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ORIGINAL ARTICLE

Effect of vitamin D deficiency on BMI in patients treated with Multi-acting Receptor Target Antipsychotics

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Abstract

OBJECTIVES: Our aim was to examine the effect of vitamin D deficiency on BMI in patients treated with Multi-acting Receptor Target Antipsychotics (MARTA).
METHODS: We measured serum 25-hydroxyvitamin D [25(OH)D] levels and body mass index (BMI) in patients with (≥1 months) and without long-term exposure to MARTA to evaluate the role of 25(OH)D deficiency on BMI.
RESULTS: The BMI was significantly higher after long-term MARTA exposure in 25(OH)D-deficient patients than in non-deficient patients. No significant difference was found in antipsychotic exposure between the long-term MARTA exposure groups. The BMI was significantly higher in long-term MARTA exposure 25(OH)D-deficient patients than in 25(OH)D-deficient patients without long-term exposure.
CONCLUSION: Vitamin D deficiency could be a risk factor for MARTA-induced weight gain. Further studies are necessary to replicate this finding.

Abbreviations:

25(OH)D	- 25-hydroxyvitamin D
AP	- antipsychotic
BMI	- Body mass index
CVD	- cardiovascular diseases
DM	- type 2 diabetes
IQR	- inter-quartile ratio
MARTA	- Multi-acting Receptor Target Antipsychotics
mg	- milligram
MetS	- Metabolic syndrome
nmol/l	- nanomole per litre
n.s.	- non significant

INTRODUCTION

There is a body of evidence for a correlation between high vitamin D concentrations and low risk and reduced prevalence of cardiovascular diseases (CVD), hypertension, ischaemic stroke, stroke, cognitive disorder, depression, high body mass index (BMI), metabolic syndrome, type 2 diabetes (DM), breast cancer and other adverse health outcomes (Streb *et al.* 2017; Theodoratou *et al.* 2014). However, the role of vitamin D in any outcome remains poorly understood (Theodoratou *et al.* 2014). An association between vitamin D deficiency and depression or schizophrenia has been recently established (Anglin *et al.* 2013; Valipour *et al.* 2014).

Metabolic syndrome (MetS) and its components are highly predictive of CVD. The pooled MetS prevalence in people with severe mental illness (major depressive disorder, bipolar disorder, schizophrenia) in a large clinical study (n = 52,678) was 33% (Vancampfort *et al.* 2015). Patients treated with any individual antipsychotic had a significantly higher MetS risk compared to antipsychotic-naive participants. Other large-scale meta-analyses confirmed that patients with severe mental illness have a significantly increased risk of CVD and CVD-related mortality (Correll *et al.* 2017). The authors suggested that elevated BMI, antipsychotic (AP) use, and CVD screening and management require urgent clinical attention. Moreover, a recent data-mining study reported that vitamin D reduced the occurrence of atypical antipsychotic-induced, DM-related adverse events (Nagashima *et al.* 2016).

Therefore, our objective was to examine the effect of vitamin D deficiency on BMI in patients treated with antipsychotics.

MATERIALS & METHODS

This was a cross-sectional, observational, retrospective study approved by the local ethics committee. The subjects gave their informed consent to participate in the study. Study subjects included 86 inpatients (47% female, older than 15 years) treated or indicated for treatment with antipsychotics in an acute closed department in the National Institute of Mental Health Czech Republic. Most patients (79%) were treated due to a primary psychotic disorders, while 11% had affective disorders, 4% had personality disorder, 3% had substance use disorders, 2% had organic brain disorders, and 1% had neurotic disorder. There were two groups of patients. One group included patients with long-term (≥ 1 months) exposure to Multi-acting Receptor Target Antipsychotics (MARTA: olanzapine, quetiapine, clozapine or MARTA combined with other antipsychotics) (n = 56) and the minimal AP exposure group included patients treated with different antipsychotics (<1 month) (n = 30).

All subjects had their serum 25(OH)D levels and BMI measured. The patients were subsequently separated based on their serum 25(OH)D levels into deficient and non-deficient groups. Since serum 25(OH)D levels have a circannual rhythm, we used the corrected 25(OH)D level for patients assessed throughout the whole year. We corrected for a mean annual level that was reached in May and November (Woitge *et al.* 2000). The serum 25(OH)D level for each month from January through December was multiplied by 1.33, 1.38, 1.33, 1.19, 1, 0.81, 0.67, 0.62, 0.67, 0.81, 1 and 1.19. The indexes were derived from the following equation for rhythm 25(OH)D analyses: y = mesor + amplitude *cos ([x-acrophase]/ 365*2π)(Woitge *et al.* 2000). The equation for rhythm 25(OH)D analyses was evaluated for a southwestern German city (latitude, 49.5°N) that is close to the latitude in Prague (50.1°N).

Based on recent studies, serum 25(OH)D deficiency is defined as ≤25 nmol/l (Nerhus *et al.* 2017; Pearce and Cheetham 2010). Serum 25(OH)D levels were analysed with electrochemiluminescence using Elecsys assays (Roche). The blood draw, weight and height measurements were obtained immediately after admission to minimise the impact of hospitalisation. The BMI was calculated with a standard formula (BMI = weight in kg/height in m^2). The demographic data and antipsychotics exposure were obtained from the medical records over the past 12 months. The olanzapine

Tab. 1. Demographic parameters and results in long-term MARTA and minimal antipsychotic exposure 25(OH)D-deficit and non-deficit patients (medians; 25th and 75th percentiles).

	MIN-AP-25(OH)D non-deficit (n = 24)	MIN-AP-25(OH)D deficit (n = 6)	MARTA-25(OH)D non-deficit (n = 43)	MARTA-25(OH)D deficit (n = 13)	*p* value
Age (years)	23.50 (20.0–25.0)	31.0 (20.75–48.5)	27.0 (22.0–35.0)	24.0 (20.0–42.5)	n.s.*, n.s. †, n.s. ‡
Male : Female	13:11	2:4	24:19	7:6	n.s.*, n.s. †, n.s. ‡
BMI	22.28 (21.11–24.91)	24.47 (21.85–26.55)	24.57 (20.88–28.38)	29.01 (25.74–31.85)	0.002*, 0.01†,0.017‡
MARTA exposure (months)	0.125 (0.0–0.5)	0.0 (0.0–0.125)	5.0 (3.0–12.0)	5.0 (2.0–10.5)	n.s. †, n.s. ‡
non-MARTA exposure (months)	0.1 (0.0–0.5)	0.5 (0.0–0.56)	1.0 (0.0–5.0)	2.0 (0.0–5.5)	n.s. †,n.s. ‡
AP equivalents (olanzapine mg *number of months)	4.0 (0.0–10)	0.0 (0.0–3.47)	93.0 (43.0–157)	102 (27.5–174)	n.s. †,n.s. ‡

BMI – body mass index; AP – antipsychotic; MARTA - Multi-acting Receptor Target Antipsychotics, MIN-AP – minimal antipsychotic exposure, * the differences among 4 groups, † the differences between MARTA groups, ‡ the differences between minimal-antipsychotic exposure groups, n.s. – non significant.

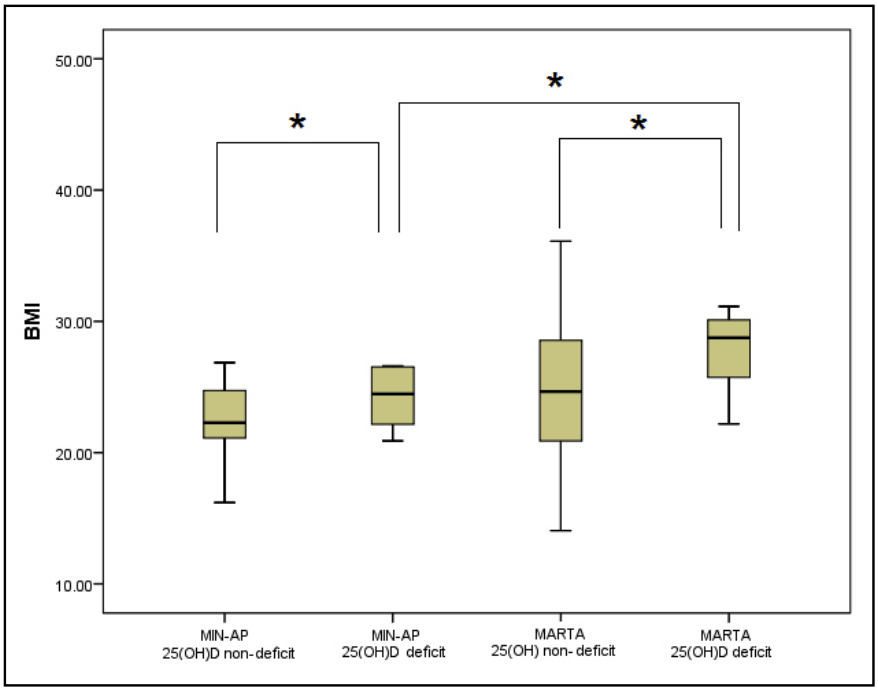

Fig. 1. Box and whisker plot of body mass index in four groups separated by MARTA or antipsychotics exposure and 25(OH)D status.
Legend: * $p < 0.05$. The central lines inside the boxes are medians, the edges of the boxes are 25th and 75th percentiles. The whiskers show 95% confidence intervals.

equivalents were calculated using a recent publication (Leucht *et al.* 2015). Data were analysed using IBM SPSS (version 23) for Windows. Nonparametric tests were used because the BMI values were not normally distributed. The independent samples Kruskal-Wallis test was used to analyse the distribution of BMI across four groups, and the Mann-Whitney U test was used to analyse the distribution between two groups with a significant p value < 0.05.

RESULTS

There were no significant differences among four groups in age and gender distribution. No difference was found in the AP exposure or AP equivalents between the long-term MARTA exposure groups as well as between the minimal AP exposure groups (Table 1).

Nineteen patients (22%) were serum 25(OH)D deficient in the whole sample. Thirteen patients (23%) were serum 25(OH)D deficient in the long-term MARTA exposure group and six (20%) in the minimal AP exposure group. No significant difference was found in the distribution of serum 25(OH)D-deficient and non-deficient patients between the groups (Chi-square, p = 0.732).

The BMI was significantly higher in serum 25(OH)D-deficient (n = 19) than non-deficient patients (n = 67) (Mann-Whitney U test, p = 0.005). The median and inter-quartile ratio (IQR) in the 25(OH)D-deficient group was 26.61 (23.88–29.07) and 23.59 (20.9–26.89) resp, in the 25(OH)D non-deficient group. The BMI was significantly higher in the long-term MARTA exposure than the minimal AP-exposure group (Mann-Whitney U test, p = 0.010). The median and IQR in the the long-term MARTA group was 25.74 (21.45–29.06) and 22.60 (21.11–25.19) resp, in the minimal AP-exposure group. The distribution of BMI was not the same across the four groups (Kruskal-Wallis test, p = 0.002) (Figure 1 and Table 1). The BMI was significantly higher in 25(OH)D-deficient patients than in non-deficient patients within the long-term MARTA exposure group, as well as compared to that of 25(OH)D-deficient minimal AP-treated patients (Mann-Whitney U test, p = 0.029 respectively, p = 0.024) (Figure 1 and Table 1).

DISCUSSION

Our results confirm previously reported higher BMI values in 25(OH)D-deficient than non-deficient patients, as well as a risk of higher BMI after MARTA treatment (Konarzewska *et al.* 2014; Leucht *et al.* 2013; Nagashima *et al.* 2016; Theodoratou *et al.* 2014). Moreover, our data shows that a combination of long-term MARTA exposure and 25(OH)D deficiency lead to higher BMI values than each factor alone. The distribution of 25(OH)D deficiency was the same in MARTA-treated and minimal AP-treated patients, suggesting that 25(OH)D deficiency is not influenced by MARTA treatment.

Recent meta-analysis confirmed that long-term vitamin D supplementation is associated with significantly reduced glycosylated haemoglobin, fasting glucose and

insulin resistance in DM patients (Mirhosseini *et al.* 2017). Furthermore, at least two animal studies reported that vitamin D supplementation was able to reduce glucose levels increased by atypical antipsychotics (Dang *et al.* 2015; Nagashima *et al.* 2016). These observations offer potential intervention against insulin resistance or weight gain and obesity induced by MARTA. Further intervention studies with cholecalciferol supplementation in patients treated with MARTA call for a cost/benefit analysis of vitamin D supplementation in the treatment of insulin resistance and obesity.

Eighty percent of serum 25(OH)D comes from UV exposure. Lower serum 25(OH)D levels may thus be a consequence of limited outdoor activities of patients. The reduced physical activity is a risk factor for obesity. Serum 25(OH)D levels may not directly influence BMI (it is not a causal factor) but could serve as biomarkers of outdoor activities of patients that could correlate with physical activities.

Our results should be evaluated as preliminary due to many limitations in our study. We used a relatively small sample size and a retrospective design. All patients were of Caucasian origins and most patients suffer from primary psychotic disorders that reduce the generalizability. We did not measure treatment compliance with antipsychotics and estimated only one year of antipsychotic exposure. Nevertheless, our study revealed that the 25(OH)D deficiency in MARTA users could be a risk factor for MARTA-induced obesity.

Further analysis is necessary to replicate this finding as well as to explain whether 25(OH)D influences BMI directly as was supported by animal studies (Dang *et al.* 2015; Nagashima *et al.* 2016) or indirectly as a biomarker of outdoor activities (Black *et al.* 2014) that could serve as a proxy marker for reduced physical activity. Results of these studies may help determine whether 25(OH)D levels will be a clinically useful biomarker for high BMI/obesity, CVD and CVD-related mortality in patients with severe mental illness.

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REFERENCES

1 Anglin RE, Samaan Z, Walter SD, McDonald SD (2013). Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br J Psychiatry **202**: 100–107.
2 Black LJ, Burrows SA, Jacoby P, Oddy WH, Beilin LJ, Chan She Ping-Delfos W, et al. (2014). Vitamin D status and predictors of serum 25-hydroxyvitamin D concentrations in Western Australian adolescents. Br J Nutr **112**: 1154–1162.
3 Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, et al. (2017). Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry **16**: 163–180.
4 Dang R, Jiang P, Cai H, Li H, Guo R, Wu Y, et al. (2015). Vitamin D deficiency exacerbates atypical antipsychotic-induced metabolic side effects in rats: involvement of the INSIG/SREBP pathway. Eur Neuropsychopharmacol **25**: 1239–1247.
5 Konarzewska B, Galinska-Skok B, Waszkiewicz N, Lazarczyk-Kirejczyk J, Malus A, Simonienko K, et al. (2014). Association between serum testosterone levels, body mass index (BMI) and insulin in male patients with schizophrenia treated with atypical antipsychotics--olanzapine or risperidone. Neuro Endocrinol Lett **35**:50–57.
6 Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet **382**: 951–962.
7 Leucht S, Samara M, Heres S, Patel MX, Furukawa T, Cipriani A, et al. (2015). Dose Equivalents for Second-Generation Antipsychotic Drugs: The Classical Mean Dose Method. Schizophr Bull **41**: 1397–1402.
8 Mirhosseini N, Vatanparast H, Mazidi M, Kimball SM (2017). The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis. J Clin Endocrinol Metab **102**: 3097–3110.
9 Nagashima T, Shirakawa H, Nakagawa T, Kaneko S (2016). Prevention of antipsychotic-induced hyperglycaemia by vitamin D: a data mining prediction followed by experimental exploration of the molecular mechanism. Sci Rep **6**: 26375.
10 Nerhus M, Berg AO, Simonsen C, Haram M, Haatveit B, Dahl SR, et al. (2017). Vitamin D Deficiency Associated With Cognitive Functioning in Psychotic Disorders. J Clin Psychiatry **78**: e750–e757.
11 Pearce SH, Cheetham TD (2010). Diagnosis and management of vitamin D deficiency. BMJ **340**: b5664.
12 Streb J, Glanowska I, Streb A, Szpor J, Kryka K, Potocki P, et al. (2017). The relationship between breast cancer treatment, tumour type and vitamin D level in pre- and postmenopausal women. Neuro Endocrinol Lett **38**: 437–440.
13 Svancer P, Andrashko V, Knytl P, Kohoutova B, Protopopova D, Hanka J, et al. (2018). Higher BMI in 25-OH vitamin D deficit than non-deficit patients treated with MARTA antipsychotics. European Psychiatry **48S**: S402.
14 Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP (2014). Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ **348**: g2035.
15 Valipour G, Saneei P, Esmaillzadeh A (2014). Serum vitamin D levels in relation to schizophrenia: a systematic review and meta-analysis of observational studies. J Clin Endocrinol Metab **99**: 3863–3872.
16 Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, et al. (2015). Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry **14**: 339–347.
17 Woitge HW, Knothe A, Witte K, Schmidt-Gayk H, Ziegler R, Lemmer B, et al. (2000). Circaannual rhythms and interactions of vitamin D metabolites, parathyroid hormone, and biochemical markers of skeletal homeostasis: a prospective study. J Bone Miner Res **15**: 2443–2450.