

Relationships between low serum Vitamin D₃, BMI and Waist in Overweight and Obesity

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Abstract

Low Serum 25 hydroxyvitamin D₃ (Vitamin D₃) is known to perturb cellular function in many tissues, including those involved in obesity such as the endocrine pancreas. Vitamin D₃ insufficiency has been linked to obesity regardless of whether obesity is assessed by body mass index (BMI), fat percentage (fat%) or waist circumference (Waist). Metabolic health risks of high total and peripheral body fat, as measured by BMI and fat% may be minimal. In contrast, a large abdominal adipose depot, as assessed by Waist, is commonly associated with the metabolic syndrome (MSX), insulin resistance and subsequently type II diabetes (TIIDM) and cardiovascular disease (CVD). This trial was designed to explore whether BMI or Waist was more closely related to low Vitamin D₃.

In this cross-sectional study of 250 adult, overweight and obese adults of different ethnicities, nearly 1/3rd had Vitamin D₃ insufficiency (< 50 nmol/L). Multivariable analyses, carried out separately for BMI and Waist, showed a decrease of 0.74 nmol/L (p=0.002) in Vitamin D₃ per 1 kg/m² increase in BMI and a decrease of 0.29 nmol/L (p=0.01) per 1cm increase in Waist, with each explaining approximately 3% of the variation in Vitamin D₃ over and above gender, age, ethnicity and season.

The similar values of the relationships of BMI and Waist to Vitamin D₃ may be coincidental, and different mechanisms relating hypovitaminosis D to obesity may be occurring concurrently. One proposed mechanism involves the fat soluble-Vitamin D₃ being preferentially dissolved in the large adipose compartment, rather than the serum, secondary to high BMI. A second, unrelated mechanism is postulated whereby central fat gain may be promoted by the insulin resistance due to low Vitamin D₃ and derivatives which impair insulin action. Thus, adequate Vitamin D₃ uptake from the

25 environment may have health benefits for hypovitaminosis D₃-associated disorders, including obesity and MSX, in many potentially Vitamin D₃ deficient populations.

Running title: Low Vitamin D₃ and high BMI and Waist

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Key words: Vitamin D₃, Hypovitaminosis D₃, BMI, Waist

Findings

Background

35 It is now known that insufficiencies of serum 25 hydroxyvitamin D₃ or calcifediol
(Vitamin D₃) and metabolites cause perturbation of many cellular functions including
in tissue relating to obesity such as the endocrine pancreas, vascular endothelium, and
immune system [1]. Recently, there has been a resurgence of hypovitaminosis D₃ in
40 many populations, including young, pale-skinned adults, previously thought to be
healthy [2] and simultaneously there has been a world-wide increase in the prevalence
of obesity [3]. Links between hypovitaminosis D₃ and obesity have been reported
when obesity is defined using body mass index (BMI) [4], body fat content (fat%) [5],
and waist circumference (Waist) [6]. High BMI and fat% are indicators of whole
body, often large peripheral hip and thigh, fat mass which can be consistent with
45 healthy metabolism [7]. Large Waist, a surrogate for abdominal obesity, is a marker
for the metabolic syndrome (MSX) as defined by the NCEP (National Cholesterol
Education Panel III) [8]. MSX is associated with many risk factors including
hypertension, dysglycaemia and dyslipidaemia, often leading to type II diabetes
mellitus (TIIDM) and atherosclerotic cardiovascular disease (CVD) [9]. In 2005, the
50 International Diabetes Federation (IDF) modified the NCEP-defined MSX requiring
Waist in the MSX definition and the cut-off for identification of risk was lowered
[10]. Whilst there is overlap in total body and abdominal obesity, the diverse
metabolic effects of the different adipose depots may underpin the surprisingly
dissimilar hypotheses for the mechanisms proposed for the inverse relationship of
55 Vitamin D₃ to obesity and MSX. Explanations include 1) Vitamin D₃, a fat soluble
vitamin, being preferentially dissolved in the large fat mass leaving the serum

deficient [11] and 2) low Vitamin D₃ altering insulin secretion and action in a conjunction with central obesity [1, 12].

This trial was designed to 1) assess whether BMI and Waist were inversely related to
60 Vitamin D₃ in overweight and obese mixed-ethnicity New Zealand adults and 2)
determine whether there was a stronger relationship between whole body [BMI] or
central [Waist] adiposity and low levels of circulating Vitamin D₃.

Methods

Population

65 Two hundred and fifty ambulant adults were recruited into a weight loss trial with
primary criteria including BMI 28-50 kg/m², age >18 y, no current weight loss agents,
no current participation in commercial weight loss programmes and a desire to lose
weight. All participants were lightly clad and measurements were done in duplicate.
Body weight was measured on calibrated digital scales (Seca, Model 708, Germany)
70 to the nearest 0.1 kg. Height was recorded using a wall-mounted stadiometer (Seca,
model 222, Germany). Waist circumference was recorded to the nearest 0.1 cm
midway between the last rib and the crest of the ileum at the natural point of waist
narrowing using a non stretch tape measure. All participants provided written
informed consent. Ethics approval for this study was obtained from the Auckland
75 Ethics Committee, Auckland, New Zealand.

Laboratory samples

Fasting blood was collected by venepuncture. 200 women and 43 men of 250
participants provided evaluable serum samples. Six samples were not obtained due to
unsuccessful venepuncture and 1 sample was lost in transit to the laboratory. Vitamin
80 D₃ was analysed using Vit D25 pre-extraction with acetonitrile, double antibody

radioimmunoassay (DiaSorin Inc Stillwater, MN, USA). Methodology details are described elsewhere [13].

Statistical Analysis

Multiple regression was performed with Vitamin D₃ as the outcome variable using
85 SAS 8.0 statistical software (Cary, NC, 2003). Explanatory variables were gender, age, ethnicity, season, and either BMI or Waist as these were likely to be correlated.

An analysis including both BMI and Waist was also carried out to investigate if one variable contributed over above the other. Ethnicity was split into Group I which consisted of New Zealand Europeans, with lightly pigmented skin, and Group II
90 which included all other ethnicities which were Maori, Pacifican (Tongan, Samoan Nuiean, Rarotongan) and Asian(East and Indian), with variably pigmented skin.

Results

The participants (mean, sd: age 47, 11.7 y; BMI 35.4, 12.8 kg/m²; Waist 100.4, 5.1 cm) had a mean Vitamin D₃ of 62.2, 22.7 nmol/L. Seventy five participants (31%) had
95 Vitamin D₃ insufficiency (< 50 nmol/L) and 11 individuals (5%) were severely deficient (\leq 15 nmol/L). More than one half of Ethnic Group II had Vitamin D₃ <50nmol/L and four fifths had Vitamin D₃ <70 nmol/L (Table 1).

Multivariable analyses showed an estimated decrease of 0.74 nmol/L (p=0.002) in
100 Vitamin D₃ per 1 kg/m² increase in BMI with the total model explaining 22% of the variation in Vitamin D₃ levels and BMI explaining 3% of the variation.

On replacing BMI by Waist, there was a decrease of 0.29 nmol/L (p=0.01) Vitamin D₃ per 1cm increase in Waist, with the total model explaining 21% of the variation in Vitamin D₃ and Waist also explaining 3%. When both BMI and waist were included
105 neither could be demonstrated to contribute over and above the other (p=0.25 and 0.67 respectively)

Discussion

Nearly 1/3rd of the 243 overweight and obese men and women had suboptimal Vitamin D₃, even those who were young, had lightly pigmented skin and in whom it has previously been thought that low Vitamin D₃ was not a significant problem. Hypovitaminosis D₃ has been detected in other similar populations [14]. The fact that Vitamin D₃ showed inverse relationships separately, but of the same magnitude, with both BMI and Waist when corrected for gender, age, ethnicity, and season may indicate different metabolic mechanisms are in action. Whilst our cross-sectional analysis cannot determine mechanisms, the following studies describe processes that could explain our results.

Firstly, it has previously been shown that whole body obesity, as defined by both BMI and fat%, is associated with or contributes to low Vitamin D₃ status [5, 11]. Wortsman et al measured Vitamin D₃ production in the skin and serum of obese and non-obese individuals after controlled ultraviolet (UV) irradiation, and deduced that the lower Vitamin D₃ in the obese could be secondary to fat mass and “Obesity-associated vitamin D insufficiency is likely due to the decreased bioavailability of vitamin D₃ from cutaneous and dietary sources because of its deposition in body fat compartments.” [11].

A second, unrelated explanation for hypovitaminosis D₃ in obesity may relate to the metabolic and insulin resistance syndromes [15]. Hydroxylation of Vitamin D₃ produces 1,25 Vitamin D₃, a factor needed for normal insulin secretion. Low Vitamin D₃ disrupts insulin action which is already deranged in MSX [16]. Furthermore, 1,25 Vitamin D₃, via its receptor which is present in many cells involved in MSX including insulin producing beta-islet cells, vascular endothelium, and immune system, is also

known to be a potent regulator of cell proliferation and differentiation [12, 17]. There is some evidence, although not definitive, that insulin resistance and hyperinsulinaemia can drive central adipose accumulation [9], and hypovitaminosis D₃ may be a contributing factor [15, 16]. Ford et al found that abdominal obesity as measured by Waist alone, in addition to MSX (defined by three of five positive markers [6]), were both related to low Vitamin D₃ in the US NHANES data, notably affecting mixed-ethnicity participants equally [8]. Furthermore, low Vitamin D₃ has been shown to be associated with other metabolic syndrome-related states such as T1DM [4, 15, 18], atherosclerotic CVD [9, 15, 16] and cancers [1, 12].

140 Increasing rates of raised BMI and large Waist have occurred world-wide in recent decades. Those individuals whose increased skin pigment levels, such as those in Ethnic Group II in our current trial, partially block solar ultraviolet light (UV)-Vitamin D₃ synthesis, are known to be at risk of Vitamin D₃ deficiency [19]. Our data support previous studies where large numbers of light-skinned groups are now shown

145 to also be at risk of deficiency. A serum Vitamin D₃ level of 70 nmol/L is currently considered the minimum for general, metabolic and bone health [20]. Modest skin exposure to sun UV light is known to efficiently induce the dermal production of healthy levels of Vitamin D₃ but excessive UV skin exposure can cause skin damage and increased skin cancer risk [12]. Discussions on recommendations given to

150 populations with different levels of skin pigment for safe solar UV exposure, Vitamin D₃ fortification, supplementation and what constitutes a healthy serum Vitamin D₃ level, that continue amongst bone metabolism and nutrition scientists, epidemiologists, endocrinologists and dermatologists [1, 8, 12, 20-23] could also be taken up by bariatricians, diabetologists and cardiologists.

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In conclusion, our trial showed that low levels of circulating Vitamin D₃ was independently and inversely related, at similar values, to both whole body adiposity as assessed by BMI and abdominal obesity as assessed by Waist. The possibility exists that different, concurrent mechanisms may be involved in these processes. On one
160 hand low serum Vitamin D₃ may be found in the obese secondary to its high fat solubility and thence deposition in the large fat mass. On the other hand low pre-existing serum Vitamin D₃ could cause or aggravate abnormal insulin secretion and activity. The link between hypovitaminosis D₃ and metabolic disorders, including obesity, MSX, TIIDM and CVD requires further investigation, particularly for those
165 most at risk of these conditions.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

A-TM conceived the study and was the senior author during manuscript preparation.

A-TM, FEL, SDP and CMS contributed to the planning, conduct, and reporting of this study. JMS, A-TM and CMS did the data entry and statistical analysis. A-TM, FEL, SDP and CMS contributed to manuscript preparation. Funds were raised by A-TM and SDP as part of a wider programme grant.

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Table 1: Fasting serum Vitamin D₃ in 250 overweight/obese adults of various ethnicities, recruited during different seasons

Group	N ¹	Vitamin D ₃ (25 hydroxyvitamin D ₃)		< 50	< 70
		Mean (sd)	Range	nmol/L	nmol/L
				(% n ¹)	(% n ¹)
Ethnic Group I ²	206	64.8 (22.1)	14-130	27	60
Ethnic Group II ²	37	48.0 (20.4)	11- 85	54	84
Female	200	62.4 (21.9)	14-130	30	64
Male	43	61.7 (26.4)	11-122	37	61
Age < 50 years	133	62.7 (23.0)	14-122	32	63
Age ≥ 50 years	110	61.7 (22.4)	11-130	30	65
Mid-Summer ³	141	68.7 (21.9)	15-130	20	61
Early Winter ³	102	53.3 (20.6)	11-113	47	78

¹243 participants provided evaluable serum samples; 6 samples were not obtained due to unsuccessful venepuncture and 1 sample was lost in transit to the laboratory

²Ethnic Group I, lightly pigmented skin; Ethnic Group II, variably pigment skin

³Southern Hemisphere Seasons: Mid-Late Summer, January-March and Autumn-Early Winter, April-June