



## Vitamin D in the Australian Aboriginal population in 2016

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## Abstract

**Objective:** To review recently published reports of calcifediol levels in Australian Indigenous people and adjudicate on their validity in the light of the current understanding of the validity of laboratory reports of its concentrations in the surveyed people.

**Methods:** A literature search within PubMed followed by professional application.

**Results and Conclusions:** Generally, both Australian Torres Strait Islander people and Aboriginal people are most likely calcifediol replete, with rare exceptions, the latter needing further study.

**Implications:** Most Indigenous Australians do not need vitamin D therapy; rare exceptions are noted. A diagnostic path forward is described.

## Prologue: the D vitamins

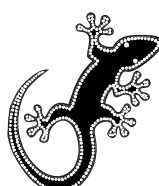
Vitamin D is vital to life. As well as its long-known role in the body's calcium economy it also has a wider variety of functions, including a role in the immune system with implications for the body's control of infection and allergic responses. Possible links with the cardiovascular system, in the glucose economy, and with one's susceptibility to cancer also have all been posited; research in these fields continues [1, 2]. The biochemistry of the D vitamins, *in vivo*, is well established and published in definitive texts such as that of Feldman [3].

The D 'vitamins' are not vitamins but are actually hormones. The D<sub>3</sub> precursor molecule, 7-dehydrocholesterol, with one hydroxyl component, is formed initially in the human liver and then modified in the skin in a process driven by sunlight, forming cholecalciferol, also known more simply as calciferol. That cholecalciferol returns to the liver to have a further hydroxyl element added, thereby forming calcifediol, and, in turn, calcifediol then travels to the kidney and a variety of other organs for the final step in the synthesis, adding a third hydroxyl and thus culminating in calcitriol, active vitamin D. The overarching hormonal controller within the calcium economy is parathyroid hormone, PTH. It and vitamin D both work to keep calcium and phosphate levels at metabolically optimal levels.

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The foetal calcium economy is similar to, but also different from that in the independent human. Calcifediol does transit the placenta but calcitriol does not. The foetal kidney can and does synthesise calcitriol from maternally sourced calcifediol but foetal calcitriol levels are low, likely due to suppression of the foetal renal  $1\alpha$ -hydroxylase by high serum calcium and phosphorus levels, those minerals actively transported across the placenta and found in higher concentrations in foetal blood than in the supporting maternal circulation, and also by low PTH. Within 2 to 3 days following delivery, the formerly foetal skin makes cholecalciferol, the calcium and phosphorus levels change to independent human levels, the free human calcium economy control system initiates and PTH rises. Within six months the newly independent infant's calcifediol concentration approximates that of adults [4].

The 'vitamin' D hormone molecules also can be synthesized commercially, *ex vivo*. Vitamin D<sub>3</sub> is marketed in pharmaceutical products, and can be found in fortified foods; it is also found in, for instance, fish, their liver and oils. Vitamin D<sub>2</sub> occurs in a variety of fruits and vegetables but is now a minor source for most humans. These two major forms, D<sub>2</sub> and D<sub>3</sub>, differ only in their side chain structure. Assays for use in Australia are deemed not to need the ability to recognise the D<sub>2</sub> form [5].

Vitamin D, being highly lipid soluble, is predominantly present in the blood stream attached to one of two carriage proteins thus effecting solubilisation. Approximately 90% is bound tightly to Vitamin D binding protein [DBP], and some 10% more loosely on albumin. DBP's history is neatly encapsulated at the OMIM website, where the historical aficionado will also find detailed references [6]. The 458-amino acid protein shares 25% and 19% sequence identity with albumin and alpha-fetoprotein, respectively, with the disulphide bridge pattern highly conserved between the three [7]. DBP evolved into being some 600 ±60 million years ago; our ancestors were then fish [8].

*In vivo* only 0.04% of the total 25(OH)D is thus present in the free form in the human blood stream, and 0.4% of 1,25(OH)<sub>2</sub>D [9]. Though the form 25(OH)D, calcifediol, is still at prohormone stage, it is more easily measured in the laboratory than is the fully formed hormone, 1,25(OH)<sub>2</sub>D, calcitriol, and is the analyte used in reference interval formulation.

How valid, in general, are the laboratory data reported to clinicians, and their patients? All the current guidelines and opinion pieces urge caution in interpreting laboratory reported results for vitamin D including Australasia's own Royal College of Pathology, the RCPA, in the pertinent Position Statement from May 2013 at its website [5]. Also in recent years several attempts have been made to establish, in particular, a representative view of where Australia's Indigenous people stand in the D scales. Are there challenges

specific to Indigenous people which may impact on the validity of their reported results, and thence on management decisions and advice?

This brief review attempts to survey and summarise the current state of our understanding of the vitamin D economy in Australia's Indigenous people. The subsequent sections defy a logically sequential arrangement. Each and all need reading before reaching a rounded conclusion; a little repetition is also unavoidable.

## Finessing 'the Indigenous'

It is necessary first to define the target population: *the Indigenous*. Australia has two distinct groups of Indigenous people, the Islanders of the Torres Strait, the TSI people, and the Aboriginal people; and, obviously, one may have ancestral roots in both groups.

Australia's Aboriginal people have been in the continent *ab origine populo*, most likely having arrived in smaller groups totalling in aggregate no more than maybe 500 people, 65,000 years ago, by sea from Timor during the then massive low stand of sea levels across the world [10]. Subsequently and quite rapidly, sea levels rose again and effectively totally isolated the small founder group of Aboriginal people for the next 60,000 years, leaving them, (and also, in their own smaller world, their New Guinean cousins), uniquely prone amongst all anatomically modern humans to prolonged genetic drift [11].

Further, sporadic genetic admixture into the Australian Aboriginal population did not begin until Asian peoples began visiting the north coast of Australia from perhaps as far back as ≥5,000 years ago, but was clearly limited to those coastal areas [12]. More intensive contact, apparently friendly and including trade, followed when Makassan trepang fishermen began seasonal work there from about the 1500s CE, ranging from what is now the coast off the Kimberley region of Western Australia, WA, to the Gulf of Carpentaria [13]. The massive admixture following the European and then Asiatic invasion from 1788 onwards involved and involves the entire continent although the Aboriginal people across the north of Australia and geographically deeper in to Australia's Northern Territory [the NT] are still most likely to be least so affected.

Indigenous Torres Strait Island people are largely Melanesian. They came down by sea from south east Asia, most likely from Taiwan, between 4,000 and 6,000 years ago and interbred, a little, with then locally present, coastal dwelling, people [14]. Their genetic heritage is different from that of the Aboriginal heritage.

Whilst calcifediol's molecular structure is the same in all humans, contrariwise, one's DBP gene and its protein product do vary, the variation indivisibly linked with one's ancestry. DBP, if ignored,

can confound the interpretation of laboratory results of assays of vitamin D, and has so done. A review of this entire subject has recently been published, initially electronically, in the *Annals of Clinical Biochemistry* where the supporting evidence is marshalled and referenced [15]. Ideally, to settle the matter, one's DBP should be genotyped, but that is not commonly done. Rather, we might look here at each individual's total ancestral input.

## Aboriginal DBP

Can we characterise Indigenous people's DBP? Serendipitously, a useful set of data facilitated by the initially English academic Robert L Kirk and the National Centre for Indigenous Genomics, the NCIG at the ANU, the Australian National University, answers this critical question. Kirk "...was the person responsible for collecting most of NCIG's biological samples ...including blood samples from Aboriginal people in the Kimberley and the Western Desert. ... [from] the late 1950s [and] until his retirement in 1986." [16]. The samples banked at the ANU were made available to later investigators including Mohammad Kamboh whose 1984 PhD thesis, Population genetic studies using isoelectric focussing in the Asian, Pacific and Australian area, Kirk supervised [17].

Kamboh published several papers from his thesis including a study of Aboriginal DBP [18]. He deployed isoelectric focussing in thin layer polyacrylamide gels, pH range 4-6.5, testing 216 from a wide range of central desert dwellers, 143 from the Kimberley in northern Western Australia, and 37 from Bathurst Island, north of Darwin. Utilising the subsequently discovered tight linkage between electrophoretic findings and the underlying genetic drivers we can be confident that the findings Kamboh submitted and published are entirely accurate.

The phenotypes GC 1/1, 1A1 and 1/2 account for 89% of all DBP he studied. The Australian variant, 1A1, the sole outstanding local variant seen, was first reported in 1963 and called GC Aborigine (GC-Ab) [19]. It occurred in the GC\*1F allele and as seen below

is far from uncommon. The African variant 1A1 was described in 1962 [20] and 1963 [21] and was originally called GC-Y. These two variants are indistinguishable by all methods for typing based on the physical properties of the protein and in studies of genomic DNA carrying the 1A1 variant from Australian Aboriginal people and from South African Bantu-speaking black people Kofler finally demonstrated that they are identical [22]. Amplification and sequencing of exon 11 showed in both cases that variant 1A1 has a point mutation in codon 429 at the second position. The finding of the same mutation in apparently widely separated ancestral groups raised the question as to whether the mutation had a common origin. Kofler further suggested however, that codon 429 is a 'hotspot' for mutation and that CG-Ab and CG-Y more likely arose independently, continents apart.

Thus, numbers (and percentages), seen by Kamboh are tabulated below (see Table 1).

The greatest prevalence of GC2 and the higher prevalence of the 1s form are both in the Kimberley. Can south Asian derived genetic admixture explain these outcomes, and in a manner impossible in the central desert? The Makassan fishermen, mentioned above, established land bases where they worked for several months each year and thus coincidental interbreeding is not impossible, and that over many generations. The pattern seen is otherwise consistent with that originally brought to Australia, from Timor, and retained. It is reminiscent of at least eastern Africa. By comparison, Europids and Asiatic people have higher proportions of DBP 1s and up to 20% of DBP 2/2 [23, 24].

The 1f and 1A1 DBP has a fourfold higher affinity constant for calcifediol than does DBP 2/2, and twice as high as 1s, and thus holds the hormone more tightly [25]. This variable affinity underlies the variation seen in performance of the immunoassays, as explained below [26]. The DBPs with higher affinity constants, however, are also present in the bloodstream in higher concentrations than are those with lower constants, a phenomenon which balances out supply of the hormone for the human [27].

Table 1. Australian Aboriginal DBP phenotypes

Site (Number and (percentage of total))	Central desert	Bathurst Island	Kimberley	Aggregate
<b>Number of people tested</b>	216	37	143	396
<b>Allele score</b>	432	74	286	792
<b>Phenotype</b>				
GC 1/1	152 (70)	24 (65)	62 (43)	238 (60)
GC 1/2	30 (14)	3 (8)	45 (32)	78 (20)
GC 2/2	3 (1)	0 (0)	8 (6)	11 (3)
<b>Allele score</b>				
1f	169 (39)	28 (38)	77 (27)	274 (35)
1s	188 (44)	32 (43)	114 (40)	334 (42)
<b>GC 1A1</b>	24 (6)	1 (1)	13 (5)	38 (5)
<b>Others</b>	10 (2)	10 (14)	16 (6)	36 (5)

Source: Kamboh [17]

This DBP genetic heritage most commonly seen in most of Australia's Aboriginal people ensures their calcifediol, and calcitriol, are very avidly retained on their DBP. Thus they are also at the most challenging end of the spectrum for the workaday laboratory which utilises immunoassays for calcifediol. The incorrectly low reporting of calcifediol concentrations it inevitably entails can cause incorrect categorisation of people's 'vitamin D' status, almost always as deficient, when in reality they are replete. The bioavailable concentrations of calcifediol in their blood stream are, more often, adequate. Contemporary epidemiological evidence supporting the validity of this outcome is marshalled immediately below. The details of the chemistry can be found in the review cited above [15].

## Aboriginal vitamin D

The recent surge of interest in vitamin D has spilled over into Indigenous medicine in Australia. Several studies have been published since 2011. The studies all report calcifediol levels, in nmol/L, though methodological confounders abound between them and their varied reporting formats challenge tabulation.

The confounding processes include:

- a variable degree of confirmation of the validity of the calcifediol results reported by the laboratory the study utilised;
- a complete neglect to consider the question of DBP, and the detail of ancestry;
- a variety of reference intervals and of categories of hormone repletion;
- an almost total lack of data relating to the patients' regular diet, usual attire, sun exposure, and renal function, amongst many potential operators.

Though not mentioned in her paper, Maple-Brown's group's data permit the calculation of finer stratification of Indigenous status and, thence, the confirmation that Torres Strait Island people have adequate calcifediol [28].

## The effect of the assays thus utilised

Pertinent ongoing regulatory data sources and several recent studies have reported on the relative accuracy and precision of immunoassays utilised for vitamin D, as calcifediol. Details can be found in the supplementary tables to the review cited above [15]. They permit the conclusion that whilst the results from Vanlint's study could be both too unsafely inaccurate and imprecise to be considered scientifically valid, those from Maple-Brown's, Tan's and Willex's patients' calcifediol levels, all assayed on Liaison immunoanalysers, are acceptably precise. As to accuracy however, the results of all of the latter three studies will consistently show

significant variance from those that would have been obtained from a Reference Measurement Procedure, an RMP, analyser utilising mass spectrometry [35, 36, 37, 38]. The extent of that inaccuracy will vary with the particular patient's DBP genotype and the particular assay used, but given the data above describing Australian Aboriginal DBP in general, it can be confidently estimated that the true total *in vivo* calcifediol for any individual will be underestimated by up to as much as 40% as shown by Heijboer in Amsterdam [26]. Critically here, our extant reference, or target, ranges have been predicated historically on mass spectrometry results.

Only Dyson's and Binks' patients, who had their calcifediol analysed by LC-MS/MS, have both accurate and precise estimates of the total, *in vivo*, prohormone. The RMP succeeds where immunoassays fail because it is preceded by a vigorous process that is totally effective in separating the hormone from its carriage protein. The thus liberated hormone is then quantified in a solution of methanol. Immunoassays do not perform this initial separation, do not thence totally liberate the hormone, and thus fail at the outset [26, 15].

The weighted mean of the adults' calcifediol results from the tabulated Liaison immunoanalysers, including the pregnant women, is 57 nmol/L, and high proportions of the populations have levels <50 nmol/L. By comparison, the mean level from the mass spectrometry studies is 87 nmol/L. Insufficient data are published to also permit calculation of confidence intervals in the immunoanalyser group. If Heijboer's findings are applied here and the immunoassay results are factored up as her data suggest to bring them into accord with results that would most likely have been attained had they been analysed on a spectrophotometer, their mean calcifediol would approach 80 nmol/L.

Without Dyson's and Binks' studies one might have concluded that being an Aboriginal person in Australia can, though need not necessarily, increase the risk that one's level of calcifediol could be lower than is found amongst similarly domiciled non-Indigenous people. The use of chromatography with mass spectrometry as the mode of analysis deployed by Dyson's and Binks' groups, however, when read in conjunction with the Heijboer findings [26], thus reveals that it is more likely that the converse is the case. Except possibly amongst Binks' ALRI affected children and their mothers, whose hormone levels were also concordantly low, Australian Aboriginal people are, broadly, calcifediol replete. When factored up by that approximate 40% most of Maple-Brown's, Tan's and Willex's patients' calcifediol levels will easily reach, and even exceed, the required target levels set in the pertinent Australian guidelines. They remain safely replete even by the more exacting challenge set by using PTH and calcium dynamics to establish minimum acceptable target levels for the hormone, targets which, presently, are not sought by those same Australian professional bodies.

Table 2. Vitamin D studies in Australian Indigenous people

Study	Location, and variation	Number	Calcifediol, target	Calcifediol, found, Indigenous	Calcifediol, found, non-Indigenous	Analyser deployed
Vanlint [29]	Adelaide	58	60	56.8±22.1 <sup>a</sup>		iSYS
	urban	51		nd		
	rural	7		nd		
Maple-Brown [28]	Northern Australia: NT, WA, Qld.	592	50	<50, 39.7%; ≥50 60.3%;		Liaison
	Aboriginal, as calculated	423		59 <sup>a</sup> 55 (40-70) <sup>b</sup>		
	TSI as calculated	169		71 <sup>a</sup> 75 (55-88) <sup>b</sup>		
Tan [30]	Western Australia	73	78, but data given also for 50	<50, 88%; ≥50, 12%;		Liaison
	urban	61		nd		
	rural	12		nd		
Willex [31]	Kalgoorlie, WA	200	50			Liaison
	All pregnant women					
	Indigenous	100		46.7±21.7 <sup>a</sup>		
	Non-Indigenous	100			65.4±18.4 <sup>a</sup>	
Dyson [32]	NT, Top End	98	Hybrid, see paper			LC-MS, in Qld.
	All children, age (mo) 59 (2-161) <sup>c</sup>					
	Indigenous	42		93.2±21.9 <sup>a,e</sup>		
	non-Indigenous	56			97.3±27.9 <sup>a,e</sup>	
Binks [33]	NT, Top End	109	Hybrid, see paper			LC-MS, in Victoria
	Mother and baby pairs					
	Mother, 32 wk	33		104, (93-115) <sup>d</sup>		
	Mother, 39 wk	106		80, (74-86) <sup>d</sup>		
	Baby, cord, no ALRI	77		56, (51-61) <sup>d,f</sup>		
	Baby, cord, with ALRI	7		37, (25-48) <sup>d,f</sup>		
[34]*	Baby at 7mo	37 (of the 84)	Hybrid, see paper	93, (86-101) <sup>d</sup>		

Notes:

1. a, mean alone, or (± SD); b, median with (IQR); c, median with (full range); d, mean with (95% CI); e, no statistically significant difference; f, P = 0.025.
2. nd, no data given; wk, weeks' gestation, median; no/with ALRI, i.e., infant without/with subsequent hospital admission for acute lower respiratory tract infection.
3. NT, Northern Territory; Qld., Queensland; WA, Western Australia.
4. LC-MS, chromatography with mass spectrometry.

\*Binks re-published all his data from his 2014 paper in 2016, the second time in the *Medical Journal of Australia*. He adds there the results of 37 of the infants whose calcifediol was able to be assayed at 7 months of life.

At the time of their studies Maple-Brown, Tan and Willex, and Vanlint, were presumably not given all the pertinent information then known by the laboratories they commissioned but, in the laboratories' defence, it also must be recorded that much of the usefully operative data cited here has only been published very recently.

A detailed discussion of the further question of the need to establish estimates of bio-available calcifediol, as opposed to total *in vivo* levels, is beyond the scope of this current review. It is however the next task on laboratorians' agendas and thus a brief explanation follows.

## Outcomes?

What can clinicians do? What is practicable and diagnostically efficient in Australia in 2016? What management is actually needed? Access to mass spectrometry is very limited and not routinely available in workaday clinical practice. Clinicians are obliged to utilise the immunoassays their pathologists provide and those pathologists need to make the shortcomings of the assays abundantly clear to their customers.

In spite of the fears raised by the several recently reported studies detailed above, it seems rather that Australian Aboriginal people may actually be more generally calcifediol and calcitriol replete and do not need therapy. Torres Strait Islander people are similarly replete.



It could be argued that where Aboriginal people are found incidentally by immunoassay to be seemingly vitamin D insufficient, or worse, deficient, then their PTH should be assayed, to clarify their calcium economy's status. And, if they live within easily reached distance of a radiographer with a DEXA [dual-energy X-ray absorptiometry] scanner, they should also have their bones assessed and their t and z scores calculated.

In the meantime, and until further studies elucidate the cause of the low hormone levels found, as for instance by Binks, perhaps all pregnant Indigenous women need a calcifediol assay at say 28 weeks' gestation, along with their 28 week glucose scan for GDM, and if they are seemingly D deficient, (perhaps even *pace* their concomitant PTH), then should be fortified until about 6 months post-partum. This will ensure they and their infant are calcifediol replete, and the baby less likely to suffer severe LRTI.

Thus, and only thus, can we ensure a secure basis for management decisions and adequately finesse vitamin D for Australia's Aboriginal people.

## Acknowledgements

The sources utilised and quoted.

I acknowledge Australia's Indigenous people whose ancestors indeed travelled to this continent long before my own ancestors journeyed, out of Africa, to Europe to become Cro-Magnons.

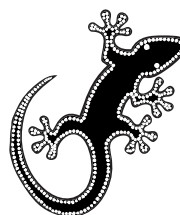
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