Vitamin D: Current Controversies and Future Issues

Prof Susan Lanham-New

Food and Drink Science Member Interest Group Meeting
Thursday 8th January 2016
Campden BRI
Introduction to vitamin D
Vitamin D requirements in the UK
Background to the D2-D3 study
  • Challenging the long-held view of equality between D2 & D3!
  • Systematic Review and Meta-analysis
Study Objectives
Study Design
D2-D3 Main Study Results
  • 25OHD, PTH, 1,25OHD, VDBP, 4th visit
D2-D3 Genetic Study Results
  • DNA SNP Analysis and RNA Gene Expression
Study Conclusions
Impact – Food Industry, Academia, Public Health
Proposed D-FORTISBI Study
Those to thank!
Vitamin D - Introduction

- The term ‘Vitamin D’ is a misnomer: is not a ‘vital amine’ in the true sense of the word. It is a pro-hormone.

- Only nutrient where main source is not one of diet but UVB exposure

- UVB exposure must be at 290-315nm

- In the UK, we only make vitamin D from sunlight between April to September
RNI for Vitamin D was set by COMA in 1991 at zero ug/d for 4-64 years as it was considered enough vitamin D was made during the summer to last during the winter.
Public Health England’s New Vitamin D Recommended Intakes Were published on 22\textsuperscript{nd} July 2015
New vitamin D requirements are recommended to be 10 μg/400 IU
Title:
Interaction between diet and sunlight exposure on vitamin D status (25OHD) and functional markers of calcium metabolism and bone health in Asian and Caucasian women living in Southern England

Duration
Start: 1\textsuperscript{st} November 2005 for 48 months; £680k

D-FINES Study
Vitamin D, Food Intake, Nutrition and Exposure to Sunlight in Southern England
Key Findings from D-FINES Study

Caucasian women consistently higher 25OHD, with seasonal change. Considerable vitamin D ‘insufficiency’ in Caucasian women in late autumn and winter. Asian women extremely deficient throughout the year.

Mixed between-within subjects ANOVA: season x group p<0.001
The D-FINES study results may influence the decision on the RNI for vitamin D in three ways:

1) The lack of an RNI for vitamin D needs to be carefully considered for two reasons: (i) a significant percentage of the Caucasian population have vitamin D deficiency and ‘insufficiency’; (ii) current late spring/summer sunlight exposure appears to be inadequate for maintaining 25OHD levels in the late autumn and winter.

2) Food fortification could be one of the ways of raising dietary vitamin D intakes in the population as there are so few foods that naturally contain vitamin D.

3) A review of the RNI for the Asian population is urgently required as 10µg/d may not be high enough given the level of 25OHD that they are starting at.
Vitamin D –
generic term for two molecules:

1) Ergocalciferol (Vitamin D2) –
derived from UV irradiation of
ergosterol that is widely
distributed in plants and other fungi

2) Cholecalciferol (Vitamin D3) –
formed from the action of UV
irradiation on the skin: form
that is found in fish, eggs etc.
Background: Vitamin D2 vs. Vitamin D3

- Vitamin D₂ and D₃ undertake identical hydroxylation steps to make the end product of calcitriol (1,25(OH)₂D)

- Some data are available that show a difference in efficacy between D₂ and D₃ in raising 25(OH)D levels

- Three factors possibly influencing this:
  - Rate of conversion of D₂ to 25(OH)D
  - D₃ thought to have a higher affinity for DBP and VDR
  - D₃ potentially the preferred substrate for hepatic 25-hydroxylase

- Continued controversy - whether vitamin D2 and vitamin D3 give the same amount of change in 25OHD status when given as supplements or fortified in foods

Vitamin D prescriptions in the UK and the USA use vitamin D2 as the source.

All food fortification in the USA use vitamin D2 as the source.

US IOM Vitamin D Requirements Report & US Endocrine Society Report say D2 & D3 are the same!
Dietary Reference Intakes for Calcium and Vitamin D

Released: November 30, 2010

REPORT AT A GLANCE

- DRIs for Calcium and Vitamin D (HTML)
- Press Release (HTML)
- Report Brief (PDF, HTML)

Calcium and vitamin D are two essential nutrients long known for their role in bone health. But since 2000, the public has heard conflicting messages about other benefits of these nutrients—especially vitamin D—and also about how much calcium and vitamin D they need to be healthy. To help clarify this issue, the United States and Canadian governments asked the IOM to assess the current data on health outcomes associated with calcium and vitamin D, as well as updating the nutrient reference values, known as Dietary Reference Intakes (DRIs).

In this report, the IOM proposes new reference values that are based on much more information and high-quality studies than were available when the values for these nutrients were first set in 1997. The IOM finds that the evidence supports a role for vitamin D and calcium in bone health but not in other health conditions. Further, emerging evidence indicates that too much of these nutrients may be harmful, challenging the concept that "more is better."

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Details

- Activity: Dietary Reference Intakes for Vitamin D and Calcium
- Type: Consensus Report
- Topics: Food and Nutrition, Public Health

Committee Members
Ergocalciferol is the chemical name of vitamin D₂, which is a precursor (provitamin) form of vitamin D. Ergocalciferol is a secosteroid formed by a photochemical bond breaking of a steroid, specifically, by the action of ultraviolet light on ergosterol.

Ergocalciferol may be used as a vitamin D supplement, and a 2011 clinical guideline considered it to be as effective as cholecalciferol (vitamin D₃) which is produced naturally by the skin when exposed to ultraviolet light. It is manufactured and marketed under various names, including Delta-In (Eli Lilly and Company), Drisdol (Sanofi-Synthelabo) and Calciodol (Patrin Pharma).

Sources

1 Sources
2 Research concerning efficacy of vitamin D2 and D3
3 Preliminary research
4 References
5 External links

Lichen

- Chlidina arbuscula specimens grown under different natural conditions: The contents of vitamin D₃ range from 0.67 to 2.04 μg/g dry matter in the thalli of C. arbuscula specimens grown under different natural conditions, while provitamin
Fortification of orange juice with vitamin D₂ or vitamin D₃ is as effective as an oral supplement in maintaining vitamin D status in adults¹-⁴


Abstract
Background: Vitamin D has been added to calcium-fortified orange juice. It is unknown whether vitamin D is as bioavailable from orange juice as it is from supplements.

Objectives: The objective was to compare the bioavailability of vitamin D₂ and vitamin D₃ from orange juice with that from vitamin D₂ and vitamin D₃ supplements. A secondary aim was to determine which form of vitamin D is more bioavailable in orange juice.

Design: A randomized, placebo-controlled, double-blind study was conducted in healthy adults aged 18-84 y (15-20/group) who received 1000 IU vitamin D₃, 1000 IU vitamin D₂, or placebo in orange juice or capsule for 11 wk at the end of winter.

Results: A total of 64% of subjects began the study deficient in vitamin D (n, 25-hydroxyvitamin D [25(OH)D] concentrations <20 ng/ml). Analysis of the area under the curve showed no significant difference in serum 25(OH)D between subjects who consumed vitamin D-fortified orange juice and those who consumed vitamin D supplements (P = 0.064). No significant difference in serum 25(OH)D was observed between subjects who consumed vitamin D₂-fortified orange juice and vitamin D₂ capsules (P > 0.1). No significant overall difference in parathyroid hormone concentrations was observed between the groups (P = 0.82).

Conclusions: Vitamin D₃ and vitamin D₂ are equally bioavailable in orange juice and capsules.

Introduction

n 12-13 in each group but n 65 is needed
Within 48 hours of publication, submitted a (frank) letter to AJCN challenging the findings.

Co-authored with two key names in vitamin D;
• Prof Robert Heaney (USA)
• Prof Reinhold Veith (Can)

Strong rebuttal to 2 of the 3 BBSRC DRINC grant reviewers
Reply to S Lanham-New et al

Dear Sir:

We were pleased that Lanham-New et al appreciated that this article has important implications for health policy. It is, however, surprising and disappointing that these 3 experts did not fully understand the design, outcomes, and conclusions of our study. This study was designed to compare not only the bioavailability of vitamin D₂ and vitamin D₃ in orange juice with that in capsules, but it also was designed to confirm the previous report (1) that vitamin D₂ is equally as effective as vitamin D₃ in raising and maintaining total serum 25-hydroxyvitamin D [25(OH)D] concentrations. In our article (2), we clearly showed that serum 25-hydroxyvitamin D₂ [25(OH)D₂] and 25-hydroxyvitamin D₃ [25(OH)D₃] increased in identical fashion, and thus the results were not ambiguous—ie, vitamin D₂ was equally as effective as vitamin D₃ in both orange juice and in capsular form in vitamin D₃ or vitamin D₂ (Table 1). Therefore, on the basis of all of these analyses, it can be concluded with a high degree of certainty that vitamin D₂ is equally as effective as vitamin D₃ in raising and maintaining serum total 25(OH)D concentrations and that vitamin D₂ is equally as bioavailable as vitamin D₃.

None of the authors declared a conflict of interest.

Rachael M Biancuzzo
Michael F Holick

Endocrine Diabetes and Nutrition Section
Department of Medicine

Reply back
Mike Holick’s group was equally frank!

They reiterated their view re D2 & D3 being the same
The D2-D3 Study:
Ergocalciferol (vitamin D2) vs. cholecalciferol (vitamin D3) food fortification: comparative efficiency in raising 25OHD status in Caucasian & South Asian women


Grant No. BB/I006192/1
Grant Dates: April 2011 – March 2015
The D2-D3 Study

PRINCIPAL STUDY OBJECTIVES

• Compare the efficiency of 15µg/d [600IU/d] of vitamin D$_2$ (ergocalciferol) vs. vitamin D$_3$ (cholecalciferol) fortification of food products in raising 25OHD levels in South Asian/Caucasian women

• Determine which vehicle for fortification (i.e. a SOLID vs. FLUID food) with vitamin D$_2$ vs. vitamin D$_3$ is more effective in raising 25OHD levels, independent of ethnicity

• Investigate if 15µg/d is effective in raising wintertime 25OHD levels above the 25OHD thresholds of 25nmol/l and 50nmol/l respectively and if there are differences in vitamin D$_2$ vs. vitamin D$_3$ fortification

• Investigate the mechanisms (genetic/enzymatic) for the differences observed in (i), (ii) & (iii).
**BACKGROUND:** Vitamin D2 vs. Vitamin D3

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<tr>
<td>Romagnoli 2008-2 (5)</td>
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<td>30.3</td>
<td>8</td>
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<tr>
<td>Trang 1998 (4)</td>
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<tr>
<td>Total (95% CI)</td>
<td>194</td>
<td>150</td>
<td>100.0%</td>
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</table>

Heterogeneity: $\tau^2 = 162.74; \chi^2 = 47.10, df = 9 (P \leq 0.00001); I^2 = 81$

Test for overall effect: $Z = 3.28 (P = 0.001)$

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AJCN Editorial: pg.1299–300; Cited 75 times.

New D2-D3 meta-analysis will be presented by Dr Tripkovic at Nutrition Society 2015 Winter Conference, London.
BACKGROUND: Vitamin D2 vs. Vitamin D3

Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis

Laura Tripkovic, Helen Lambert, Kathryn Hart, Colin P Smith, Giselda Bucca, Simon Penson, Gemma Chope, Elinna Hypponen, Jacqueline Berry, Reinhold Vieth, and Susan Lantham-New

ABSTRACT
Background: Currently, there is a lack of clarity in the literature as to whether there is a definitive difference between the effects of vitamins D₂ and D₃ in the raising of serum 25-hydroxyvitamin D [25(OH)D].

D₂ or D₃? That is the question

Laura Tripkovic BSc (Hons), PhD, RD, Department of Nutritional Sciences, Faculty of Health and Medical Sciences, University of Surrey

D₂ or D₃? That is the question

Vitamin D is a nutrient vital to supporting skeletal health throughout the life stages. With vitamin D research rapidly expanding and interest increasing in both skeletal and non-skeletal benefits of vitamin D, gaps in knowledge have emerged. One of the most important questions at present is whether the two forms of vitamin D (vitamin D₂ and D₃) are equal in their physiological effect.

Metabolism of vitamin D
Whether vitamin D has been sourced from the diet or produced endogenously in the skin, vitamin D₂ and D₃ are both pro-hormones and so do not have a biological effect on the body when they initially enter the bloodstream⁷. Regardless of source, a two-step hydroxylation process is required to produce the active form of vitamin D – calcitriol⁸.

Nutrition Bulletin

Vitamin D₂ vs. vitamin D₃: Are they one and the same?

L. Tripkovic
Department of Nutritional Sciences, University of Surrey, UK

Summary
It is firmly established that humans need to obtain sufficient vitamin D in order to optimise calcium absorption and thus ensure robust skeletal health throughout the life stages. Vitamin D research is rapidly expanding, with significant interest in the


Circ. 35,000 healthcare professionals


Circ. 27,000

Associated editorial: pg.1299–300
Impact Factor: 6.7
Study Design

Cohort 1 ran October 2011 to March 2012
Cohort 2 ran October 2012 to March 2013

Week 0
- Informed Consent
- Height & weight
- Waist circumference
- Blood pressure
- Fasted blood sample
- pQCT scan of radius
- Food diary
- Dosimeter
- Assigned intervention products

Week 6
- Adverse event & compliance interview
- Weight
- Waist circumference
- Blood pressure
- Fasted blood sample
- Continue with intervention products

Week 12
- Adverse event & compliance interview
- Weight
- Waist circumference
- Blood pressure
- Fasted blood sample
- Food diary
- Dosimeter

Week 16
- Weight
- Waist circumference
- Blood pressure
- Fasted blood sample
Intervention Products
Randomisation of participants

Old study design

Screening
Check inclusion/exclusion criteria

Screening failures

Randomisation
Caucasian $n=348$, S.Asian $n=114$

Solid Food Product
*Biscuit consumed for 12 weeks*

Group A
600IU/15µg Ergocalciferol (Vitamin D$_2$)
Caucasian $n=58$, S.Asian $n=19$

Group C
600IU/15µg Cholecalciferol (Vitamin D$_3$)
Caucasian $n=58$, S.Asian $n=19$

Group E
Placebo
Caucasian $n=58$, S.Asian $n=19$

Liquid Food Product
*Juice drink consumed for 12 weeks*

Group B
600IU/15µg Ergocalciferol (Vitamin D$_2$)
Caucasian $n=58$, S.Asian $n=19$

Group D
600IU/15µg Cholecalciferol (Vitamin D$_3$)
Caucasian $n=58$, S.Asian $n=19$

Group F
Placebo
Caucasian $n=58$, S.Asian $n=19$

19, 404 juices
19, 404 biscuits
**TOTAL 38,808**

28,140 juices
28,140 biscuits
**TOTAL 56,280**
• Randomisation of participants

• New study design

**Screening**
- Informed consent
- Medical history & Screening bloods
- Check inclusion/exclusion criteria

**Randomisation**
- Caucasian *n=235*, S.Asian *n=70*

**Group A**
- BISCUIT: 600IU/15µg Ergocalciferol (Vitamin D₂)
- JUICE: Placebo
- Caucasian *n=47*, S.Asian *n=14*

**Group B**
- JUICE: 600IU/15µg Ergocalciferol (Vitamin D₂)
- BISCUIT: Placebo
- Caucasian *n=47*, S.Asian *n=14*

**Group C**
- BISCUIT: 600IU/15µg Cholecalciferol (Vitamin D₃)
- JUICE: Placebo
- Caucasian *n=47*, S.Asian *n=14*

**Group D**
- JUICE: 600IU/15µg Cholecalciferol (Vitamin D₃)
- BISCUIT: Placebo
- Caucasian *n=47*, S.Asian *n=14*

**Group E**
- JUICE & BISCUIT: Placebo
- Caucasian *n=47*, S.Asian *n=14*
• Randomisation of participants
• New study design

**Screening**
- Informed consent
- Medical history & Screening bloods
- Check inclusion/exclusion criteria

**Randomisation**
Caucasian \(n=245\), S.Asian \(n=90\)

**Group A**
- BISCUIT: 600IU/15µg Ergocalciferol (Vitamin D\(_2\))
- JUICE: Placebo
  - Caucasian \(n=47\), S.Asian \(n=17\)

**Group B**
- JUICE: 600IU/15µg Ergocalciferol (Vitamin D\(_2\))
- BISCUIT: Placebo
  - Caucasian \(n=49\), S.Asian \(n=18\)

**Group C**
- BISCUIT: 600IU/15µg Cholecalciferol (Vitamin D\(_3\))
- JUICE: Placebo
  - Caucasian \(n=51\), S.Asian \(n=19\)

**Group D**
- JUICE: 600IU/15µg Cholecalciferol (Vitamin D\(_3\))
- BISCUIT: Placebo
  - Caucasian \(n=49\), S.Asian \(n=19\)

**Group E**
- JUICE & BISCUIT: Placebo
  - Caucasian \(n=49\), S.Asian \(n=17\)
This study is the largest and most powerful study to have ever been conducted, focusing specifically on the comparison of efficacy between vitamin D2 and D3 on raising serum 25OHD levels.

Although both vitamin D2 and D3 raise and maintain serum 25OHD levels to within a healthy range during the winter-time (the most vulnerable season for vitamin D deficiency), the data proves that vitamin D3 is the most efficacious form.

This study also provides clear evidence that use of diverse food matrices – such as juice and biscuits – do not have a detrimental impact upon the bioavailability of either vitamin D2 or D3.

Gene expression analysis reveals differential-expression of many genes in diverse pathways and surprisingly that the response is different between D2 and D3 supplemented subjects. Not been found before!

New work now urgently required to look at food fortification in staple foods. Must be evidence based ...............
The D2 – D3 Study has provided:

- **The Food Industry:** which form & vehicle of vitamin D gives more value for money
- **The Scientific Community:** with detailed data on the mechanisms of action of any such differences.
- **The General Population:** with examples of how to improve vitamin D intakes through food fortification.

**REF 2020 Impact Cases:**

The D2 – D3 Study has achieved:

- **Four Awards:** including YI Award at UK Osteoporosis Conference & an Oral at 14th International conference on Vitamin D in the USA
- **57 Abstracts & Presentations:** with detailed data on the mechanisms of action of any such differences.
- **Training:** 12 UG, 4 PG project students as well as summer school student placements.
Further funding secured

‘Food-based solutions for Optimal vitamin D Nutrition and health through the life cycle’

- University of Surrey are WP4 leaders (Lanham-New, Hart & Tripkovic)
- Responsible for co-ordinating three RCTs in pregnant women, children (4-8yrs) and adolescents (14-18yrs) to be conducted at UCC, UniS and UCPH
- Taryn Smith, ODIN PhD Student 2014-2017

MoD Funded Vitamin D Research

- D-SAF – Vitamin D3 RCT in 5000 Royal Marines; 2014-2020
- D-SUB - Vitamin D Status Longitudinal Study in 4 Submarines 300 Submariners (24 wk study)
- MoD are looking at future food fortification for British Military
The D-FORTISBI Study

Vitamin D Fortification of Staple Foods: A Systems Biology Approach to Improving Vitamin D Status in the UK population

- Bread & Dairy Vitamin D Fortification including Chapatti Flour
- Caucasian, South Asians & Afro-Carribean populations groups
- Systems Biology Approach – both Gene Expression & Epigenetics
- Cost-benefit analysis and detailed Dissemination
D2-D3 Study Team

- University of Surrey – Dr Laura Tripkovic and Louise Wilson
  Dr Kath Hart, Dr Ruan Elliott, Dr Giselda Bucca, Dr Carla Moller-Levet, Dr Jo Sier, Dr Sig Johnsen, Prof Colin Smith

- University of Manchester – Dr Jacqueline Berry

- Campden BRI – Dr Simon Penson and Dr Gemma Chope

- Institute of Child Health, UCL – Prof Elina Hyppönen

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**BBSRC**

**DRINC • DIET AND HEALTH RESEARCH INDUSTRY CLUB**
Opportunities Thanks to BBSRC DRINC

Biosciences KTN Early Career Researchers Food Sector Event, 23rd May 2013
*LT & LW Prize Winners - a day at Nestle PTC (York)

LW attended Vitae UK GRADschool, 22nd-24th Oct 2013

LT & LW took part in BioMedical YES Workshop & Competition, 13th-15th Nov 2013

YI Award for LT at 2014 UK Osteoporosis Conference

LT – permanent Teaching Fellow (Research Active) position at

For LW, Sept-Dec 2015 at