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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

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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[H]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.

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List of Abbreviations

$1,25(OH)_2D$	1α,25dihydroxyvitamin D or calcitriol
25(OH)D	25-hydroxyvitamin D
AD	Atopic dermatitis
ALRI	Acute lower respiratory infection
AMP	Antimicrobial protein
APC	Antigen presenting cell
AUC	Area under the curve
BMI	Body mass index
CD28	Cluster of differentiation 28
CD4+	CD4 lymphocyte antigen
CI	Confidence intervals
CYP27A1	Gene member of cytochrome P450 family
DBP	Vitamin D binding protein
DC	Dendritic cell
EASI	Eczema Area and Severity Index
FFQ	Food frequency questionnaire
FGF-23	Fibroblast growth factor
FOX P3+	Regulatory T cell
GINA	Global Initiative for Asthma
IFN-γ	Interferon γ
IgE	Immunoglobulin E
IL-12	Interleukin-12
IU	International unit
ISAAC	International Studies of Asthma and Allergies in Childhood
LC-MS/MS	Liquid chromatography with tandem mass spectrometry detection
LRI	Lower respiratory infection
MED	Minimal erythemal dose
mRNA	Messenger RNA
NESS	Nottingham Eczema Severity Score
NHANES	National Health and Nutrition Examination Survey
NHMRC	National Health and Medical Research Council
NMF	Natural moisturising factor

NPV	Negative predictive value
NZ	New Zealand
OR	Odds ratio
P450C1	1-α-hydroxylase gene
PBMC	Peripheral blood mononuclear cells
PTH	Parathyroid hormone
PPV	Positive predictive value
RCT	Randomised controlled trial
RIA	Radioimmunoassay
ROC	Receiver Operating Characteristics
RSV	Respiratory syncytial virus
RXR	Retinoid X receptor
SCORAD	SCORing Atopic Dermatitis
SMS	Short message service or text
SNP	single nucleotide polymorphism
Th	T Helper cell
TLR	Toll like receptor
TNR-α	Tumor necrosis factor α
Treg	T regulatory cell
URI	Upper respiratory infection
US	United States
UV	Ultraviolet
UVB	Ultraviolet beta radiation
UVR	Ultraviolet radiation
VDR	Vitamin D receptor
WHO	World Health Organization
ZO1	Tight junction protein

Contributions of the Study Team

Study Team Member	Contribution
Carolyn Cairncross School of Food and Nutrition, Massey University, Auckland, New Zealand	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
Dr Pamela von Hurst School of Food and Nutrition, Massey University, Auckland, New Zealand	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.
Associate Professor Welma Stonehouse School of Food and Nutrition, Massey University, Auckland, New Zealand; CSIRO Food and Nutrition Flagship, Adelaide, Australia	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.
Associate Professor Cameron Grant Department of Paediatrics, University of Auckland; General Paediatrics, Starship Children's Hospital, Auckland, New Zealand	Co-supervisor of PhD; assisted with development of questionnaire, advisor for paediatric, allergic and respiratory diseases, revised and approved final thesis.
Dr Cath Conlon School of Food and Nutrition, Massey University, Auckland, New Zealand	Co-supervisor of PhD, assisted with development of questionnaire, trained pharmacy staff, conducted fingerprick tests, revised and approved final thesis.
Dr Barry McDonald Institute of Natural and Mathematical Sciences, Massey University, Auckland, New Zealand	Advised and assisted statistical analysis.

Study Team Member	Contribution
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.