Vitamin D deficiency

Synthesis and metabolism of vitamin D in the regulation of calcium, phosphorus, and bone metabolism

Vitamine D et Métabolisme Minéral et Osseux
Vitamin D deficiency

Metabolism of 25-Hydroxy-vitamin D to 1,25-Dihydroxy-vitamin D for Nonskeletal Functions

1. CASR cell surface G protein – coupled receptor; extracellular Ca^{++}
2. Vitamin D receptor nuclear receptor controlling gene transcription
3. Uncharacterized phosphate sensor
4. FGF23 is a negative regulator of parathyroid function

Quarles LD: Kidney Int 68 (S96): S24-S28, 2005

Universiteit Antwerpen
Consequences of phosphate accumulation in CRF

Behets G, PhD thesis, 2005
Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease:

Results of the study to evaluate early kidney disease


- Early increase of FGF23
- Decrease in Vit D receptors
- Decrease in Ca sensing receptors on PTH gland
- SECUNDARY HYPERPARATHYROIDISM

No relation to the renal mass
Hypocalciuria
Tendency to hypocalcemia
Activated injectable vitamin D and hemodialysis survival:  
A historical cohort study

1,25-Dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system

Effect of VDR inactivation on renin expression and plasma Ang II production

Effect of VDR inactivation on blood pressure and heart weight/body weight ratio

Li YC et al: JCI 110: 229-238, 2002
1,25-Dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system.

1,25-Dihydoxyvitamin D3 suppresses renin expression in wild-type mice.

Renin upregulation is independent of the calcium status.

Li YC et al: JCI 110: 229-238, 2002
Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency

Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency

Limitations:

- Patients were clinically stable with normal lipid status, no malnutrition, no inflammation
- Non-supplemented vitamin D deficient patients
- Observational nature of the study – hypothesis generating


FMD flow mediated dilation
Renoprotective role of the vitamin D receptor (VDR) in mice with streptozotocin (STZ)-induced diabetic nephropathy

Effect of vitamin D on RAS expression in mesangial and JG cells.

* P<0.05 vs. low glucose (LG)
* P<0.05 vs. high glucose (HG)

Renoprotective role of the vitamin D receptor (VDR) in mice with streptozotocin (STZ)-induced diabetic nephropathy

Effect of vitamin D on TGF-β and nephrin expression in cell cultures

* P<0.05 vs. low glucose (LG)
* P<0.05 vs. high glucose (HG)

Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response


Comparison of gene expression profiles in human primary monocytes and macrophages and dendritic cells

Infected cells Myc Tuberc.

TLR2/1L: Ligand: Mycob Tuberc derived peptide

Reduced viability

Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response


Monocyte response to 1,25(OH)$_2$D$_3$

Cath=Cathelicidin
Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response

Role of the vitamin D pathway in induction of cathelicidin mRNA and antimicrobial activity

TLR2/1 = toll like receptors
TLR2/1L = synt lipopeptide
VAZ = VDR antagonist

Sunlight treatment for tuberculosis

Brehmer & Trudeau

Niels Ryberg Finsen
Denmark
Nobel Prize 1903
Comparison of alfacalcidol and paricalcitol for treatment of secondary hyperparathyroidism in hemodialysis patients. A randomised cross-over study

**Alfacalcidol-Paricalcitol (AP)**
- n=34

**Paricalcitol-Alfacalcidol (PA)**
- n=37

Week 0-6 and week 22-28 were washout periods.

*P<0.05, unpaired t-test.

Comparison with baseline (week 6 in period 1 and week 28 in period 2)
- P<0.05, paired t-test for both AP and PA group.
- #P<0.05, paired t-test AP-group
- §P<0.05, paired t-test PA-group

Comparison of alfacalcidol and paricalcitol for treatment of secondary hyperparathyroidism in hemodialysis patients. A randomised cross-over study


Low baseline PTH ≤ 600 pg/ml:
- Alfacalcidol
  - n=24
- Paricalcitol
  - n=34

High baseline PTH > 600 pg/ml:
- Alfacalcidol
  - n=14
- Paricalcitol
  - n=8

*P<0.05 and high PTH groups
P<0.05 (unpaired t-test)
Comparison of alfacalcidol and paricalcitol for treatment of secondary hyperparathyroidism in hemodialysis patients.  
*A randomised cross-over study*

<table>
<thead>
<tr>
<th></th>
<th>Number (%) of patients</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alfacalcidol n=38</td>
<td>Paricalcitol n=42</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia (ionized calcium $&gt; 1.30$ mmol/l) at least once</td>
<td>21 (55%)</td>
<td>24 (57%)</td>
<td>0.866</td>
</tr>
<tr>
<td>Hypercalcemia (ionized calcium $&gt; 1.30$ mmol/l) at least two consecutive measurements</td>
<td>12 (32%)</td>
<td>16 (38%)</td>
<td>0.542</td>
</tr>
<tr>
<td>Hyperphosphatemia (phosphate $&gt; 1.80$ mmol/l) at least once</td>
<td>29 (76%)</td>
<td>29 (69%)</td>
<td>0.467</td>
</tr>
<tr>
<td>Hyperphosphatemia (phosphate $&gt; 1.80$ mmol/l) at least two consecutive measurements</td>
<td>17 (45%)</td>
<td>14 (33%)</td>
<td>0.296</td>
</tr>
<tr>
<td>Elevated $\text{Ca} \times \text{P} \geq 2.3$ mmol$^2$/l$^2$ at least once</td>
<td>25 (66%)</td>
<td>29 (69%)</td>
<td>0.756</td>
</tr>
<tr>
<td>Elevated $\text{Ca} \times \text{P} \geq 2.3$ mmol$^2$/l$^2$ at least two consecutive measurements</td>
<td>14 (37%)</td>
<td>16 (38%)</td>
<td>0.908</td>
</tr>
</tbody>
</table>
Short-term effects of vitamin D receptor activation on serum creatinine, creatinine generation, and glomerular filtration rate

Short-term effects of vitamin D receptor activation on serum creatinine, creatinine generation, and glomerular filtration rate

Short-term effects of vitamin D receptor activation on serum creatinine, creatinine generation, and glomerular filtration rate

HOW TO SUPPLEMENT?
### Recommended blood concentrations

<table>
<thead>
<tr>
<th>25 OH vitamine D</th>
<th>nmol/L</th>
<th>ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deficiency</strong> (1)</td>
<td>&lt; 25</td>
<td>&lt; 10</td>
</tr>
<tr>
<td><strong>Insufficiency</strong> (2)</td>
<td>25 - 75</td>
<td>10 - 30</td>
</tr>
<tr>
<td><strong>Aim</strong> (2)</td>
<td>75 - 125</td>
<td>30 - 50</td>
</tr>
<tr>
<td><strong>Hypervitaminose</strong> (3)</td>
<td>≥ 250</td>
<td>≥ 100</td>
</tr>
</tbody>
</table>

---

## Available Native Vitamin D

*G Jean et al, Néphrologie & Thérapeutique (2009) 5, 520—532*

### Tableau 1  Les vitamines D natives et le calcifédiol.

<table>
<thead>
<tr>
<th>Vitamine D</th>
<th>Spécialité</th>
<th>Dosage</th>
<th>Demi-vie</th>
<th>Posologie</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergocalciférol (vitamine D$_2$)</td>
<td>Sterogyl®</td>
<td>1 goutte = 400 UI = 10 µg</td>
<td>15–45 j</td>
<td>800–2000 UI/j</td>
</tr>
<tr>
<td></td>
<td>Sterogyl® 15</td>
<td>1 amp = 600 000 UI</td>
<td>15–45 j</td>
<td>1 amp 1–2 × /an</td>
</tr>
<tr>
<td></td>
<td>Uvesterol® D</td>
<td>1 ml = 1500 UI</td>
<td>15–45 j</td>
<td>800–2000 UI/j</td>
</tr>
<tr>
<td>Colécalciférol (vitamine D$_3$)</td>
<td>Zyma D®</td>
<td>1 goutte = 300 UI</td>
<td>600–1800 UI/j</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 amp = 80 000 et 200 000 UI</td>
<td></td>
<td>80 000 UI/1–2 mois 200 000 UI/3 à 6 mois</td>
</tr>
<tr>
<td></td>
<td>Uvedose®</td>
<td>1 amp 100 000 UI</td>
<td>15–45 j</td>
<td>1 amp/1–2 mois</td>
</tr>
<tr>
<td></td>
<td>Vitamine D3 Bon®</td>
<td>1 amp 200 000 UI</td>
<td>15–45 j</td>
<td>1 amp/2–3 mois</td>
</tr>
<tr>
<td></td>
<td>Dedrogyl®</td>
<td>1 goutte = 5 µg</td>
<td>18–21 j</td>
<td>$10–5 \mu g/j$</td>
</tr>
</tbody>
</table>

amp : ampoule.
### Table 3. (Continued.)

<table>
<thead>
<tr>
<th>Cause of Deficiency†</th>
<th>Preventive and Maintenance Measures to Avoid Deficiency</th>
<th>Treatment of Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary or tertiary hyperparathyroidism</td>
<td>800–1000 IU of vitamin D₃/day, 50,000 IU of vitamin D₂ every 2 wk (serum calcium levels will not increase), maintenance dose is 50,000 IU of vitamin D₂ every 2 or 4 wk;‡</td>
<td>50,000 IU of vitamin D₂ once a wk for 8 wk; repeat for another 8 wk if 25-hydroxyvitamin D &lt;30 ng/ml</td>
</tr>
<tr>
<td>Nephrotic syndrome²,³,⁶,⁷,⁹¹-⁹⁴</td>
<td>1000–2000 IU of vitamin D₃/day, 50,000 IU of vitamin D₂ once or twice/wk,²,⁹⁴ maintenance dose is 50,000 IU of vitamin D₂ every 2 or 4 wk;‡</td>
<td>50,000 IU of vitamin D₂ twice/wk for 8–12 wk;²,⁹⁴; repeat for another 8–12 wk if 25-hydroxyvitamin D &lt;30 ng/ml;‡</td>
</tr>
<tr>
<td><strong>Chronic kidney disease§</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stages 2 and 3</td>
<td>Control serum phosphate,⁶ 1000 IU of vitamin D₃/day, 50,000 IU of vitamin D₂ every 2 wk,²,⁹¹,⁹⁴ maintenance dose is 50,000 IU of vitamin D₂ every 2 or 4 wk; may also need to treat with an active vitamin D analog when vitamin D sufficiency is obtained;‡</td>
<td>50,000 IU of vitamin D₂ once/wk for 8 wk,⁹¹,⁹⁴; repeat for another 8 wk if 25-hydroxyvitamin D &lt;30 ng/ml;‡</td>
</tr>
<tr>
<td>Stages 4 and 5</td>
<td>1000 IU of vitamin D₃/day,²¹ 50,000 IU of vitamin D₂ every 2 wk, need to treat with 1,25-dihydroxyvitamin D₃ or active analogue;‡</td>
<td>0.25–1.0 μg of 1,25-dihydroxyvitamin D₃ (calcitriol)²,⁶,⁹¹,⁹₃,⁹₄ by mouth twice a day or one of the following: 1–2 μg of paricalcitol IV every 3 days,⁶,⁹¹,⁹₃,⁹₄ 0.04–0.1 μg/kg IV every other day initially and can increase to 0.24 μg/kg, 2–4 μg by mouth three times/wk,⁶,⁹¹,⁹₃,⁹₄ or doxercalciferol⁶,⁹¹,⁹₃,⁹₄ 10–20 μg by mouth three times/wk or 2–6 μg IV three times/wk</td>
</tr>
</tbody>
</table>
Armas L, Hollis B, Heaney R. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab 2004; 89: 5387-91

Holick MF, Biancuzzo RM, Chen TC et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxy vitamin D J Clin Endocrinol Metab 2008; 93: 677-681.
Effet du cholécalciférol 100 000 mensuel en dialyse

Table 2. Changes in vitamin D and mineral metabolism parameters

<table>
<thead>
<tr>
<th>Months</th>
<th>M-3</th>
<th>M0</th>
<th>M1</th>
<th>M3</th>
<th>M9</th>
<th>M15</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D (nmol/L) (range)</td>
<td>31 ± 11 (3–55)</td>
<td>32 ± 13 (7–56)</td>
<td>68.3 ± 19 (30–130)**†</td>
<td>97.7 ± 28 (45–198)**†</td>
<td>105.7 ± 28 (49–190)**</td>
<td>105.8 ± 27 (52–192)**</td>
</tr>
<tr>
<td>% 25(OH)D &gt; 75 nmol/L</td>
<td>0</td>
<td>0</td>
<td>46**†</td>
<td>82**†</td>
<td>88**</td>
<td>91**</td>
</tr>
<tr>
<td>1,25(OH)2D (pmol/L) (range)</td>
<td>14 ± 14 (4–56)</td>
<td>13.7 ± 14 (4–55)</td>
<td>23.8 ± 14 (4–70)**†</td>
<td>30.7 ± 14 (4–82)**†</td>
<td>49.2 ± 17 (13–88)**†</td>
<td>45 ± 13 (21–86)**†</td>
</tr>
<tr>
<td>PTH (pg/mL) (median, i.q. range)</td>
<td>254 (180–435)</td>
<td>295 (190–450)</td>
<td>249 (158–379)**†</td>
<td>220 (113–300)**†</td>
<td>200 (145–280)**†</td>
<td>190 (110–273)**†</td>
</tr>
<tr>
<td>BALP (μg/L) (range)</td>
<td>21 ± 10 (6–45)</td>
<td>20.5 ± 9 (7–41)</td>
<td>18.7 ± 9 (6–37)</td>
<td>16.5 ± 6 (6–35)**†</td>
<td>17 ± 7 (6–35)**†</td>
<td>17.1 ± 7 (6–35)**†</td>
</tr>
<tr>
<td>β-cross-laps (μg/L) (range)</td>
<td>2.5 ± 1 (0.8–6)</td>
<td>2.5 ± 1 (0.9–5)</td>
<td>2.27 ± 1 (0.6–5)</td>
<td>2.1 ± 1 (0.64–8)**†</td>
<td>2.05 ± 0.8 (0.7–4.2)**†</td>
<td>2.07 ± 0.8 (0.5–4.1)**†</td>
</tr>
<tr>
<td>Calcaemia (mmol/L) (range)</td>
<td>2.27 ± 0.14 (1.9–2.53)</td>
<td>2.24 ± 0.12 (2–2.5)</td>
<td>2.28 ± 0.1 (2–2.5)</td>
<td>2.28 ± 0.1 (2–2.5)</td>
<td>2.25 ± 0.1 (2–2.5)</td>
<td>2.25 ± 0.1 (2–2.5)</td>
</tr>
<tr>
<td>Phosphataemia (mmol/L) (range)</td>
<td>1.34 ± 0.3 (0.8–2.2)</td>
<td>1.32 ± 0.3 (0.8–2)</td>
<td>1.36 ± 0.3 (0.7–2.3)</td>
<td>1.33 ± 0.3 (0.7–1.9)</td>
<td>1.36 ± 0.3 (0.8–1.9)</td>
<td>1.31 ± 0.3 (0.8–2.1)</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.001 with the previous value, †P < 0.05 with the baseline value.
CONCLUSIONS: Pleiotropic effects of vitamin D

Vitamin D and analogs in mineral metabolism:

• Suppression of cell growth
• Regulation of apoptosis
• Modulation of immune response
• Control of insulin secretion
• Control of Calcium and P metabolism
• Tuberculosis
Meta-analysis: vitamin D compounds in chronic kidney disease

1. Based on current epidemiologic standards for assessing the validity of interventions, vitamin D is of unproven efficacy in CKD, except for its effects on some biochemical indexes

2. Newer vitamin D analogues have not been shown to be superior to established vitamin D compounds

3. Intravenous administration is unlikely to be superior to oral dosing

4. Biochemical and experimental data suggest that they may have opposing effects on mortality in this high-risk population, but they have been studied in only around 3000 people, with mortality reported in 8 trials (627 patients)

5. It is essential for the nephrology community to better address the effects of intervention with these widely used agents on patient-based outcomes

Conclusion

- Vitamin D is an hormonal system controlling many genes
- Many targets
- Favourable effect on survival
- Deficiency and insufficiency in CKD
- 1-alpha hydroxylase is ubiquitous
- substitution/supplementation using native Vitamin D
Apports alimentaires

Très peu d’aliments contiennent de la vitamine D en quantité significative

<table>
<thead>
<tr>
<th></th>
<th>Ration quotidienne nécessaire pour couvrir les besoins (^{(1,2)})</th>
<th>Ration hebdomadaire nécessaire pour couvrir les besoins (^{(1,2)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huile de foie de morue</td>
<td>1,5 cuillère à café</td>
<td>10,5 cuillères à café</td>
</tr>
<tr>
<td>Girolles</td>
<td>12 portions de 60 g</td>
<td>84 portions de 60 g</td>
</tr>
<tr>
<td>Harengs au vinaigre</td>
<td>2 portions de 60 g</td>
<td>14 portions de 60 g</td>
</tr>
<tr>
<td>Sardines à l’huile</td>
<td>20 sardines</td>
<td>140 sardines</td>
</tr>
<tr>
<td>Œuf dur</td>
<td>22 œufs moyens</td>
<td>154 œufs moyens</td>
</tr>
<tr>
<td>Foie de veau</td>
<td>50 tranches de 100 g</td>
<td>350 tranches de 100 g</td>
</tr>
<tr>
<td>Beurre</td>
<td>5 plaquettes de 250 g</td>
<td>35 plaquettes de 250 g</td>
</tr>
</tbody>
</table>

Trial quality in nephrology: how are we measuring up?

Renal articles in leading medical journals

- Journal of Clinical Investigation
- New England Journal of Medicine
- Nature Medicine

Al Quati Q, Snelders E, De Broe ME
Consequences of phosphate accumulation in CRF

Effect of Vitamin D deficiency

BONE
resorption

PARATHYROID GLAND

Ca++↑

PARATHYROID GLAND

5

BLOOD

Ca++↓

Ca++

PARATHYROID GLAND

4

KIDNEY
(RENAL FAILURE)

Ca reabs.↑

hypocalciuria

PARATHYROID GLAND

3

1,25(OH)2D3↓

INTESTINE

Ca++ abs.

PARATHYROID GLAND

2

Behets G, PhD thesis, 2005
Circulating 25(OH)D as a Function of Oral Vitamin D₃ Intake

![Graph showing the relationship between 25(OH)D levels and time, with different intake levels of Vitamin D₃ (10,000 IU/d, 5,000 IU/d, 1,000 IU/d, 400 IU/d).](image)
### Table: Serum Phosphorus Levels in CKD

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Treatment</th>
<th>Control</th>
<th>Random Weighted Mean Difference (95% CI)</th>
<th>Weight %</th>
<th>Random Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, n</td>
<td>Mean (SD)</td>
<td>Patients, n</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Established vitamin D vs. placebo</td>
<td>Coen et al., 1994 (48)</td>
<td>30</td>
<td>1.45 (0.29)</td>
<td>30</td>
<td>1.38 (0.32)</td>
</tr>
<tr>
<td></td>
<td>Morinibire et al., 1985 (42)</td>
<td>12</td>
<td>1.81 (0.45)</td>
<td>15</td>
<td>1.62 (0.39)</td>
</tr>
<tr>
<td></td>
<td>Przedlacki et al., 1995 (54)</td>
<td>13</td>
<td>1.63 (0.32)</td>
<td>12</td>
<td>1.32 (0.38)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>55</td>
<td>1.45 (0.29)</td>
<td>57</td>
<td>1.38 (0.32)</td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity: chi-square = 2.33 (P = 0.31), I² = 14.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newer vitamin D vs. placebo</td>
<td>Coburn et al., 2004 (32)</td>
<td>27</td>
<td>1.38 (0.21)</td>
<td>28</td>
<td>1.27 (0.21)</td>
</tr>
<tr>
<td></td>
<td>Martin et al., 1998 (38)</td>
<td>40</td>
<td>2.00 (0.64)</td>
<td>38</td>
<td>1.75 (0.53)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>67</td>
<td>1.38 (0.21)</td>
<td>66</td>
<td>1.27 (0.21)</td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity: chi-square = 0.94 (P = 0.33), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newer vs. established vitamin D</td>
<td>Hayashi et al., 2004 (36)</td>
<td>35</td>
<td>2.00 (0.52)</td>
<td>38</td>
<td>1.90 (0.52)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>35</td>
<td>2.00 (0.52)</td>
<td>38</td>
<td>1.90 (0.52)</td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous vs. oral vitamin D</td>
<td>Fischer and Harris, 1993 (33)</td>
<td>6</td>
<td>1.82 (0.32)</td>
<td>4</td>
<td>2.20 (0.40)</td>
</tr>
<tr>
<td></td>
<td>Caravaca et al., 1995 (79)</td>
<td>11</td>
<td>2.10 (0.44)</td>
<td>8</td>
<td>2.20 (0.36)</td>
</tr>
<tr>
<td></td>
<td>Indridason et al., 2000 (81)</td>
<td>19</td>
<td>1.57 (0.39)</td>
<td>17</td>
<td>1.66 (0.43)</td>
</tr>
<tr>
<td></td>
<td>Bacchini et al., 1997 (77)</td>
<td>10</td>
<td>1.69 (0.13)</td>
<td>10</td>
<td>1.78 (0.10)</td>
</tr>
<tr>
<td></td>
<td>Türk et al., 2002 (86)</td>
<td>14</td>
<td>1.87 (0.61)</td>
<td>13</td>
<td>1.87 (0.52)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>60</td>
<td>1.82 (0.32)</td>
<td>52</td>
<td>1.87 (0.52)</td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity: chi-square = 1.62 (P = 0.80), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent vs. daily vitamin D</td>
<td>Caravaca et al., 1995 (79)</td>
<td>8</td>
<td>2.20 (0.36)</td>
<td>7</td>
<td>2.32 (0.32)</td>
</tr>
<tr>
<td></td>
<td>Indridason et al., 2000 (81)</td>
<td>19</td>
<td>1.57 (0.39)</td>
<td>17</td>
<td>1.66 (0.43)</td>
</tr>
<tr>
<td></td>
<td>Moe et al., 1998 (40)</td>
<td>10</td>
<td>1.67 (0.58)</td>
<td>8</td>
<td>1.52 (0.29)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>37</td>
<td>2.20 (0.36)</td>
<td>32</td>
<td>2.32 (0.32)</td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity: chi-square = 1.15 (P = 0.56), I² = 0%</td>
<td></td>
<td></td>
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