

Format for ANSWERING REVIEWERS



Dec 7, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6416(R1).doc).

Title: Excess vitamins: an unrecognized family of endocrine disruptors possibly contributing to obesity

Author: Shi-Sheng Zhou, Yiming Zhou

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 6416

The manuscript has been improved according to the suggestions of reviewers (# = our response):

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

(1) reviewer 1

General comment

The manuscript "Excess vitamins: an unrecognized family of endocrine disruptors possibly contributing to obesity" reviewed the effect of excess vitamins in the neuroendocrine system. It is an interesting topic, however little literature is available. The authors need to better express literature's finding in a complete literature review, pointing out the real data, reducing the speculation in few occasions. More endocrinological data are needed to establish a real relationship between vitamin excess and obesity. In the conclusion the authors wrote that "The causal relationship between long-term synthetic vitamin exposure and the increasing prevalence of obesity needs to be established". If so, which would be the role of the manuscript? Which will be the sense of figure 6? The authors should clarify which would be the neuroendocrine connection between vitamin and obesity. The manuscript should be revised by a native English speaker.

The title has been changed to "**Excess vitamin intake: an unrecognized risk factor for obesity**". Existing studies have demonstrated that B vitamins promote fat synthesis and may cause insulin resistance and glucose intolerance. In the revised MS, we review the literature on the role of excess vitamins in the development of obesity, and only briefly discuss the possibility that excess vitamins may also disturb the metabolism of monoamine neurotransmitters.

Specific Comments

Pag.3: "Since the prevalence... added simultaneously to their food system". This is a long sentence, would be useful to reduce it or reformulate.

Revised.

"Formula feeding" should be explicated.

More information on formula feeding is provided.

Moreover articles regarding the relationship between vitamin and obesity should be cited.

We have added.

Pag.4: the sentence "Vitamin deficiency or excess can affect the function of neuroendocrine system" has no reference, please add it. The author must clarify the topic, because along the manuscript they wrote about "neuroendocrine system", however they only use one reference regarding Autism (ref.21), which does not describe the neuroendocrine system. Data on this topic are lacking in the manuscript. Which would be the neuroendocrine connection between vitamin and obesity?

The title has been changed (please see the above response). The references on the role of monoamine neurotransmitters in food intake regulation are cited.

Pag.7: the sentence "That is to say, consumption..." should be written in a correct language.

This sentence has been deleted.

Pag.7: Formula-fed infants should be explicated.

Revised. Data on infant formulas are given (see Table 3).

Pag.8: "In fact, the increased vitamin exposure is accompanied by increased prevalence of obesity and diabetes". Reference should be added.

Revised. Relevant references on vitamin fortification and the prevalence of obesity in many countries are presented.

The role of vitamin B should be clarified.

Please see the sections: "MECHANISM OF EXCESS VITAMINS-INDUCED OBESITY" and "NON-MONOTONIC EFFECT OF VITAMINS ON WEIGHT GAIN".

Figure 5 is not clear. It should be reformulated.

It has been modified.

Figure 6 has not sense.

It has been deleted.

Which are the neurotransmitters and hormone involved?

The topic is not focus on this, please see the response to the General comment.

(2) reviewer 2

The authors should have their manuscript revised by a fluent English speaker (e.g. the expressions "It is thought that multi-factors" and "Although decreased energy expenditure is thought to be play a significant role in obesity" are not correct).

Improved.

The authors should extend their manuscript to better discuss the pathways through which vitamins may contribute to obesity.

According to this suggestion, we have increased the information on the B vitamins used in grain fortification (B1, B2 and B3) and infant formulas. Because B3 (niacin) has long been known to induce insulin resistance and glucose intolerance, more attention is paid on niacin in the revised version.

The data from Figure 5 and 6 are discussed too briefly.

Figure 6 is deleted, and the discussion for Figure 5 is improved.

These should be discussed in greater detail.

We have done.

(3) reviewer 3

The obesity epidemic and the diabetes epidemic and indeed the increase in longevity have all come upon us in the last 30 or so years and although most people believe that the causes are multi-factorial, it is exciting to think that perhaps one factor might be predominantly involved. Cancer is more difficult because some cancers are on the increase and some on the decrease. There are myths, perceptions and facts. Myths can become facts through new research and facts can be overturned by new research. The present review very reasonably suggests in the title that there is a possibility that excess vitamins might contribute to obesity. I would have expected that this sort of review would have examined the experimental evidence that has led to the possibility of the proposition being more than a myth. Instead the majority of the references refer to reviews which would appear to, at best, propagate a presumption and at worst the myth. In particular, there is almost no information on animal research that shows that feeding vitamins increases body weight. and statements such as "emerging evidence suggests that vitamin fortification might play a role in emergence of obesity is referenced by 2 papers that really do not give scientific evidence to promote the concept, but they of course do not contradict the concept that they might play a role in the development of obesity and diabetes. It is difficult to see where the present article increases our knowledge to make the myth more of a fact rather than a presumption.

We have provided the references on B vitamins-induced fat gain, please see the sections: 'MECHANISM OF EXCESS VITAMINS-INDUCED OBESITY' and 'NON-MONOTONIC EFFECT OF VITAMINS ON WEIGHT GAIN'.

The article is very strong on epidemiology of artificial synthetic vitamins but there is very little on the mechanism of alteration in hormones which might affect metabolic centre or hormones or both.

Considering this comment, we have changed the title, and mainly reviewed the role of B vitamins in the development of obesity.

The suggestion that postprandial reactive hypoglycaemia might stimulate the appetite and lead to increased calorie intake is persuasive, but the evidence that vitamins and other endocrine disrupters increase appetite further might be expanded and particularly the dosages of niacin used in the developing rats might be discussed in more detail, since the dosages appear to me to be far in excess of anything that humans are likely to encounter in adulthood.

Please see the sections: 'MECHANISM OF EXCESS VITAMINS-INDUCED OBESITY' and 'NON-MONOTONIC EFFECT OF VITAMINS ON WEIGHT GAIN'.

As an aside It might be interesting for the authors to consider the difference between late onset obesity and childhood obesity that disappears in adulthood and childhood obesity that continues into adulthood.

We have discussed how the obesity occurs in infants, children and adults.

I am not sure that the para on epigenetic changes is relevant and the authors should try to explain how this change would affect the neuro-endocrine system.

We recently found that maternal nicotinamide supplementation can disturb fetal brain one-carbon metabolism. We have cited this paper in the revised manuscript.

Fig 5 is interesting but does the change in insulin sensitivity occur before or after the obesity?

We have modified this figure, and given more information to it, including that B vitamins increase fat synthesis.

In conclusion a review article that in its present form does not help to promote endocrine disrupters as a contributing factor to obesity. A more in depth evaluation of the scientific articles that have

attempted to address the subject would be of more interest than review articles. The outcome of the OBELIX study may well change our perceptions.

In the revised MS, more references have been cited. We have provided the evidence indicating that the effect of vitamins follows the Bertrand's rule, and discussed why the weigh-gain-promoting effect of vitamins has been long neglected, please see the section: "NON-MONOTONIC EFFECT OF VITAMINS ON WEIGHT GAIN".

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Diabetes*.

Sincerely yours,



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