.
5. Conclusions suggest effectiveness of maternal-mediated exercise programs within the VLBW population, and also reiterate the value of exercise on bone growth and mineral acquisition during the early weeks of postnatal life.

Interpretations, Considerations, and Recommendations

A certain logic exists when considering the potential positive impact of exercise on bone development and strength. A rational assumption is anything replicating movements and bone stressors of the in utero environment must be valid interventions for bone health of VLBW neonates. Yet research thus far has not been overwhelmingly consistent in supporting these assumptions. Several reasons can be considered, most of which pertain to lack of standardization in screening and diagnosis.

Lab studies are a weak area in the OOP arena. Without a consensus as to what constitutes OOP, it is difficult to accurately interpret the current research. PTH is becoming a common biomarker in research: It is recommended to become a routine nutrition lab value for the VLBW neonate. PTH levels are particularly valuable when serum calcium is monitored. The PTH level informs the provider if the serum calcium is maintained secondary to increased bone resorption. Calcitonin is a hormone whose action is to impede bone resorption and renal filtration of calcium (Williford, Pare, & Carlson, 2008). Calcitonin does not directly increase mineral deposition into

bone matrix; therefore this hormone level would of little value in the screening and management of OOP.

Alkaline phosphotase is a commonly used diagnostic lab value. Significant elevations are widely accepted as proof of OOP. However, even an elevated alkaline phosphotase can be deceiving. Alk phos is a total measure of three types of phosphotase; bone, liver, and intestinal. A rise in any type can raise the total result. Bone phosphotase is further separated into subtypes—one released when building bone and one released when remodeling bone—and can increase as a result of either bone mineralization or bone remodeling (Land & Schoenau, 2008). Therefore, total alk phos can rise in response to bone mineralization, not just born resorption (Williford, Pare, & Carlson, 2008). A more sensitive measure is bone-specific alkaline phosphotase (BSAP or BALP).

BALP is found on the surface of osteoblasts, and is released into the bloodstream during matrix formation (So & Ng, 2005). Therefore, an elevated BALP in light of an elevated alk phos would point towards active bone building rather than bone remodeling and poor nutritional status as the reason for an elevated alk phos (Lam, So, & Ng, 2007). It is recommended to add BALP levels when alk phos reaches the standard threshold for OOP.

Standard testing parameters for research studies do not exist, again increasing the difficulty of determining the value and relevancy of the study conclusions. Comparing study results based on calcium/PTH levels to study results based on PICD/Pyd levels is an exercise in futility. The same holds true when comparing bone measurements by various instruments such as DEXA, pDXA, single-beam photo absorptiometry, standard radiograph, and QUS-SOS. Each instrument measures somewhat different parameters. And some experts question what “good bones” really mean to the VLBW neonate. Does it mean heavy bones, as in high bone mineral density? Or does is mean

stable bones, as in bone area and bone mineral content? Again, no consensus exists to apply to the available studies or to current practice.

Early studies showing the most benefits from exercise including joint compression were limited to healthy preterm neonates who were no longer dealing with other OOP risk factors (TPN, diuretics, corticosteroids, methylxanthines, feeding intolerance, etc). Studies are now capturing the VLBW population at the very beginning of their lives in the NICU. This may explain the seemingly "less convincing" results of late. Or it could also signal a reduced impact of exercise so early in life. It is these questions and others which require more focused research. Multi-center double-blinded RCT's with larger numbers of participants would lend more strength to the conclusions as well. At the current time, it is recommended for NICUs to continue with the exercise/joint compression protocol already in place, as no study has documented negative participant effects secondary to the exercise protocol. VLBW neonates should also receive at least 400 IU of vitamin D daily to promote proper metabolism of calcium intake (Land & Schoenau, 2008).

Parental/family education and support

In the spirit of informed consent, all parents of VLBW neonates should be informed of potential risks for their infants. OOP is one of those risks. Part of the discussion should include measures undertaken by the provider and NICU staff to minimize the OOP risk and/or treat OOP once diagnosed. Discussing the side effects of OOP such as fractures is considered part of open family communication. Offer parents up-to-date printed information to discuss with other support persons. A quality website such as MedlinePlus at http://www.nlm.nih.gov/medlineplus offers families the ability to search osteopenia of prematurity and obtain information as well as

radiographical images of this disease. OOP is just one of many concerns facing the VLBW neonate and their families. Compassionate care and family counseling are often helpful in managing feelings of grief, negotiating cultural concerns, coping with financial worries, and identifying changes in family dynamics (Subramanian, Barton, & Muntazami, 2001). Referring the parents to a unit-based social worker or parent advocate would be appropriate.

Professional staff resources

Staff knowledge and expertise is exceedingly important in the care of the VLBW neonate and the family. Professional staff in all roles has an abundance of resources to utilize. An easy resource to access is online search engines; just spell out the disease name rather than using OOP. Searching for osteopenia of prematurity in Google Scholar brings up journal and research articles from the past 20-30 years. Providers can appreciate the historical perspective of the discovery and development of OOP as a disease entity. Furthermore, NICU staff can access high-quality neonatal care reference books by editors/authors such as Fanaroff et al, MacDonald et al (Avery), Gomella et al, and Cloherty et al.

Conclusions

Prematurely born infants face extended hospitalizations and risks of further medical problems. These risks increase when the neonate is born during the second trimester and is of very low birth weight. In particular, osteopenia of prematurity becomes a greater concern secondary to the neonate's lack of exposure to the hypercalcemic circulation of the third trimester. Solid strides have been made to lessen the occurrence and severity of OOP in the VLBW population. Increased calcium and phosphorus intake is possible with the routine use of fortified breastmilk to 24 cal/oz and/or specialized 24 cal/oz premature formula. Regular administration of vitamin D is an

emerging intervention in consideration of its role in calcium metabolism and bone mineralization. Patient management geared towards earlier enteral feedings is helpful, especially when one considers there was once a time in neonatal history when neonates were not enterally fed if an umbilical artery catheter was in place.

The next significant step is sorting out the role of joint compression and other forms of exercise therapy. The world of neonatology is constantly trying to "recreate the womb" in hopes of reducing morbidity and mortality. The type and intensity of fetal movement in utero has yet to be replicated ex utero or solidly proven to be beneficial. Range-of-motion only studies fail to consider weight-bearing movement in utero. Large number, multi-center, double-blinded RCT's are needed to assist in defining "normal" and "standard" in OOP assessment and management. Only then will the neonatal community be able to develop best-practice standards and interventions. Toward that goal, it need not be left to interested physicians, occupational therapists, and/or nutritionists to move forward. As active, engaged team members in the primary care management of premature neonates, it is the rightful place and responsibility of today's NNPs to lead research efforts in the prevention and management of osteopenia of prematurity.

Table 1

AUTHOR (YEAR) **JOURNAL** **STUDY LOCATION**	Moyer-Mileur, Brunstetter, McNaught, Gill, & Chan (2006) *The Journal of Pediatrics* University Hospital, Salt Lake City	Aly, Moustafa, Hassanein, Massaro, Amer, & Patel, (2004) *Journal of Perinatology* Ain Shams University Hospital, Cairo
DESIGN **COHORT** **# OF SUBJECTS**	Randomized clinical trial; data collected until attainment of 2kg in weight (ave. 26.8 EX, and 23.8 C) BW: 80-1600 gr CGA: 26-32 wks Enteral fds: ≥110kcal/kg/d Meds: vitamins only n=16 each EX & C groups	Prospective double-blinded randomized trial; data collected until attainment of 1.8kg in weight CGA: 28-35 wks BW mean: 955g PNA: < 2wks Enteral fds: full Meds: vitamins only n=15 each EX & C groups
INTERVENTIONS OF STUDY	EX group: Joint compression & ROM to four extremities, 5 repetitions each movement daily C group: 5 minutes per day of holding/stroking	EX group: joint compression, ROM, massage x5 repetitions daily C group: no focused tactile touch or intervention
RESULTS	EX group: -greater wt gain from start of study to 2kg in weight -greater forearm length, bone area, bone mineral content at 2kg -no change in PICP levels (bone deposition) whereas C group had decreasing PICP levels	EX group: -increased and significantly higher PICP levels at end of study (bone deposition) -same alk phos/Pyd levels throughout (bone resorption) -increased PTH level compared to C group
LIMITATIONS **RECOMMENDATIONS**	Limitations: low number of participants, testing the healthiest VLBW, unblended, limited ability to generalize. Recommendations: common sense interventions from a bone physiology perspective; blinded randomized RCT's with large numbers needed to confirm results and refine interventions	Limitations: study not specifically geared to premature; unknown parameters such as average number of day on the study of each group, low number of participants Recommendations: common sense interventions from a bone physiology perspective; questionable relevance without knowing average gestational age of cohorts

Table 2

AUTHOR (YEAR) **JOURNAL** **STUDY LOCATION**	Litmanovitz et al (2003) *Pediatrics* Meir General Hospital, Kfar Saba, Israel	Litmanovitz et al (2006) *Calcif Tissue Int* Meir Medical Center, Kfar Saba, Israel
DESIGN	Randomized clinical trial; data collected for four weeks	Randomized clinical trial; data collected for eight weeks
COHORT	BW: < 1500 gr, AGA PNA: < 1 wk	BW: < 1500 gr, AGA PNA: < 1 wk
# OF SUBJECTS	n=12 each EX & C groups	n=8 each EX & C groups
INTERVENTIONS OF STUDY	EX group: ROM to four extremities, 5 repetitions each movement once daily, five time per week x4 wks C group: 5 minutes per day of focused holding/stroking, QD, 5x/week, x4 wks	EX group: ROM to four extremities, 5 repetitions each movement once daily, five time per week x8 wks C group: 5 minutes per day of focused holding/stroking, QD, 5x/week, x8 wks
RESULTS	EX group: -no difference in initial or ending growth parameters (wt, lgt, OFC) vs. C group -stable tibial SOS vs. decreased in C group -no difference in biomarkers of bone turnover	EX group: -no change in tibial SOS although C group showed significant decrease -increased BSAP and decreased ICTP were not significantly greater than C group -most gains occurred in first four weeks
LIMITATIONS **RECOMMENDATIONS**	Limitations: low number of subjects, not blinded, Recommendations: blinded randomized RCT's with large numbers needed specifically to study younger, more unstable VLBW such as these participants	Limitations: low number of subjects, not blinded Recommendations: blinded randomized RCT's with large numbers needed specifically to study younger, more unstable VLBW such as these participants

Table 3

AUTHOR (YEAR)	Moyer-Mileur, Ball, Brunstetter, & Chan, 2008
JOURNAL	*Journal of Perinatology*
STUDY LOCATION	University Hospital, Salt Lake City
DESIGN	Randomized clinical trial
COHORT	BW: 800-1550 gr CGA: 26-31 weeks, AGA Enteral feeds: <110 kcal/kg/day of breastmilk fortified to 24 cal/oz Medications: none other than vitamin supplements
# OF SUBJECTS	n=11 each group MOM/OT/C
INTERVENTIONS OF STUDY	MOM: ROM to all extremities by the mother, five repetitions each daily until neonate reaches 2kg in weight OT: ROM to all extremities by the OT, five repetitions each daily until neonate reaches 2kg in weight C group: focused touch/stroking, five minutes per day, daily until neonate reaches 2kg in weight
RESULTS	-final body weight higher in MOM/OT groups, but daily rate of wt. gain no different vs. C group -MOM/OT groups exhibited greater forearm bone area at 2kg; also had greater gains in bone area and bone mineral content by 2kg -no difference in serum and urine biomarkers for bone turnover vs. C group -no difference in results between MOM group and OT group
LIMITATIONS	Limitations: small numbers in study make it difficult to generalize, lacks joint compression component, not blinded
RECOMMENDATIONS	Recommendations: large number, double-blinded RCT's are needed to properly research outcomes and establish outcome-based interventions.

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