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# Is vitamin D deficiency an independent risk factor for obesity and abdominal obesity in women?

## Czy niedobór witaminy D jest niezależnym czynnikiem ryzyka otyłości i otyłości brzusznej u kobiet?

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**Abstract**

**Introduction:** Vitamin D has been determined to have some effects on $\beta$ cell function and insulin sensitivity, and it is known that type 2 diabetes mellitus and hyperparathyroidism can cause obesity. The aim of our study was to investigate if vitamin D deficiency without diabetes mellitus and metabolic syndrome is associated with obesity and abdominal obesity.

**Material and methods:** The study included 276 healthy premenopausal women. To exclude other causes of obesity, postmenopausal women and subjects with diabetes mellitus and metabolic syndrome were excluded. Women were divided into two groups depending on their 25-hydroxyvitamin$D_3$ [25(OH)$D_3$] levels: subjects with vitamin D deficiency (Group 1) and subjects without vitamin D deficiency (Group 2). Body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) were compared between the two groups.

**Results:** BMI, WC, WHR, rates of obesity, and abdominal obesity according to WC and WHR of Group 2 were lower than those of Group 1 ($p = 0.0005$, $p = 0.0001$, $p = 0.0045$, $p = 0.032$, $p = 0.002$, $p = 0.011$, respectively). 25(OH)$D_3$ levels negatively correlated with BMIs ($r = –0.480$, $p < 0.0001$), WCs ($r = –0.480$, $p < 0.0001$) and WHRs ($r = –0.312$, $p < 0.05$). There were no differences between serum parathormone, calcium and phosphorus levels of Group 1 and 2 ($p = 0.239$, $p = 0.354$, $p = 0.95$, respectively).

**Conclusion:** Vitamin D deficiency without diabetes mellitus and hyperparathyroidism may be associated with obesity and abdominal obesity. **(Pol J Endocrinol 2012; 63 (3): 196–201)**

***Key words:*** *obesity, abdominal obesity, vitamin D deficiency, 25-hydroxyvitamin$D_3$, body mass index*

**Streszczenie**

**Wstęp:** Wykazano, że witamina D wpływa na czynność komórek $\beta$ i wrażliwość na insulinę. Wiadomo również, że cukrzyca typu 2 i nadczynność przytarczyc mogą powodować otyłość. Celem badania było ustalenie, czy niedobór witaminy D u osób bez cukrzycy i zespołu metabolicznego wiąże się z otyłością i otyłością brzuszną.

**Materiał i metody:** Do badania włączono 276 zdrowych kobiet przed menopauzą. W celu wyeliminowania innych przyczyn otyłości z badania wykluczono kobiety po menopauzie, chore na cukrzycę i osoby, u których rozpoznano zespół metaboliczny. Uczestniczki badania podzielono na 2 grupy w zależności od stężenia witaminy 25-hydroksy$D_3$ [25(OH)$D_3$]: grupa 1 — osoby z niedoborem witaminy D, grupa 2 — osoby z prawidłowym stężeniem witaminy D. Porównano wskaźniki masy ciała (BMI, *body mass index*), obwody talii (WC, *waist circumference*) i współczynniki talia/biodra (WHR, *waist-to-hip ratio*) w obu grupach.

**Wyniki:** Wartości BMI, WC, WHR, odsetek osób otyłych i częstość otyłości brzusznej, określone na podstawie WC i WHR, były mniejsze w grupie 2, niż w grupie 1, (odpowiednio $p = 0{,}0005$; $p = 0{,}0001$; $p = 0{,}0045$; $p = 0{,}032$; $p = 0{,}002$; $p = 0{,}011$). Stężenia 25(OH)$D_3$ były ujemnie skorelowane z wartościami BMI ($r = –0{,}480$; $p < 0{,}0001$); WC ($r = –0{,}480$; $p < 0{,}0001$) i WHR ($r = –0{,}312$; $p < 0{,}05$). Nie stwierdzono różnic między grupami pod względem stężeń parathormonu, wapnia i fosforu w surowicy (odpowiednio $p = 0{,}239$; $p = 0{,}354$; $p = 0{,}95$).

**Wnioski:** Niedobór witaminy D u osób bez cukrzycy i nadczynności przytarczyc może się wiązać z otyłością i otyłością brzuszną. **(Endokrynol Pol 2012; 63 (3): 196–201)**

***Słowa kluczowe:*** *otyłość, otyłość brzuszna, niedobór witaminy D, 25-hydroksy$D_3$, wskaźnik masy ciała*

## Introduction

Humans get vitamin D from exposure to sunlight, from their diet, and from dietary supplements. Solar ultraviolet B radiation (wavelength, 290 to 315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin $D_3$, which is rapidly converted to vitamin $D_3$ [1–5].

The best food sources of vitamin D are fatty fish or their liver oils; however, small amounts are also found in butter, cream and egg yolk. Human and cows' milk are poor sources of vitamin D [6]. Vitamin D from the skin and diet is metabolised in the liver to 25hydroxyvitamin $D_3$ [25(OH)$D_3$], which is used to determine the vitamin D status of a patient; 25(OH)$D_3$

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is metabolised in the kidneys by the enzyme 25-hydroxyvitamin D-1$\alpha$-hydroxylase to its active form, 1,25-dihydroxyvitamin $D_3$. The renal production of 1,25dihydroxyvitamin $D_3$ is tightly regulated by serum parathyroid hormone, calcium and phosphorus levels [5].

The action of vitamin D on the small intestine and the bone is well known [1, 3, 5]. In the bone, vitamin D induces the differentiation of pre-osteoclasts to mature osteoclasts, ultimately promoting the removal of calcium and phosphorus from the bone [5].

In recent years, discussion of the actions of vitamin D has extended well beyond calcium metabolism. Nowadays, there is great interest in its role in decreasing the risk of many chronic diseases, including obesity which is associated with chronic inflammation in adipose tissue. It has been shown that vitamin D regulates calcium metabolism through its endocrine function and its noncalciotropic effects such as cellular differentiation and replication in many organs via its paracrine and autocrine role. These noncalciotropic functions comprise the immune system, liver, skeletal muscles, adipocytes and endocrine pancreas which have important roles in obesity and diabetes mellitus [7–12]. Vitamin D deficiency has been shown to impair insulin synthesis and secretion in human and animal models of diabetes, suggesting a role in the development of type 2 diabetes, which is one of the common causes of obesity and abdominal obesity [6, 13].

Moreover, vitamin D decreases production of tumour necrosis factor $\alpha$ (TNF-$\alpha$) which leads to impaired glucose metabolism in adipose tissue and skeletal muscle [14]. Besides, low levels of 25(OH)$D_3$ result in hyperparathyroidism and are among the endocrine derangements of adult obesity [15].

In this study, we hypothesise that obesity and abdominal obesity are more common in vitamin D deficiency independent of diabetes mellitus. With this aim, after excluding patients with diabetes mellitus and metabolic syndrome, which are common causes of obesity and abdominal obesity, we investigated body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), rates of obesity and abdominal obesity in subjects with and without vitamin D deficiency and compared them with one another.

## Materials and methods

This study was approved by our institutional Ethics Committee (approval date and number: 21 Feb 2008, 44/E) and the study subjects have therefore been assessed in accordance with the ethical standards set out in the Declaration of Helsinki. All subjects gave informed consent prior to their inclusion in the study.

### *Subjects*

Two hundred and seventy six healthy premenopausal female volunteers were included in the present study. It has been determined that the loss of oestrogen at the menopause causes weight gain [16]. Therefore only premenopausal females were included in the study. According to their serum 25 (OH) $D_3$ vitamin levels, subjects were divided into two subgroups: 162 subjects (58.69%) with vitamin D deficiency (the VDD Group), and 114 subjects (41.30%) without vitamin D deficiency (the NVDD Group).

Serum levels of calcium, phosphorus, parathormone (PTH) and 25 hydroxyvitamin $D_3$ [25 (OH) $D_3$] were measured in all subjects. Hip and waist circumferences were determined and BMIs and WHRs of all the participants were calculated. To exclude subjects with type 2 diabetes mellitus and metabolic syndrome (the diagnosis of metabolic syndrome was determined by the criteria of the Adult Treatment Panel III guidelines) [17], fasting and postprandial glucose levels, WCs, blood pressures, triglyceride and high density lipoprotein cholesterol (HDL-C) levels were measured. To exclude postmenopausal women, serum oestradiol, follicle-stimulating hormone (FSH), and luteinising hormone (LH) levels of all the subjects were measured. Subjects with diabetes mellitus, metabolic syndrome, liver disorders, thyroid dysfunction, renal disorders, congestive heart failure, lactose or gluten intolerance (coeliac disease), metabolic bone disorders, primary hyperparathyroidism, epilepsy on anticonvulsant therapy, or who were on other medications that might alter 25(OH)$D_3$ vitamin, 1,25$(OH)_2D_3$ vitamin metabolism, body weight, and thyroid functions, or subjects being treated with supplemental calcium, vitamin D, steroids, thiazides, or who had recently quit smoking , pregnant women, and those currently involved in a weight loss programme, were excluded from the study.

Body mass index was calculated as body weight (kg) divided by height (m) squared, and obesity was defined as BMI of 30 or above (kg/m$^2$) [18–20].

Waist circumferences were measured at the plane between anterior superior iliac spines and lower costal margins at the narrowest part of the waistline while patients were standing during slight expiration. For women, a WC > 88 cm was accepted as abdominal obesity [19–21].

Hip circumferences were measured horizontally over the farthest points of trochanters while standing with feet 20–30 cm apart. A WHR of > 0.85 was accepted as abdominal obesity [19, 20].

Since decreased physical activity is thought to play an important role in the pathogenesis of obesity [21], all the subjects were questioned about their normal physical activity. If they did exercise, they were also

questioned about how often they exercised regularly. Regular exercise was defined as a minimum of 45 minutes walking, at least four days a week or its calorie equivalent [16].

The study was conducted between October 2008 and February 2009.

### *Laboratory investigation*

Since the key diagnostic test in vitamin D deficiency is demonstration of a decreased serum 25 hydroxyvitamin $D_3$ [25 (OH) $D_3$] vitamin value, we determined serum 25 (OH) $D_3$ level for vitamin D deficiency. The 1,25 $(OH)_2D_3$ levels may be normal in vitamin D deficiency, because of the maximal stimulation of 1$\alpha$hydroxylase by the low serum phosphorus and high PTH levels [22]. Serum levels of 25(OH) $D_3$ lower than 20 ng/ml were accepted as vitamin D deficiency [5, 23].

To measure serum 25 $(OH)D_3$ levels, venous blood samples were collected into plain tubes, and serum was separated and stored at –70 °C for up to a week until analysis. Levels of 25 $(OH)D_3$ were estimated using a kit 25 $(OH)D_3$-Ria-CT (Brussels, Belgium). The treated samples were then assayed using a competitive binding radioimmunoassay (RIA) technique. Serum PTH (reference interval: 15-65 pg/mL); LH (reference interval for follicular phase: 2.4–12.6 mU/mL; for luteal phase: 1–11.4 mU/mL, for midcycle: 14–96 mU/mL); FSH (reference interval for follicular phase: 3.5–12.5 mU/mL; for luteal phase: 1.7–7.7 mU/mL, for midcycle: 4.7––21.5 mU/mL); and oestradiol levels (reference interval for follicular phase: 12.5–166 pg/mL; for luteal phase: 43.8–211 pg/mL, for midcycle: 85.5–498 pg/mL) were measured by electrochemiluminescent immunoassay (ECLIA) (Modular Analytics E170, Roche Diagnostics, Mannheim, Germany). Other biochemical parameters included in this study were glucose (reference interval: 70–100 mg/dL), triglyceride (reference interval: 0–150 mg/dL), HDL (reference interval: 35–55 mg/dL), albumin (reference interval: 3.5–5.2 gr/dL), calcium (reference interval: 8.8–10.6 mg/dL), and phosphorus (reference interval: 2.5–4.5 mg/dL). Serum levels of these biochemical parameters were determined according to standard laboratory procedures on an auto-analyser Olympus 2700 (Tokyo, Japan). Corrected calcium levels were calculated on the basis of albumin levels.

### *Statistical analysis*

All analyses in the statistical evaluation were carried out with SPSS v.13.0 software. VDD and NVDD groups were compared with independent samples t-test for continuous variables which show a normal distribution according to Shapiro-Wilk and Kolmogorov-Smirnov tests. Chi-square test was used for categorical variables to compare two groups. Spearman correlations were used to assess the correlations between BMI and 25$(OH)D_3$, between WC and 25$(OH)D_3$ and between WHR and 25$(OH)D_3$ as well as the potential covariates. $p \leq 0.05$ was considered to have statistical significance.

## Results

The present study included 162 female subjects with vitamin D deficiency (the VDD Group) and 114 without vitamin D deficiency (the NVDD Group). Characteristics of all the subjects are set out in Table 1. There were no significant differences in the regular exercise rates or the ages of the subjects between the VDD and the NVDD groups ($p = 0.076$, $p = 0.087$).

Body mass index, WC, WHR, rates of obesity, and abdominal obesity according to WC and WHR of the NVDD group were lower than those of the VDD group ($p = 0.0005$, $p = 0.0001$, $p = 0.0045$, $p = 0.032$, $p = 0.002$, $p = 0.011$, respectively) (Table I). However, there were no significant differences between serum calcium, phosphorus or PTH levels of the NVDD and VDD groups ($p = 0.22$, $p = 0.92$, $p = 0.23$, respectively) (Table I). Neither were there any significant differences between serum calcium, phosphorus or PTH levels of obese and nonobese subjects in the VDD group ($p = 0.354$, $p = 0.95$, $p = 0.239$, respectively) (Table II). In all subjects, 25$(OH)D_3$ vitamin levels were negatively correlated with BMIs, WCs and WHRs ($r = –0.480$, $p < 0.0001$; $r = –0.416$, $p < 0.0001$; $r = –0.312$, $p \leq 0.05$, respectively).

## Discussion

In recent years, there has been a worldwide increase in the prevalence of obesity, a problem that continues to grow. The same period has also exhibited an increasing interest in the role of vitamin D in chronic diseases [24], including obesity [25, 26].

Low serum 25$(OH)D_3$ is known to deteriorate cellular function in many tissues, including endocrine pancreas, which are involved in obesity and type 2 diabetes mellitus (T2DM). Vitamin D deficiency has been linked to obesity, whether obesity is assessed by body mass index (BMI) or waist circumference. Central obesity, using the waist as the surrogate, is associated with metabolic syndrome, insulin resistance, T2DM and atherosclerotic cardiovascular disease [13, 27]. Different mechanisms have been suggested about the association between vitamin D deficiency and obesity. Previously reviewed mechanisms include the following:

1) low vitamin $D_3$ may impair insulin action, glucose metabolism and various other metabolic processes in adipose and lean tissue [13];

**Table I.** *Comparison of characteristics of subjects with and without vitamin D deficiency (VDD)*
**Tabela I.** *Porównanie charakterystyki osób z niedoborem i bez niedoboru witaminy D (VDD, vitamin D deficiency)*

| | Subjects with VDD (n = 162) | Subjects without VDD (n = 114) | p |
|---|---|---|---|
| Age | 33.66 ± 5.73 | 31.55 ± 5.86 | 0.879 |
| Rates of the subjects who do exercise on a regular basis | 24 (14.8%) | 3 (2.6%) | 0.076 |
| 25(OH)$D_3$ vitamin [ng/mL] | 9.80 ± 5.14 | 54.29 ± 24.17 | 0.0005 |
| Calcium [mg/dL] | 9.42 ± 0.38 | 9.32 ± 0.4 | 0.22 |
| Phosphorus [mg/dL] | 3.58 ± 0.54 | 3.59 ± 0.41 | 0.92 |
| PTH [pg/mL] | 41.06 ± 12.83 | 44.61 ± 14.67 | 0.23 |
| BMI | 28.16 ± 5.56 | 23.22 ± 4.47 | 0.0005 |
| WC [cm] | 88.19 ± 11.75 | 77.71 ± 12.28 | 0.0001 |
| WHR | 0.82 ± 0.07 | 0.77 ± 0.08 | 0.0045 |
| Rate of obesity | 42 (25.9%) | 9 (8.1%) | 0.032 |
| Rate of abdominal obesity according to WC | 75 (46.3%) | 18 (15.8%) | 0.002 |
| Rate of abdominal obesity according to WHR | 48 (29.6%) | 9 (7.9%) | 0.011 |

BMI — body mass index; WC — waist circumference; WHR — waist-to-hip ratio; PTH — parathormone

**Table II.** *Comparisons of serum calcium, phosphorus and PTH levels of obese and non-obese subjects with vitamin D deficiency (VDD)*
**Tabela II.** *Porównanie stężeń wapnia, fosforu i PTH w surowicy między otyłymi i nieotyłymi kobietami z niedoborem witaminy D (VDD)*

| | Obese subjects with VDD (n = 42) | Non-obese subjects with VDD (n = 120) | p |
|---|---|---|---|
| 25(OH)$D_3$ vitamin [ng/mL] | 10.05 ± 5.35 | 9.72 ± 5.13 | 0.84 |
| Calcium [mg/dL] | 9.51 ± 0.31 | 9.40 ± 0.40 | 0.35 |
| Phosphorus [mg/dL] | 3.59 ± 0.56 | 3.58 ± 0.54 | 0.24 |
| PTH [pg/mL] | 37.56 ± 8.26 | 42.29 ± 13.97 | 0.95 |

PTH — parathormone

2) fat soluble vitamin $D_3$ is sequestered in large adipose compartment and low in serum [13];

3) obese people may be sensitive about their body shape, minimising their skin exposure to view and sunlight (not tested) [13];

4) abnormal serum calcium metabolism has been associated with weight gain [28], and a high calcium intake is believed to prevent obesity [29];

5) 1,25 $(OH)_2D_3$ is reported to inhibit the expression of adipocyte uncoupling protein 2 (UCP-2), which would stimulate lipogenesis and inhibit lipolysis [30, 31];

6) Physiologic increase in parathyroid hormone levels in response to hypovitaminosis D state is believed to increase intracellular calcium in adipocytes, which leads to increased lipogenesis and weight gain [32];

7) obesity is associated with chronic inflammation in adipose tissue, as evidenced by increased levels of cytokines including tumour necrosis factor $\alpha$ (TNF-$\alpha$), and accumulation and activation of macrophages and T cells [33]. Recently in a study performed in mice, TNF-$\alpha$ has been determined to promote lipogenesis, induce lipolysis [34] and interfere with insulin signalling, which would lead to impaired glucose metabolism in adipose tissue and skeletal muscle [14].

It has been proposed that proinflammatory cytokines are causally linked to the development of insulin resistance [35, 36] and islet cell inflammation which is involved in the regulation of $\beta$-cell function in type 2 diabetes [14, 37]. Th1 cell-derived interferon (IFN)-$\gamma$ has been determined to regulate fat inflammation and glucose homeostasis in mice [33]. Vitamin D receptors are found in significant concentrations in the T lymphocyte and macrophage population which have been detected in adipose tissue with increased infiltration in obesity.

Vitamin D decreases not only the proliferation of purified T (helper) h cells but also the production of important cytokines in the pathogenesis of obesity such as interferon (IFN)-$\gamma$ and TNF-$\alpha$ [38, 39].

Konradsen et al. [40] who studied 2,187 subjects recruited from a metabolic and medical lifestyle man-

agement clinic in Norway, observed that increasing BMI was accompanied by a significant reduction in serum $25(OH)D_3$ and $1,25(OH)_2D_3$ concentrations, and that those with a BMI of > 39.9 kg/m$^2$ had a 24% lower serum $25(OH)D_3$ concentration and an 18% lower $1,25(OH)_2D_3$ concentration than those with a BMI of < 25 kg/m$^2$. These results support the findings of Rodriguez's study, in which it was noted that a BMI of < 27.7 kg/m$^2$ favoured a serum vitamin D concentration of > 90 nmol/l. Furthermore, Rodriguez found a negative and significant correlation between $25(OH)D_3$ concentrations and BMI in women with BMI ≥ 30 kg/m$^2$ [25].

Worstman et al. [41] also found a similar association when they studied 13 obese (BMI > 30 km/m$^2$) white individuals and 13 controls to evaluate the serum levels of $25(OH)D_3$ and its response after exposure to UVB radiation or an oral dose of vitamin $D_2$. They reported that BMI was inversely correlated with serum $25(OH)D_3$ concentrations after irradiation, and that the increase in vitamin $D_3$ levels was 57% less in obese than in nonobese subjects post irradiation to UVB rays. This finding suggests that the subcutaneous fat, which is known to store vitamin $D_3$, sequesters more of the synthesised vitamin $D_3$ in obese than in nonobese subjects, because there is more fat available for this process.

Rodriguez reported that women who had high $25(OH)D_3$ levels, had lower BMIs, and also had smaller waist circumferences, than women who had low $25(OH)D_3$ levels [25]. These results comply with those reported by McGill [13], who, in a study of 250 ambulant New Zealanders aged > 18 years with a BMI of 28––50 kg/m$^2$ reported a reduction of 0.29 nmol/L ($p = 0.01$) in serum $25(OH)D_3$ for every 1 cm increase in waist circumference. This finding highlights well the relationship between adiposity and serum $25(OH)D_3$ concentration, since waist circumference is a better marker of abdominal fat accumulation than BMI [42].

In the large USA NHANES dataset, Ford et al. found that abdominal obesity as measured by waist circumference alone, in addition to metabolic syndrome, was related to low $25(OH)D_3$, notably affecting mixed-ethnicity participants equally [43].

In the present study, BMI, WC and WHR were higher, and obesity and abdominal obesity were commoner, in subjects with vitamin D deficiency than in subjects without vitamin D deficiency.

In their studies, Alemzadeh et al. observed that subjects with hypovitaminosis D had decreased insulin sensitivity compared to vitamin D–sufficient subjects, corresponding to significantly higher BMI and fat mass in the subjects with hypovitaminosis D. Consequently, it was determined that lower serum $25(OH)\ D_3$ in obese people was most likely the cause of higher intact (i)PTH concentrations; and serum iPTH levels were positively correlated with the degree of adiposity and were higher only in the vitamin D-deficient and insufficient subjects compared to the vitamin D–sufficient subjects [15, 44–47].

However, in the present study, as an interesting finding, no difference was found between serum PTH levels of the subjects with and without vitamin D deficiency. This finding could be explained by blunted parathyroid hormone response to vitamin D deficiency by hypomagnesaemia, which means that parathyroid hormone levels are often normal when 25-hydroxyvitamin $D_3$ levels fall below 20 ng/mL [5].

Thus, we suggest that vitamin D deficiency is associated with obesity and abdominal obesity independently of primary and secondary hyperparathyroidism in response to vitamin D deficiency. However, we did not determine serum magnesium levels of the subjects with and without vitamin D deficiency. This is a weakness of our study.

Chiu et al. observed a positive correlation between vitamin D status and insulin sensitivity index in adults. In addition, they showed that vitamin D levels negatively correlated with both first and second phase insulin responses during a hyperglycaemic clamp and glucose levels during an oral glucose tolerance test. Thus, they suggested that subjects with hypovitaminosis D displayed more impaired $\beta$-cell function causing impaired glucose homeostasis, and increased risk of developing insulin resistance and metabolic syndrome, compared to vitamin D-sufficient subjects [48].

Although some studies have been conducted about the association between vitamin D deficiency and obesity, our study is important and different from others, because in our study, obesity and abdominal obesity were commoner in vitamin D-deficient subjects who did not have other important causes of obesity such as diabetes mellitus, metabolic syndrome [16, 41] and hyperparathyroidism [32]. Hyperparathyroidism causes obesity by increasing intracellular calcium in adipocytes, which leads to increased lipogenesis and weight gain [32].

## Conclusions

In conclusion, we suggest that vitamin D deficiency may be associated with obesity and abdominal obesity independently of its effects on T2DM, metabolic syndrome and hyperparathyroidism. Determining vitamin D levels may be beneficial for obese and abdominally obese people. Vitamin D administration in the winter to obese and abdominally obese people with vitamin D deficiency is also a subject worth investigating, especially for countries like ours whose food products are not supplemented with vitamin D. However, it may be bet-

ter for all countries to supplement food products with vitamin D to prevent inflammatory diseases including obesity which have been linked to vitamin D deficiency.

## Conflict of interest

The authors declare that there is no conflict of interest.

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