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MINIREVIEWS

Vitamin paradox in obesity: Deficiency or excess?

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Abstract

Since synthetic vitamins were used to fortify food and as supplements in the late 1930s, vitamin intake has significantly increased. This has been accompanied by an increased prevalence of obesity, a condition associated with diabetes, hypertension, cardiovascular disease, asthma and cancer. Paradoxically, obesity is often associated with low levels of fasting serum vitamins, such as folate and vitamin D. Recent studies on folic acid fortification have revealed another paradoxical phenomenon: obesity exhibits low fasting serum but high erythrocyte folate concentrations, with high levels of serum folate oxidation products. High erythrocyte folate status is known to reflect long-term excess folic acid intake, while increased folate oxidation products suggest an increased folate degradation because obesity shows an increased activity of cytochrome P450 2E1, a monooxygenase enzyme that can use folic acid as a substrate. There is also evidence that obesity increases niacin degradation, manifested by increased activity/expression of niacin-degrading enzymes and high levels of niacin metabolites. Moreover, obesity most commonly occurs in those with a low excretory reserve capacity (*e.g.,* due to low birth weight/preterm birth) and/or a low sweat gland activity (black race and physical inactivity). These lines of evidence raise the possibility that low fasting serum vitamin status in obesity may be a compensatory response to chronic excess vitamin intake, rather than vitamin deficiency, and that obesity could be one of the manifestations of chronic vitamin poisoning. In this article, we discuss vitamin paradox in obesity from the perspective of vitamin homeostasis.

Key words: Obesity; Type 2 diabetes; Developmental

origin of disease; Folic acid; Vitamin D; Niacin; Oxidative stress; Insulin resistance; Vitamin fortification

Core tip: Obesity rates have dramatically increased among the United States population, including children, since the 1980s. Considering the lag time between risk exposure and the development of child obesity, the risk must have been imposed on the whole United States population around the late 1970s. Although evidence suggests that the risk is high vitamin intake due to the update of vitamin fortification in 1974 and the implementation of the Infant Formula Act of 1980, why do obese individuals paradoxically show low levels of fasting serum vitamins? In this paper, we try to give an answer to this question based on the current understanding of vitamin homeostasis.

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INTRODUCTION

Obesity, a global health problem, is associated with co-morbidities such as metabolic syndrome, diabetes, hypertension, asthma, nonalcoholic fatty liver disease, renal disease, cardiovascular disease and cancer, which are thought to be of developmental origin[1]. Since the late 1930s, when synthetic vitamins, thiamin, riboflavin and niacin (nicotinic acid and nicotinamide), were used to fortify foods or as dietary supplements, the daily intake of vitamins of the United States population has significantly increased, especially after the update of mandatory fortification in 1974[2] and the implementation of the Infant Formula Act of 1980 (without setting an upper limit for most vitamins)[3]. In fact, the introduction of synthetic vitamins into the diet was followed by a dramatic increase in the prevalence of obesity among all age groups in the United States[4,5]. Similar correlations between increased obesity and vitamin fortification were observed in other vitamin-fortified countries, such as Canada and Saudi Arabia[2]. Over the past 20-30 years, China has also been experiencing a rapid growth in the rates of obesity[6] after having shifted from a low to a high vitamin intake, due to a combination of increased intake of animal-derived foods (rich in vitamin B_1, B_2 and niacin)[7] and mandatory flour fortification with these vitamins, which was introduced in China in the late 1980s and was been mandatorily implemented in 1994[2]. Paradoxically, it is frequently reported that obesity and type 2 diabetes are associated with low levels of fasting serum vitamins, including vitamin B_1, D, and folate[8-10]. Although the mechanism of the paradox remains unclear, it is generally thought that the low vitamin status in obesity is due to inadequate intake.

Since 1998, enriched grain products in the United States have been fortified with folic acid to prevent neural tube defects. Recent studies on folic acid fortification show that obese individuals also show lower fasting serum folate concentrations, but, paradoxically, their red blood cell (RBC) folate concentrations and MeFox (5-methyltetrahydrofolate oxidation product) are significantly higher, when compared with nonobese individuals[11,12]. Moreover, obesity is also found to be associated with increased activity of cytochrome P450 (CYP) 2E1, a monooxygenase enzyme that can use folic acid as a substrate[13]. Folate content in RBC is known to reflect long-term average consumption and tissue stores because RBC only accumulates folate during erythropoiesis[14], and increased serum MeFox suggests increased degradation of folic acid. Moreover, recent evidence shows that obesity is associated with high fasting serum N^1-methylnicotinamide without significant changes in nicotinamide levels[15] and that plasma N^1-methylnicotinamide correlates with increased tissue expression of nicotinamide *N*-methyltransferase (NNMT, a major enzyme responsible for the degradation of nicotinamide to N^1-methylnicotinamide) and the degree of insulin resistance[16]. Collectively, these observations raise the possibility that the vitamin paradox in obesity may involve vitamin excess rather than deficiency. After more than seven decades of practice of vitamin fortification and painful global experience of increasing prevalence of obesity and related diseases worldwide, it is time for us to examine the relationship between vitamin fortification and vitamin paradox from the perspective of vitamin homeostasis.

VITAMIN HOMEOSTASIS AND OXIDATIVE STRESS

Vitamins are essential micronutrients needed by the body in small amounts. Vitamin homeostasis is a balance between vitamin intake and clearance. A deficiency or excess may lead to deleterious effects. Since the introduction of synthetic vitamins into food, high vitamin intake is very common during a person's lifespan from conception through to old age[2]. In this case, the removal of excess vitamins becomes particularly important in maintaining vitamin homeostasis. This depends on the efficiency of both excretory organs and drug-metabolizing enzymes.

Excretion of vitamins

The kidneys and sweat glands are the two major excretory organs responsible for the elimination of water-soluble vitamins, and the sebaceous glands excrete lipid-soluble vitamins in the sebum[17]. The excretion of vitamins is positively related to their intake. Aging is known to be associated with decreasing function

of excretory organs[18,19] and thus may reduce the clearance of vitamins. It is noteworthy that sweat excretion may be particularly important in eliminating excess water-soluble vitamins, because vitamins (*e.g.*, folate[20], nicotinic acid and nicotinamide[2,21]) are barely excreted in the urine before degradation due to the reabsorption by the renal tubules, but they can be easily excreted in the sweat[22-24]. The efficiency of sweat excretion is determined by several factors, including genetic background, intrauterine and early postnatal development, environmental temperature and physical activity. Compared with whites, blacks have a high sweating threshold, manifested by lower skin conductance (*i.e.*, low insensible perspiration)[25] and sweating rates[26] under the same ambient temperature condition, suggesting that blacks may have lower sweat excretion of vitamins than whites.

The formation of functional sweat glands begins at week 36 of gestation and completes within 10 wk of postnatal life[27,28]. This process is affected not only by gestational age but also by the environmental temperature during the early postnatal period. As demonstrated in the literature, preterm birth is associated not only with a lower renal reserve capacity[29] but also with a low sweating function[30,31]. Low temperature may cause newborn hypothermia[32], which may occur even in summer season[32]. Reduced sweat gland function (*i.e.*, low skin conductance) has been found to be associated with a winter birth in schizophrenia[33]. Therefore, preterm birth and newborn hypothermia may be associated with decreased vitamin clearance.

Ambient temperature and physical activity are two important factors affecting the excretion rates of sweat and sebum. For example, a decrease in temperature from 30 ℃ to 22 ℃ reduces insensible perspiration from about 700 mL/d to 380 mL/d in adults[34], and a one-degree decrease in local skin temperature decreases the sebum excretion rate by 10%[35]. There is evidence showing that the levels of plasma vitamin A and E are lower in summer than in winter[36], and a similar seasonal variation is found in blood drug concentrations[37]. Thus, it is conceivable that physical inactivity and winter or cold weather would decrease the tolerance to high vitamin intake.

On the other hand, it should be noted that excess sweat vitamin excretion may cause or worsen water-soluble-vitamin deficiency if there is poor vitamin intake. A good example may be pellagra, a niacin-deficiency disease that affects those who live in poverty without sufficient animal-source foods (rich in nicotinamide), with the symptoms occurring during the summer[38], a season with the highest sweat excretion rates. However, over the past decades, both natural and artificial sources (*i.e.*, vitamin fortification and supplementation) of vitamins have significantly increased[2], while sweat excretion has significantly decreased due to physical inactivity and the widespread use of air conditioning. These dietary and lifestyle changes may increase the risk of excess accumulation of vitamins in the body, especially in those with reduced excretory capacity and/or activity.

Degradation of vitamins

Besides being directly excreted, vitamins also undergo degradation through phase Ⅰ (including oxidation, reduction, and hydrolysis) and phase Ⅱ metabolisms (*e.g.*, sulpfation, methylation and glutathione conjugation), which are catalysed by phase Ⅰ and phase Ⅱ drug-metabolizing enzymes, respectively. After phase Ⅰ and/or phase Ⅱ degradation, vitamins become more water-soluble and then can be more easily excreted from the body. Excess vitamins are degraded very rapidly. For example, cumulative administration of 2000 mg nicotinic acid [166 times the estimated average daily requirement (EAR)] in 13 h 10 min is found to only increase the levels of its metabolites in the plasma, without significantly changing plasma nicotinic acid concentrations[39]. We found that, at 5 h after oral administration of 100 mg nicotinamide (8.3 times the EAR), plasma nicotinamide had returned to near baseline levels, while its metabolite N^1-methylnicotinamide remained at high levels[24]. Thus, it is clear that a transient increase in vitamin intake may not change fasting vitamin levels.

Vitamins, xenobiotics, neurotransmitters and hormones share the same drug-metabolizing enzyme system, so they may interact with one another in their metabolism by inducing and competing for the enzymes[3,40]. For example, CYP2E1, highly expressed in obesity and type 2 diabetes[13], has more than 50 compounds, including some vitamins and ethanol[41]. Thus, it is conceivable that alcohol may cause low fasting vitamin levels by induced CYP2E1.

Phase Ⅱ metabolism of vitamins consumes detoxification resources, such as methyl-group donors, sulphate donors and glutathione, which are also necessary for the degradation of neurotransmitters and hormones. Therefore, excess vitamins can disturb the phase Ⅱ metabolism of neurotransmitters and hormones by competing for the limited detoxification resources[3]. Here, we take niacin methylation as an example to explain how excess vitamins affect metabolism of neurotransmitters and hormones. Methylation is a methyl-group transfer reaction from a methyl donor to a substrate, which is mediated by the methionine-homocysteine cycle. Methyl donors, including betaine and choline, are non-renewable resources in the body, while other components in the methylation system, including methionine, folate, vitamin B_{12} and relevant enzymes, can be repeatedly used in the reaction system. Choline can be used as a methyl donor only after being converted to betaine in the liver and kidneys. According to the relationship of the components in the methylation reaction system shown in Figure 1, it is quite clear that an increase in the levels of substrates will mainly increase the demand for betaine. Since niacin is degraded mainly through

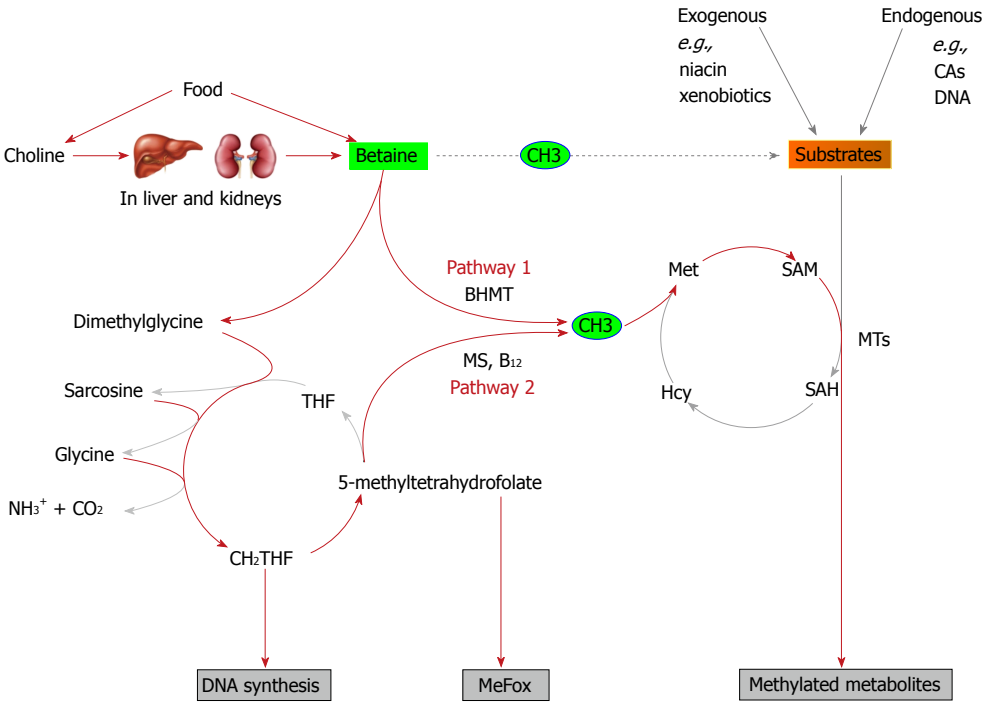

Figure 1 Relationship between methyl donors and mediators in the methylation of substrates. Methylation is a methyl-group transfer reaction from a methyl donor to a substrate, which is mediated by the methionine (Met) cycle. The deep red-arrow lines indicate the flow/transfer of methyl groups/one-carbon units from dietary sources to substrates. In this regard, methylation can be considered as a reaction between betaine and substrates (dashed line). An increase in the levels of substrates will increase the demand for betaine rather than for methylation mediators, *e.g.*, folate and vitamin B_{12} (B_{12}), because betaine is a non-renewable resource, while the mediators can be recycled if there is an adequate supply of methyl donors. Pathway 1: Betaine-dependent homocysteine (Hcy) remethylation; Pathway 2: Folate-dependent Hcy remethylation. BHMT: Betaine-homocysteine-methyltransferase; CAs: Catecholamines; CH_2-THF: 5,10-methylene tetrahydrofolate; CH3: Methyl groups; MeFox: An oxidation product of 5-methyltetrahydrofolate; MS: Methionine synthase; MTs: Methyltransferases; SAH: *S*-adenosylhomocysteine; SAM: *S*-adenosylmethionine; THF: Tetrahydrofolate.

methylation, niacin fortification/supplementation (usually using its nicotinamide form) increases the demand for methyl groups on the one hand, and on the other hand, it can reduce the utilization of choline as a methyl donor by causing hepatic and renal oxidative injury, as demonstrated in a rat model[42]. As a result, excess nicotinamide reduces the size of betaine pool and subsequently inhibits the methylation of endogenous substrates (*e.g.*, catecholamines and DNA), leading to an increase in plasma norepinephrine levels[43] and DNA hypomethylation, an important epigenetic alteration in human diseases[42,44].

Relationship between vitamin excretion and degradation

There is close cooperation between the excretory system and the drug-metabolizing enzyme system in maintaining vitamin homeostasis. If the body's excretory capacity is too low to effectively eliminate excess vitamins, the activity/expression of the drug-metabolizing enzyme system will compensatorily increase due to induction by their substrates[45]. Blacks have a lower sweat rate[2], but have a higher drug/vitamin-metabolizing activity than whites[46]. For example, compared with whites, blacks have a significantly higher catechol-*O*-methyltransferase (a phase Ⅱ enzyme that converted norepinephrine to epinephrine)[47] activity and norepinephrine clearance rate[48] and, during exercise stress, they show lower venous plasma norepinephrine and higher epinephrine[49]. Blacks are prone to low fasting serum vitamin D and folate levels[12,50] and need a higher vitamin D doses to achieve a desired serum 25-hydroxyvitamin D concentration[51]. This suggests an increase in plasma vitamin clearance. Given that the levels of plasma and urinary vitamin metabolites are linked to vitamin intake and that vitamins can induce their own degrading enzymes, the findings that increased activity/expression of drug-metabolizing enzymes (*e.g.*, CYP2E1[13,52] and NNMT[16]) and high levels of vitamin metabolites (*e.g.*, MeFox[12], N^1-methylnicotinamide[15,16] and nicotinuric acid[53]) can be considered as increased compensation for decreased vitamin excretion in response to high vitamin intake.

The degradation of vitamins is accompanied by the generation of reactive oxygen species (ROS). Although ROS at physiological levels functions as signalling molecules, at large levels they can induce cellular toxicity and insulin resistance. In our previous study, we found that co-administration of nicotinamide and glucose (like grain fortification with niacin) can induce insulin resistance due to excess ROS and subsequent reactive hypoglycaemia, demonstrating that vitamin-fortified grains can increase appetite[2,5]. This may explain the sharp increase in prevalence of obesity in the United States after the levels of vitamin fortification

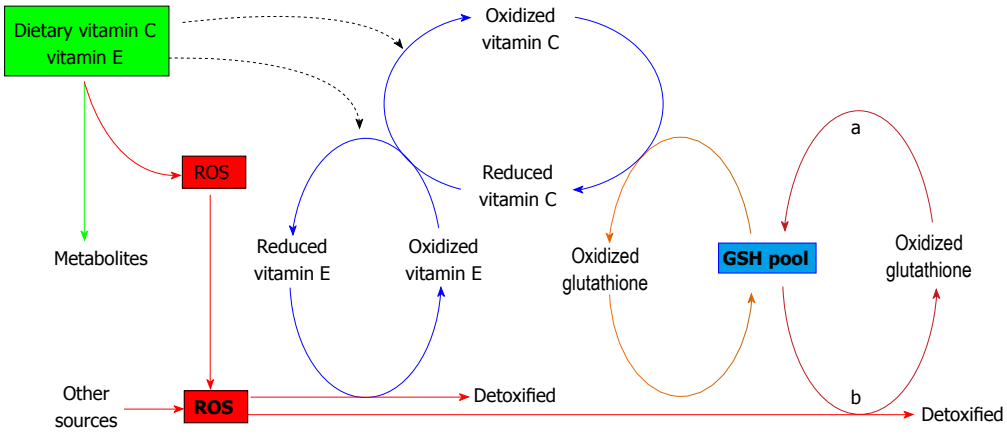

Figure 2 Glutathione-vitamin C-vitamin E interrelationship in the detoxification of reactive oxygen species. The endogenous glutathione antioxidant system maintains vitamin C and vitamin E recycling and actually determines the antioxidant effect of these vitamins. GSH: Reduced glutathione; a: Glutathione reductase; b: Glutathione peroxidase; ROS: Reactive oxygen species.

were increased in 1974[4,5]. Because decreased sweat excretion may increase enzymatic vitamin degradation and thereby ROS generation, individuals with reduced excretory capacity are at increased risk of insulin resistance, obesity and related diseases when exposed to identical high-vitamin diets.

As shown in Figure 2, it is clear that although vitamin E and C can scavenge ROS, their antioxidant effect actually depends on the capacity of the endogenous glutathione antioxidant system, by which vitamin C and vitamin E recycling is maintained[54]. Because the endogenous glutathione antioxidant system *per se* directly scavenges free radicals, high levels of supplementation of vitamin C and vitamin E are not only unnecessary but harmful due to increasing the burden of the glutathione antioxidant system. It is obvious that excess vitamin intake may provide an additional source of ROS. Thus, it is not surprising that some randomized clinical trials show that high-dosage vitamin E supplementation may increase, rather than decrease, cardiovascular events and all-cause mortality[55].

FOLIC ACID FORTIFICATION-INDUCED PARADOX

Although mandatory vitamin fortification has been implemented since the early 1940s and updated in 1974, unfortunately it is hard to determine the relationship between vitamin fortification and the increased prevalence of obesity, mainly because of the lack of studies regarding the effects of vitamin fortification and excess vitamin degradation on the metabolism of the body. Fortunately, the effects of the mandatory folic acid fortification that was started in 1998 in the United States are closely monitored based on the data from National Health and Nutrition Examination Surveys (NHANES). This provides a valuable opportunity for us to understand the vitamin paradox in obesity. The major results of studies on folic acid fortification are summarized as follows: (1) Blood folate concentrations in the United States population show first a sharp increase from pre- to postfortification (2.5 times for serum and 1.5 times for RBC folate) and then a decline over time (decreased by 17% for serum and 12% for RBC folate during 1999–2010)[56]; (2) Unmetabolized folic acid was detected in nearly all serum samples measured, and serum unmetabolized folic acid concentrations > 1 nmol/L are associated with being older, non-Hispanic black, nonfasting (< 8 h), higher total folic acid intake (diet and supplements), and higher RBC folate concentrations[57]; (3) Serum and RBC total folate concentrations, including MeFox (an oxidation product of folate), are high in older adults and individuals with low renal function[12]; (4) Body mass index is associated negatively with serum unmetabolized folic acid and 5-methyltetrahydrofolate, but positively with serum MeFox and RBC folate concentrations[12]; (5) Compared with non-Hispanic whites, non-Hispanic blacks have lower serum and RBC total folate concentrations[12]; (6) In folic acid supplement users, it was found that non-Hispanic black users have lower serum 5-methyltetrahydrofolate concentrations than non-Hispanic-white users[57]; and (7) Alcohol intake is negatively associated with serum unmetabolized folic acid, 5-methyltetrahydrofolate and MeFox, without significantly affecting RBC folate concentrations[12].

Evidently, there are significant differences in response to folic acid fortification among the United States population. From the perspective of vitamin homeostasis, the differences may actually reflect differences in folic acid excretion and degradation. Because folic acid is not a natural form of folate, the detection of unmetabolized folic acid in fasting serum suggests a folic acid overload. This overload is more evident in individuals with low excretion capacity, including either low renal function or sweat excretion (in non-Hispanic blacks), or both (in older adults).

The decline in post-fortification serum and RBC folate concentration over time in the United States

population[56], and the association between increased MeFox levels and decreased renal function[12] suggests a compensatory increase in folic acid degradation. As mentioned above, blacks may have a higher drug-metabolizing activity to compensate for their reduced sweat excretion. This may account for the finding that non-Hispanic blacks have low serum and RBC total folate concentrations. The association between unmetabolized folic acid concentrations > 1 nmol/L and non-Hispanic blacks[57] suggests that folic acid intake in this population may exceed their folic acid clearance capacity. Moreover, the low serum 5-methyltetrahydrofolate concentrations in non-Hispanic black users[57] may suggest a lack of one-carbon donors (due to the increased drug-metabolizing activity in blacks), because the formation of 5-methyltetrahydrofolate consumes one-carbon donors (Figure 1).

Many obesity risk factors, such as being blacks[11], having a low birth weight/preterm birth[58], a winter (or cold weather) birth[59,60], or physical inactivity[61], are related to decreased sweat-gland function. This is also supported by the finding that an equivalent dose of folic acid (by body weight) caused a greater increase in serum folate in obese than non-obese individuals[62]. Given that obesity is associated with folate-degrading enzyme CYP2E1[13,52], the association of increased serum MeFox and RBC folate levels and low fasting serum folate levels in obesity may reflect a severe folic acid overload. From this point of view, the finding that the inverse association between body mass index and serum folate is no longer evident among folic acid supplement users in the United States[63] can be considered as saturation of the compensatory capacity of the drug-metabolizing enzyme system in obesity.

Ethanol is known to induce drug-metabolizing enzymes[64,65], including CYP2E1[66]. This may explain the association between alcohol consumption and low fasting serum folate status. It should be pointed out that alcohol consumption-induced low fasting serum folate does not mean folate deficiency, because there is no significant decrease in RBC folate concentrations[12].

Overall, four conclusions can be reached: (1) the current folic acid intake of Americans has exceeded their excretory capacity; (2) there is increased compensation for increased folic acid intake, especially in individuals with low excretion capacity; (3) further folic acid supplementation after fortification can saturate the drug metabolizing enzyme system; and (4) the production of MeFox suggests that excess folic acid may increase the consumption of one-carbon units (Figure 1) and provide a source of ROS.

MECHANISM BEHIND LOW VITAMIN D STATUS

There is also a paradox after vitamin D is used in fortification and as a supplement. Vitamin D, although considered a vitamin, can be produced in the skin by sun exposure. Numerous studies have documented an association between low serum concentrations of 25-hydroxyvitamin D and many non-skeletal disorders. Many studies have examined the effect of vitamin D supplementation on the disorders[67], including obesity[68], diabetes[69], hypertension[70], dyslipidemia[71], cardiovascular disease[72], cancer[73], depression[74], and asthma[75]. Unfortunately, most, if not all, of published meta-analyses have failed to show a significant benefit of vitamin D supplementation with or without calcium[68-75]. It is likely that low fasting serum 25-hydroxyvitamin D status may be not the cause of these diseases.

The skin is a major determinant of 25-hydroxyvitamin D status. Besides synthesizing vitamin D, the skin also functions as a powerful excretory organ[17]. Notably, the skin functions fluctuate with seasonal temperature fluctuation, with the highest activities in summer and lowest activities in winter. Thus, it is likely that decreased skin excretory function may be a cause of human diseases. In fact, although not directly focusing on the excretory function of the skin, many studies have suggested a direct link of between the levels of plasma compounds and skin excretory function. For example, sebum excretion decreases in winter[76,77] and inhibition of sebum excretion increases the levels of blood triglycerides and cholesterol[78]. Sweat-inhibiting factors (*e.g.*, acute cold exposure[79,80]) increases plasma norepinephrine levels. Decreased sweating function is found to be closely linked to diseases, for example, skin conductance non-response in schizophrenia and depression[81], low skin conductance in hypertension[82] and type 2 diabetes[83], and the association between psoriasis and metabolic syndrome[84]. Moreover, many well-known chronic disease risk factors, such as being of black origin, having a preterm birth or winter birth, or physical inactivity, are associated with decreased skin excretory function, as mentioned above. Taken together, it can be concluded that decreased skin excretory function may play a major role in diseases, and 25-hydroxyvitamin D status may be an indicator of skin excretory function.

Interestingly, there is a graded relationship between vitamin D status and body mass index[85]. Sadiya *et al*[86] found that it is difficult to achieve target levels of 25-hydroxyvitamin D above 75 nmol/L in type 2 diabetic obese subjects with a relatively high daily dose of vitamin D_3. Recently, Didriksen *et al*[87] performed a 5-year intervention study with vitamin D_3 at a dose of 20000 IU (500 μg) per week *vs* placebo in subjects with impaired glucose tolerance and/or impaired fasting glucose, and they found that those given vitamin D_3 had significantly higher vitamin D concentration in their adipose tissue (about 6.5 times the placebo group), while their median serum 25-hydroxyvitamin D level only increased from the baseline of 61 to 99 nmol/L. This study clearly demonstrates that large amounts of vitamin D_3 are stored in adipose tissue after vitamin D_3 supplementation, and suggests that overweight and

obese subjects may store more vitamin D than normal-weight subjects because they have larger amounts of adipose tissue. Moreover, vitamin D is known to induce drug-metabolizing enzymes[88]. Thus, it seems likely that the prevalence of low 25-hydroxyvitamin D status after the introduction of vitamin D fortification may share a similar mechanism to that of low folate status: increased degradation and storage in compensation for excess intake.

THE CLINICAL SIGNIFICANCE OF THE VITAMIN PARADOX

Understanding the vitamin paradox in obesity and related diseases is crucial in determining how to manage the low vitamin status in these diseases. From the above analysis, it is apparent that the vitamin paradox in obesity may be due to increased vitamin degradation and storage in compensation for decreased vitamin excretion. This condition will continue until drug-metabolizing enzymes are saturated by their substrates, in which high expression of vitamin-degrading enzymes and elevated vitamin-metabolite levels may serve as indicators. The vitamin paradox can be resolved by reducing vitamin intake and increasing sweat rates, rather than by giving vitamin supplementation. Indeed, a recent study shows that bariatric surgery (restricting food intake) and exercise are associated with a significant reduction in NNMT expression plasma MNA levels[16]. This can be explained by decreased niacin intake and increased sweat excretion.

Excess vitamins have three major detrimental effects: (1) increasing ROS generation and subsequently leading to oxidative tissue damage and insulin resistance; (2) disturbing the degradation of neurotransmitters and hormones by competing for drug metabolizing enzymes and detoxification resources; and (3) causing epigenetic changes (*e.g.*, altered DNA methylation) by depleting the body's methyl-group pool[2,89]. Thus, fortification-induced sustained excess vitamin intake may deplete the drug-metabolizing system (*e.g.*, manifested by high levels of unmetabolized vitamins) and the antioxidant system, and eventually cause a variety of metabolic disorders and oxidative tissue damage. This may play a causal role in the increased prevalence of obesity and related diseases, as hypothesized in our previous work[2,4,5].

The association between high vitamin intake and chronic diseases can be considered as vitamin poisoning. Vitamin poisoning is dose dependent. For example, high-dosage vitamin E may increase cardiovascular events and all-cause mortality[55]. Two recent large-scale randomized niacin trials (nicotinic acid, 1500-2000 mg/d) show that nicotinic acid has many adverse effects, including loss of glycaemic control among persons with diabetes, new-onset diabetes[90,91] and increased risk of death, with borderline statistical significance (P = 0.08)[90]. There are three factors that can increase the risk of vitamin poisoning: (1) the function of excretory organs is too low to effectively remove excess vitamins from the body, for example, due to early-life malnutrition-induced renal insufficiency[92]; (2) the amount of vitamin intake has exceeded the excretory capacity of individuals without any developmental defect, which may account for excess chronic diseases in blacks and those with physical inactivity; and (3) the combination of both (1) and (2), accounting for the high rates of chronic diseases in subjects born preterm after the implementation of vitamin fortification. Because the reserve capacity of excretory/detoxifying organs has been determined in early life, whether or not chronic diseases occur will depend on whether there are chemical overloads of the excretory/detoxifying organs in late life. This may be the mechanism of the origin of chronic diseases. Excess vitamin is a kind of chemical overload, accounting for the association between the prevalence of obesity and diabetes and increased B-vitamin intake[4].

CONCLUSION

In summary, it can be concluded that the vitamin paradox in obesity may be a reflection of excess vitamin intake, rather than a vitamin deficiency. Given that there is a correlation between high vitamin intake and the increased prevalence of obesity, it can be assumed that obesity could be one of manifestations of chronic vitamin poisoning. Susceptible individuals to high vitamin intake are those with a low reserve capacity of excretory organs. Therefore, on an individual basis, prevention of obesity should focus on reducing their intake of vitamin-fortified foods, and for a country, more attention needs to be paid to the role of vitamin fortification and abuse in the increased prevalence of obesity and related diseases.

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