### Introduction

More than 90% of peak skeletal mass is present by age 18 years. Bone mass accumulation in childhood and adolescence is a major determinant of peak bone mass and fracture risk, making childhood and adolescence a critical period for establishment of life-long bone health. Attainment of optimal peak bone mass by young adulthood is thought to be the best protection against osteoporosis in later life.

Osteoporosis is defined as a systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. Osteoporosis has historically been considered a disease that affects adults, however in recent years it has been increasingly recognized in children.

Long term use of glucocorticoids (GC) has been shown to have a damaging effect on the skeleton and is a recognized cause of osteoporosis. The widespread use of GC as an anti-inflammatory drug to treat a number of medical conditions has led to an increased incidence of GC induced osteoporosis.

The purpose of this Clinical Practice Guideline (CPG) is to assist clinicians in the prevention and management of glucocorticoid induced osteoporosis in children at SickKids using current knowledge. This is a dynamic topic with much study in progress.

### Target Population

**Inclusion criteria:**
- Child started on $\geq 0.15 \text{ mg / kg / day}$ of prednisone equivalent for a planned course of 3 months or more; and/or
- Child receiving intensive courses of glucocorticoid therapy often with additional pulse therapy over a period of months or years (e.g. Leukemia, Lymphoma or those with severe Graft vs. Host Disease).

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Approximate Equivalent dose (mg)</th>
<th>Half-life (Biologic) hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>5</td>
<td>8-12</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>4</td>
<td>8-12</td>
</tr>
<tr>
<td><strong>Intermediate-Acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MethylPREDNISolone</td>
<td>0.8</td>
<td>18-36</td>
</tr>
<tr>
<td>PredNISOLONE</td>
<td>1</td>
<td>18-36</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>1</td>
<td>18-36</td>
</tr>
</tbody>
</table>
Maintaining Bone Health & Prevention of Glucocorticoid Induced Osteoporosis

<table>
<thead>
<tr>
<th></th>
<th>Long-Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>0.12 - 0.15</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Exclusion criteria:
- Chronic Kidney Disease - stages 3-5

Target Users:
- physicians, nurse practitioners, nurses, dietitians, physiotherapists and occupational therapists and other health care professionals who look after children with a potential risk of developing impaired bone health due to glucocorticoid use

Definitions
- **Glucocorticoid**: Any steroid-like compound capable of significantly influencing intermediary metabolism such as promotion of hepatic glycogen deposition, and of exerting a clinically useful antiinflammatory effect.
- **RDA - Recommended Dietary Allowance**: The average daily dietary nutrient intake level that is sufficient to meet the nutrient requirements of nearly all (97-98 percent) healthy individuals in a particular life stage and gender group.
- **RDI - Recommended Dietary Intake**: An informal term generated for the purpose of this policy to reconcile dietary guidance for the healthy population (RDAs: Level A evidence) with evidence (Level C) suggesting higher intakes of nutrients may be indicated for children with chronic disease.
- **Vertebral compression fracture**: Loss of 20% or more of vertebral height (thoracolumbar)
- **z-score**: number of standard deviations from the mean for a child of the same age, race and sex.
- **EOS**: Low dose anterior-posterior (AP) and lateral thorocolumbar x-ray that renders images in 3D. EOS has been shown to reduce radiation exposure up to 9 times that of standard x-rays (Descheness, S. 2010).
- **Biochemical markers of bone turnover**: Indirect indices of skeletal metabolism that rely on the measurement, in serum or urine, of enzymes, matrix proteins and collagen degradation products that are released into the body fluids during bone modeling and remodeling.
Recommendations

- Glucocorticosteroid therapy should be used for the minimal amount of time and at the minimal dose possible to provide a therapeutic effect for the patient's disease activity.

Prevention

Vitamin D & Calcium

- Despite existing Health Canada and Canadian Paediatric Society Guidelines, many children and adolescents do not take in enough vitamin D and calcium to meet recommended minimum daily requirements. As a result, vitamin D deficiency continues to be a problem among both healthy Canadian children and those with chronic disease. The addition of glucocorticoids further affects calcium and vitamin D metabolism increasing the potential for a deficiency. Although it has not been definitively proven that calcium and vitamin D therapy prevent osteoporosis in children, as a general health and nutrition measure, it is standard-of-care that a child's calcium & vitamin D intake and/or supplementation meet current guidelines.

- When starting glucocorticoid treatment, ensure total daily intake of vitamin D is 600-1000 IU. If Recommended Dietary Intake (RDI) is not met, a supplement may be required. Doses of 2-3 times the RDI may be indicated for children with chronic illness. (Holick, M.F. 2011) The purpose of this supplementation is to achieve a 25 OH vitamin D level between 50-125 nmol/L.

- Calcium intake should be assessed using a dietary history (questionnaire or Calcium calculator). If Recommended Dietary Allowance (RDA) for age range is not met through dietary intake, a supplement may be needed.

<table>
<thead>
<tr>
<th>Age (Yrs)</th>
<th>Calcium (mg)</th>
<th>Vitamin D (600-1000 units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>700</td>
<td></td>
</tr>
<tr>
<td>4-8</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>9-18</td>
<td>1300</td>
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</tbody>
</table>

Institute of Medicine, 2011, Holick, M.F. 2011

- Adequacy and potential complications of calcium and vitamin D intake and/or supplementation should be monitored. Blood work to assess safety and adequacy (calcium, phosphate, alkaline phosphatase, 25 OH vitamin D, PTH) & urine test (calcium, creatinine, osmolality) on a spot urine or 24 hour collection should be completed on initiation of long term glucocorticoid therapy, after 3 months and at least every 6 months while the patient remains on...
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glucocorticoids. Adjust supplementation accordingly based on results. See algorithm: “Monitoring Calcium & Vitamin D During Long Term Glucocorticoid Therapy” below.

- A high resolution renal ultrasound (U/S) should be considered if two urine samples show hypercalciuria (ca: creatinine ratio greater than 0.7). If the patient has hypercalciuria (using ca: creatinine) and a low muscle mass, confirm the hypercalciuria before undertaking the renal U/S using the formula below. (Richmond, W., 2005; Mir, S., 2005). If the high resolution renal U/S shows nephrocalcinosis refer to Nephrology.
  1. Convert calcium to non SI units first: mg/dL = mmol/L divided by 0.2495
  2. Convert to mg/L (multiple by 10)
  3. Divide by measured osmolality
  4. A value of greater than 0.25 correlates well with true hypercalciuria

Sample Ca/osmolality calculation:

Calcium = 11.87 mmol/L = Ca/0.2495 = 47.5 mg/dL x 10 = 475 mg/L
Creatinine = 5896 umol/L
Osmolality = 472 mosm/kg H2O
Ca/creat = 2
Ca/osmolality = 475/472 = 1 (i.e. true hypercalciuria)

- Consideration should be given to an annual dietary assessment by a Dietitian.
Child receiving calcium and vitamin D supplementation

Complete baseline blood work including: calcium, phosphate, 25 OH vitamin D, PTH, and urine (calcium: creatinine ratio)

While child is on steroids, recheck blood work and urine after 3 months and then at least every 6 months

Are all results within normal limits?

YES

Follow recommendations for abnormal results

NO

Continue with current diet and recommendations

Recommendations for abnormal blood work ranges

IF 25 OH Vit D < 50 nmol/L and PTH is normal

25 OH Vit D < 50 nmol/L → Add 1000 units

IF 25 OH Vit D < 50 nmol/L and PTH < 20 or > 50 ng/L

25 OH Vit D < 50 nmol/L → Add 1000 units
Dietitian to complete a nutritional assessment. Adjust calcium supplement as required.

IF 25 OH Vit D is normal and PTH < 20 or > 50 ng/L

Dietitian to complete a nutritional assessment. Adjust calcium supplement as required.

IF 25 OH Vit D > 125 nmol/L

Adjust Vitamin D intake accordingly based on PTH and urinary ca: creatinine ratio.
**Exercise**

The benefits of exercise on bone mass and bone strength have been shown in healthy children (Hind, K., 2007). Evidence shows that childhood and adolescence is an opportune period during which bone adapts efficiently to loading through weight bearing exercise. The optimal intervention program however has not yet been defined. There are currently no RCTs looking at exercise and bone health in children with diseases requiring the use of glucocorticoid treatment.

- Regular weight bearing exercise (e.g. physiotherapy, walking, skipping/jumping, etc.) should be encouraged as part of a management strategy for glucocorticoid induced impaired bone health.
- The level of activity should be individualized based on the child's level of sickness / disease stage.
- Aim to progress exercise as per Health Canada’s Physical Activity Guide for Children & Youth.

**Investigations**

**Diagnostic Imaging**

- A baseline Dual-energy X-ray Absorptiometry (DEXA) at L1-4 should be performed if a child is to receive greater than or equal to 0.15 mg/kg/day of glucocorticoids for 3+ months. DEXA is not routinely ordered for children less than 5 years of age due to the lack of normal values. An AP and lateral spine x-ray may be considered if the child is symptomatic (e.g. fractures).
- If z-score < -2 then add EOS (low radiation; lateral thoracolumbar spine).
- If z-score ≤ to -2 and/or compression fracture is present refer to bone health clinic for follow up and potential treatment.
- If patient remains on glucocorticoid treatment after 1 year, consider repeat DEXA.

**Bone Turnover Markers** (Bachrach, L. & Ward)

- There is currently no evidence to support the use of biomarkers of bone turnover in routine clinical care. (Thornton, J., 2008)
- Biomarkers of bone turnover may be considered for use with patients in conjunction with a research trial.
Treatment

- Bisphosphonates should only be used in exceptional cases unless a bone biopsy is completed which shows evidence of high turnover osteoporosis, due to lack of evidence regarding toxicity, long term bone health and timing of administration (early vs. late).

- For symptomatic compression fractures, referral to the Bone Health Clinic should be made for further assessment and treatment.
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Child requires steroid treatment
- Dose ≥ 0.15 mg/kg/day for ≥ 3 months
  - NO: Exclude from clinical pathway
  - YES: Complete dietary history
    - Diet meets RDA for vitamin D and calcium?
      - NO
        - Add calcium and/or vitamin D supplement
          - YES: Is child < 5 years?
            - YES: Complete bloodwork / urine
              - Within normal ranges?
                - NO: Follow recommended supplements as per Ca/vitamin D monitoring algorithm
                  - NO: Refer to Bone Health Clinic
                    - NO: Repeat bloodwork / urine at 3 months and then every 6 months while on steroids
                      - NO: At the child on steroids after 1 year?
                        - NO: Remove from CPG
                        - YES: Repeat DEXA annually while on steroids
                          - Z score ≤ -2 or compression fracture?
                            - NO: Complete EOS (low radiation)
                              - YES: Z score < -2
                                - NO: Complete DEXA
                                  - YES: Repeat DEXA
                                    - NO: Bone Health Clinic Referral Criteria
                                      - Child on glucocorticoids for > 6 months
                                        - BMD Z score < -2
                                          - Moderate to severe osteopenia on X spine
                                            - Compression fractures on X spine

- YES: Complete DEXA
  - Within normal ranges?
    - NO: Follow recommended supplements as per Ca/vitamin D monitoring algorithm
      - NO: Remove from CPG
      - YES: Refer to Bone Health Clinic

Normal Ranges
- 25 OH Vitamin D = 50 - 125 nmol/L
- PTH = 20 - 50 ng/L
- Urine calcium : creatinine ratio = 0.1 – 0.7

Recommended daily dietary intake (RDI) of calcium and vitamin D from all sources (total diet & supplement)

<table>
<thead>
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Bone Health Clinic: Referral Criteria
- Child on glucocorticoids for > 6 months
- BMD Z score < -2
- Moderate to severe osteopenia on X spine
- Compression fractures on X spine

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Related Documents

Clinician Tools
- [Calcium Calculator](BC Dairy Foundation, 2011)
- [Quick Reference Guide for Health Care Professionals](Bone Health Tracking Form)
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Patient / Family Education Resources

- AboutKidsHealth
- Osteoporosis Canada

Attachments:

References.docx

Monitoring Calcium and Vitamin D During Long Term Glucocorticoid Therapy_june 18.pdf

Maintaining Bone Health and Prevention of Glucocorticoid Induced Osteoporosis_june 18.pdf

Bone Health Tracking Form Dec 11.pdf

calcium calculator 2011.pdf

Quick Reference Guide Steroid Induced OP CPG Dec 11.pdf