Author's response to reviews

Title: Relationships of Low Serum Vitamin D3 with Anthropometry and Markers of the Metabolic Syndrome and Diabetes in Overweight and Obesity

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Covering Letter to:

The Editor
Nutrition Journal

Dear Sir/Madam

Please find attached a SHORT REPORT.

This is a RESUBMISSION and following is a POINT-BY-POINT COMMENTARY ON THE REVIEWERS’ CRITIQUES.

Original Title

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

Submission #

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Revised Title:

Relationships of Low Serum Vitamin D3 with Anthropometry and Markers of Metabolic Syndrome and Diabetes in Overweight and Obesity

Editor and Reviewers Critiques with Comments on Revision

“Dear Dr. McGill,

Your manuscript entitled "Relationships between low serum Vitamin D3, BMI and Waist in Overweight and Obesity." has been reviewed by the Editor and outside reviewers. Unfortunately, this manuscript cannot be accepted in this form. However, we will be pleased to review your revised manuscript, if you appropriately revise it according to the reviewer's suggestions.
Please send a corrected version, with a separate point-by-point answers to the reviewer in a cover letter. If you disagree with their comments on any particular point, please explain your position.

You must resubmit the modified manuscript as a new version using the same MS number just like you did in the first place using the electronic submission system.

We look forward to hearing from you.

Yours sincerely,

Hiromichi Kumagai, M.D.
Deputy-Editor-in-Chief, Nutrition J

Comments from the reviewer,

Reviewer 1,

This manuscript poses a novel, valid question: is there a difference between the relationship of BMI and serum Vitamin D3 to that of Waist and serum Vitamin D3? This distinction has not yet been discussed in current literature, as obesity studies often compare Vitamin D3 to BMI, fat percentage and Waist as markers for obesity.

As investigation in this area progresses, it will be important to elucidate how each factor is specifically linked to low serum Vitamin D3 in obesity.

*More factors have been reviewed in the current edit*

Unfortunately, there are not any molecular studies to support McGill’s hypotheses regarding the separate contributions that BMI and Waist have to obesity, low serum Vitamin D3 and the metabolic syndrome.

The manuscript suggests a difference in metabolic effect of the different adipose depots, which should be focused on more, as it has important public health implications for screening and treatment of patients in the future.

*We have discussed metabolic differences between peripheral and central adipose depots, with central depots having deleterious metabolic sequelae and peripheral (hip and thigh) having positive metabolic attributes.*

One result discusses when both BMI and Waist were included in the multivariable analysis, but neither could be demonstrated to contribute over and above the other. This result weakens the argument that there is a difference in the contribution of these two factors.

*We agree. The analysis was done to investigate this hypothesis. The wording in the paper has been changed to clarify this. The hypothesis is that relationship may be close as the there is a relationship of BMI and waist. However arguments are made from the*
literature that they metabolism can vary widely in those with high BMI as muscle and other lean tissue and fat are measured but waist is a fair approximation of upper body and visceral fat which is generally a metabolic risk for TIIDM and CVD.

Although this manuscript presents a novel way to look at studying the link between markers of obesity and low serum Vitamin D3, it lacks empirical evidence to support the possible mechanisms explaining the low serum Vitamin D3 and also does not clearly demonstrate there being a different metabolic effect of the different adipose depots when both markers for the depots are both included in the multivariable analysis. The study needs to proceed deeper into investigating the connection between BMI and Waist and Vitamin D3 to diseases mentioned in the manuscript.

Evidence has been gleaned from assessing the metabolic syndrome markers and a count of positive markers and other metabolic parameters such as HbA1c from the data in the study. Surprisingly, metabolic syndrome was not related to vitamin D3 on linear regression, nor was body fat %, but severe glucose dysmetabolism was related.

We have gone on to discuss these findings.

This manuscript presents an original topic of investigation, with potentially important public health implications. The suggestion of different metabolic effects of different adipose depots provides a new direction of research in this area of study; however, the lack of evidence from multivariable analysis, as well as the lack of molecular evidence detracts from bolstering the hypotheses presented by McGill et al.

We have modified the text to better fit with our findings.

By linking the study’s main result to its effect on disease outcome, this paper will be much stronger. As of this point, the manuscript is on its way to elucidating a difference between BMI and Waist and Vitamin D3 and the connection to disease. It is not clear that demonstrating an independent inverse link between BMI and Waist to low serum Vitamin D3 is sufficient information for a stand-alone paper.

Suggestions:

--Include more data about your study population regarding their disease status.

We have included more baseline data on metabolic syndrome status, including TIIDM.

Possibly re-examine the data to see how you can design a cross-sectional prospective study that will look at Waist measurements and BMI measurements and the incidence of metabolic syndrome in subjects with hypovitaminosis D3.

Metabolic Syndrome profile and markers and TIIDM prevalence have been included and analysed.

This will help tie in the obesity markers and Vitamin D3 to the disease states mentioned in the paper as potential endpoints of this physical state.
Reviewer 2,

This is an interesting study trying to examine the association between low Vitamin D3 and whole body obesity or central obesity. The results indicated that there were significant inverse associations between Vitamin D3 and BMI and vitamin D3 and waist, both correlation coefficients being similar. There are 2 major concerns in this study.

1. The data presentation is poorly organized.

**Clearer baseline data is presented, including metabolic syndrome markers.**

The author should firstly indicate the simple correlations between Vitamin D3 concentration and various obesity markers, then proceed to the multiple regression analysis.

*Linear regressions were performed on all metabolic syndrome markers, marker count, presence of the metabolic syndrome and other metabolic and anthropometric markers.*

Some graphical presentations could provide more information to the reader.

**A series of linear regression graphs of important relationships have been included.**

2. The representation about the second hypothesis between low Vitamin D3 and central obesity or MSX is too strong. The cause and result relationship between these factors is essentially unknown. These descriptions should be modified in the abstract and the discussion.

*On bringing in the metabolic syndrome and markers surprising results emerged and T2DM looks more important than the metabolic syndrome. As fat percentage was not significant in this study we have mentioned issues to do with lean tissue, and the different metabolic attributes of the different adipose depots.*

Minor points,
1. Mean and SD should be written using ± or mean (SD) in the results.

**This point has been addressed.**

**Reasons to Publish:**
We think this short report should be published to inform researchers and others that the links between obesity, the metabolic syndrome, type II diabetes mellitus and low serum Vitamin D₃ are not simple and that there may be a number of different mechanisms occurring.

We provide further evidence that hypovitaminosis D₃ relates to body mass index and waist circumference, separately. Metabolic syndrome and body fat % however do not appear to be related to Vitamin D₃ but two important markers of TIIDM (waist and HbA₁c) are. The notable part of this paper is that whilst work was starting to show a link with metabolic syndrome we have not found this, although we do show modest evidence that glucose derangement is related. We do not confirm the mechanisms. These debates are important in the light of secular increases in obesity and TIIDM, and the levels and modes of vitamin D₃ we should acquire for health.

**Preferred Reviewers:**
The reviewers we would prefer are those who understand the metabolic syndrome, obesity and Vitamin D rather than those who work with bone and Vitamin D.

A list for you to consider is:-

Holick MF
Peterlik M
Ford ES
Vieth R
Chiu KC

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Abstract

Low serum 25 hydroxyvitamin D_3 (vitamin D_3) is known to perturb cellular function in many tissues, including the endocrine pancreas, which are involved in obesity and type II diabetes mellitus (TIIDM). Vitamin D_3 insufficiency has been linked to obesity, whether obesity is assessed by body mass index (BMI) or waist circumference (waist). Central obesity, using waist as the surrogate, is associated with the metabolic syndrome (MetSyn), insulin resistance, TIIDM and atherosclerotic cardiovascular disease (CVD).
We tested how vitamin D₃ was related to measures of fat mass, MetSyn markers, haemoglobin A₁c (HbA₁c) and MetSyn in a cross-sectional sample of 250 overweight and obese adults of different ethnicities. There were modest inverse associations of vitamin D₃ with body weight (weight) (r=-0.21, p=0.0009), BMI (r=-0.18, p=0.005), waist (r=-0.14, p=0.03), [but not body fat % (r=-0.08, p=0.24)], and HbA₁c (r=-0.16, p=0.01).

Multivariable regression 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 1 cm increase in waist, with each explaining approximately 3% of the variation in vitamin D₃ over and above gender, age, ethnicity and season.

The similar relationships of BMI and waist with vitamin D₃ may have been due to associations between BMI and waist or coincidental, where different mechanisms relating hypovitaminosis D₃ to obesity occur concurrently. Previously reviewed mechanisms include that 1) the promotion of central fat gain by insulin resistance, driven by low vitamin D₃, may impair insulin action and glucose metabolism, 2) fat soluble-vitamin D₃ is sequestered in the large adipose compartment, and low in serum, 3) obese people may be sensitive about their body shape, minimising their skin exposure to view and sunlight (not tested). We showed evidence for the first theory but no evidence to support the second.

In the current study, serum vitamin D₃ was inversely related to weight, BMI and markers of TIIDM (large waist, raised HbA₁c) but not to adipose mass nor to MetSyn per se.

**Word count:** abstract 334 (incl 1 header), text (incl 8 headers) 1500, References 32
Running title: Low vitamin D₃ with high BMI, waist and HbA₁c but not with metabolic syndrome per se.

Key words: Obesity, Vitamin D₃, Hypovitaminosis D₃, BMI, Waist, HbA₁c, Metabolic Syndrome, Diabetes.

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.

Authority
I confirm all authors have approved this paper for submission to the Nutrition Journal

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Jeannette Eis, Cathelijne Reincke, Shannon McCarthy, Jenneke van Drunen (Research Assistants) and the 250 participants.

Yours truly,

Anne-Thea McGill