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Vitamin D and Preschool Children – predictors of status and relationship with allergic and respiratory diseases in New Zealand

A thesis presented in partial fulfilment of the requirements for the degree of

Doctor of Philosophy
in
Nutritional Science

at Massey University, Albany
New Zealand

Carolyn Tina Cairncross
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Abstract

Background

The role of vitamin D in allergic and respiratory conditions is increasingly being recognised through an immune-modulatory role. The current evidence is inconsistent, with very limited data in preschool children, a target group with high prevalence of early childhood allergic and respiratory disease. There are little data on the vitamin D status and factors associated with vitamin D deficiency in the preschool age group in New Zealand. Knowledge of these factors can assist prediction of preschool children at risk of vitamin D deficiency, improving health outcomes.

Aims and Objectives

To describe the vitamin D status of a self-selected sample of preschool children and determine predictors of vitamin D deficiency in order to develop a predictive questionnaire to assess vitamin D deficiency in this age group, and to investigate the relationship of vitamin D status and prevalence of allergic diseases - eczema, food allergy, allergic rhinoconjunctivitis and asthma – and respiratory infections.

Method

A cross-sectional sample of 1329 preschool children aged 2 to <5 years from throughout New Zealand enrolled during late-winter to early-spring in 2012. 25-hydroxyvitamin D (25[OH]D) was analysed from dried blood spots collected using capillary sampling. Caregivers completed a survey describing their child’s demographics, factors known to affect vitamin D status and medical history of allergic and respiratory diseases. Predictors of vitamin D deficiency (25[OH]D <25nmol/L) were identified using multivariable logistic regression in a randomly selected sub-sample (n=929) for development of a predictive questionnaire, which was then validated by receiver operating characteristics (ROC) analysis (n=400).

Results

Mean (SD) dried blood spot 25(OH)D concentration was 52 (19)nmol/L. Vitamin D deficiency was present in 86 (7%) and vitamin D insufficiency (25[OH]D <50nmol/L) in 642 (48%)children. Factors independently associated with the risk of vitamin D deficiency were female gender (OR=1.92, 95%CI 1.17-3.14), children of other non-European ethnicities (not including Maori or Pacific)
(3.51, 1.89-6.50), children whose mothers had less than secondary school qualifications (5.00, 2.44-10.21), who had olive-dark skin colour (4.52, 2.22-9.16), who did not take vitamin D supplements (2.56, 1.06-6.18) and who lived in more deprived households (1.27, 1.06-1.53). There were no children who drank toddler milk with 25(OH)D concentrations <25nmol/L thus these children had a zero risk of vitamin D deficiency. The predictive questionnaire had low sensitivity for the identification of children at risk of vitamin D deficiency (sensitivity 42%, specificity 97%).

Children with 25(OH)D concentrations ≥75nmol/L had a two-fold increased risk for parent reported, doctor diagnosed food allergy (OR=2.21, 95%CI 1.33-3.68). No association was present between 25(OH)D concentration and prevalence of eczema, allergic rhinoconjunctivitis, asthma or respiratory infection.

**Conclusion**

Dried blood spot methods facilitated the measurement of 25(OH)D concentrations in a large sample of preschool children from throughout New Zealand. Prevalence of deficiency in winter was low (7%). The predictors of deficiency were consistent with those in previous studies of other age groups in New Zealand. The predictive questionnaire identified less than half of the children with vitamin D deficiency, so has limited diagnostic ability. In this sample of preschool children, vitamin D deficiency was not associated with allergic diseases or respiratory infections. In contrast, high vitamin D concentrations were associated with a two-fold increased risk of food allergy. This relationship between vitamin D status and allergic diseases is complex, and needs to be further investigated in the preschool age group.
Acknowledgements

I would like express my gratitude to my four PhD supervisors, firstly Pamela von Hurst and Cath Conlon from Massey University, for their advice, guidance and support throughout this journey. I wish to thank Welma Stonehouse for her continuous feedback and guidance, both at Massey University in Auckland and long-distance from CSIRO, Adelaide. My thanks to Cameron Grant, from The University of Auckland, for sharing his knowledge of paediatric allergy as well as his advice and encouragement throughout this PhD. I was fortunate to have the support of a distinguished group of co-investigators; Carlos Camargo, Jane Coad, Darryl Eyles and Lisa Houghton, I appreciate their scientific critique and advice. Barry McDonald was readily available with statistical guidance, and I thank him for his patience in navigating predictive questionnaires together.

Thank you to all the study participants, the willingness of so many parents to allow their children to be part of this study was humbling.

The support of pharmacists, and their staff, for this study continually amazed me. This study would not have been possible without the donation of their time, resources and goodwill. I also acknowledge and appreciate the support of Waitemata PHO and Te Puna Haora in allowing their B4School teams to participate in the study.

Conducting fingerpricks on young children proved a steep learning curve and created quite a community feeling. I would like to acknowledge and sincerely thank the many testers: over 100 pharmacy staff members, Dr Annie Judkins and Claudine Harvey (Wellington), Jenny McKenzie (Dunedin), the nurses of the B4School Check teams at Waitemata PHO and Te Puna Haora, and Cherie Wong, Peter Cairncross and Cath Conlon (Auckland). Lisa Houghton provided invaluable assistance in recruitment and testing in Dunedin, and I am very grateful for her support throughout the data collection period.

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When collecting data, one dreams of working in a well-oiled machine. I was extremely fortunate to have Cherie Wong, Sherina Holland and Pete as my co-workers with their unstinting work over the ten weeks contacting parents, sending letters, testing children and data-entry. Their quiet efficiency, chocolates and laughter made our recruitment and testing a success as well as a memorable experience, and they have my deepest gratitude.

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<th>Abbreviation</th>
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<tr>
<td>1,25(OH)$_2$D</td>
<td>1α,25dihydroxyvitamin D or calcitriol</td>
</tr>
<tr>
<td>25(OH)D</td>
<td>25-hydroxyvitamin D</td>
</tr>
<tr>
<td>AD</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>ALRI</td>
<td>Acute lower respiratory infection</td>
</tr>
<tr>
<td>AMP</td>
<td>Antimicrobial protein</td>
</tr>
<tr>
<td>APC</td>
<td>Antigen presenting cell</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CD28</td>
<td>Cluster of differentiation 28</td>
</tr>
<tr>
<td>CD4+</td>
<td>CD4 lymphocyte antigen</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence intervals</td>
</tr>
<tr>
<td>CYP27A1</td>
<td>Gene member of cytochrome P450 family</td>
</tr>
<tr>
<td>DBP</td>
<td>Vitamin D binding protein</td>
</tr>
<tr>
<td>DC</td>
<td>Dendritic cell</td>
</tr>
<tr>
<td>EASI</td>
<td>Eczema Area and Severity Index</td>
</tr>
<tr>
<td>FFQ</td>
<td>Food frequency questionnaire</td>
</tr>
<tr>
<td>FGF-23</td>
<td>Fibroblast growth factor</td>
</tr>
<tr>
<td>FOX P3+</td>
<td>Regulatory T cell</td>
</tr>
<tr>
<td>GINA</td>
<td>Global Initiative for Asthma</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Interferon γ</td>
</tr>
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<td>Immunoglobulin E</td>
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<td>IL-12</td>
<td>Interleukin-12</td>
</tr>
<tr>
<td>IU</td>
<td>International unit</td>
</tr>
<tr>
<td>ISAAC</td>
<td>International Studies of Asthma and Allergies in Childhood</td>
</tr>
<tr>
<td>LC-MS/MS</td>
<td>Liquid chromatography with tandem mass spectrometry detection</td>
</tr>
<tr>
<td>LRI</td>
<td>Lower respiratory infection</td>
</tr>
<tr>
<td>MED</td>
<td>Minimal erythemal dose</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger RNA</td>
</tr>
<tr>
<td>NESS</td>
<td>Nottingham Eczema Severity Score</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NMF</td>
<td>Natural moisturising factor</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>P450C1</td>
<td>1-α-hydroxylase gene</td>
</tr>
<tr>
<td>PBMC</td>
<td>Peripheral blood mononuclear cells</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RIA</td>
<td>Radioimmunoassay</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristics</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>RXR</td>
<td>Retinoid X receptor</td>
</tr>
<tr>
<td>SCORAD</td>
<td>SCORing Atopic Dermatitis</td>
</tr>
<tr>
<td>SMS</td>
<td>Short message service or text</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>Th</td>
<td>T Helper cell</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll like receptor</td>
</tr>
<tr>
<td>TNR-α</td>
<td>Tumor necrosis factor α</td>
</tr>
<tr>
<td>Treg</td>
<td>T regulatory cell</td>
</tr>
<tr>
<td>URI</td>
<td>Upper respiratory infection</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>UVB</td>
<td>Ultraviolet beta radiation</td>
</tr>
<tr>
<td>UVR</td>
<td>Ultraviolet radiation</td>
</tr>
<tr>
<td>VDR</td>
<td>Vitamin D receptor</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>ZO1</td>
<td>Tight junction protein</td>
</tr>
</tbody>
</table>
Contributions of the Study Team

<table>
<thead>
<tr>
<th>Study Team Member</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carolyn Cairncross</strong></td>
<td>Planned and managed the execution of the research, designed study questionnaire, obtained ethics approval, study manager, recruited and co-ordinated pharmacies, trained pharmacy staff, recruited participants, conducted research, analysed data, performed statistical analysis, interpreted the results, author of thesis</td>
</tr>
<tr>
<td><strong>Dr Pamela von Hurst</strong></td>
<td>Main supervisor of PhD, conceptualised and principal investigator of the research, compiled the study team, obtained HRC funding for the research, supervised development of questionnaire, initial contact and negotiations with Pharmacy Brands, contributed to training of pharmacy staff, revised and approved final thesis.</td>
</tr>
<tr>
<td><strong>Associate Professor Welma Stonehouse</strong></td>
<td>Co-supervisor of PhD; contributed to design of research and obtaining of funding, assisted with development of questionnaire, supervised statistical analysis of data, revised and approved final thesis.</td>
</tr>
<tr>
<td><strong>Associate Professor Cameron Grant</strong></td>
<td>Co-supervisor of PhD; assisted with development of questionnaire, advisor for paediatric, allergic and respiratory diseases, revised and approved final thesis.</td>
</tr>
<tr>
<td><strong>Dr Cath Conlon</strong></td>
<td>Co-supervisor of PhD, assisted with development of questionnaire, trained pharmacy staff, conducted fingerprick tests, revised and approved final thesis.</td>
</tr>
<tr>
<td><strong>Dr Barry McDonald</strong></td>
<td>Advised and assisted statistical analysis.</td>
</tr>
<tr>
<td>Study Team Member</td>
<td>Contribution</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tbody>
</table>
| **Associate Professor Darryl Eyles**  
Queensland Brain Institute, University of Queensland; Queensland Centre for Mental Health Research, Australia | Contributed to the design of the research, advised and assisted with the development of standard fingerprick procedures, developed and performed the biochemical tests for analysing 25(OH)D in dried blood spots. |
| **Dr Lisa Houghton**  
Nutrition Department, University of Otago, Dunedin, New Zealand                | Expertise in vitamin D in paediatric age groups, assisted with the development of questionnaire, recruited pharmacies in the Dunedin area of the South Island, recruited participants, trained pharmacy staff, conducted fingerprick tests. |
| **Associate Professor Jane Coad**  
School of Food and Nutrition, Massey University, Palmerston North, New Zealand   | Contributed to design of the research, recruited pharmacies in the Palmerston North area, trained pharmacy staff.                                                                                                                                                 |
| **Professor Carlos Camargo Jr**  
Department of Emergency Medicine, Massachusetts General Hospital, Boston, USA    | Expertise in vitamin D and allergic and respiratory diseases and consultant on research; assisted with design of the research, assisted with development of questionnaire.                                             |