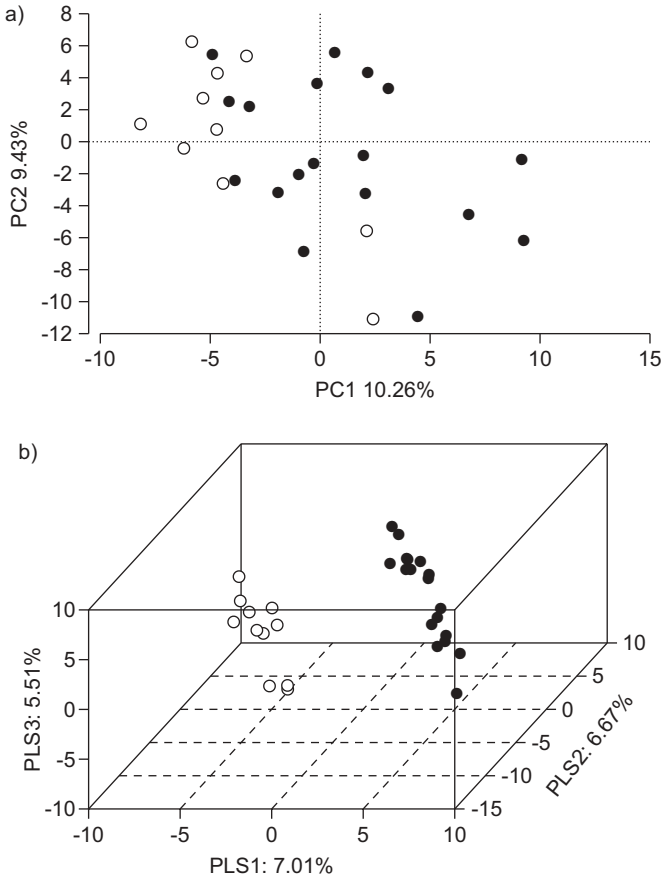

FIGURE 3. Multivariate analysis using ultra-performance liquid chromatography coupled to a time-of-flight mass spectrometer spectra of exhaled breath condensate from healthy and chronic obstructive pulmonary disease (COPD) subjects. a) Principal components analysis (PCA) score plot shows a separation between groups, which is clearly confirmed by b) partial least squares (PLS) analysis. ○: control; ●: COPD. PC1 and 2 are the first two principal components; PLS1 and 2 are the first two partial least squares.

required to observe the endogenous metabolites presented in the EBC. Finally, we propose UPLC-MS and the use of non-reusable devices as a standard metabolomic approach in the analysis of EBC.

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Hypercalcaemia in asymptomatic sarcoidosis unmasked by a vitamin D loading dose

To the Editors:

The risk of occurrence of hypercalcaemia induced by vitamin D in certain conditions has recently been summarised by KALLAS *et al.* [1]. Despite the high prevalence of vitamin D deficiency among the healthy population and observational associations with cardiovascular disease, autoimmune diseases, some types of cancer, tuberculosis and mortality [2, 3], there are currently no data to justify widespread use of vitamin D supplementation, taking into account the lack of large prospective randomised controlled trials.

We would like to share our experience with calcitriol-mediated hypercalcaemia in an apparently healthy individual. A 26-yr-old obese female with a body mass index of 48.4 kg·m^{-2} was transferred to the endocrinology outpatient clinic of the

TABLE 1 Overview of laboratory findings

	Normal range	March 10	May 10	June 10
Serum calcium mM	2.20–2.65	2.23	3.12	2.44
Urinary calcium mmol·24 h^{-1}	<8		16.25	
25-OH-D ng·mL^{-1}	>30	11.7		59.1
1,25-$(OH)_2$-D pM	39–193	70	409	242
PTH pg·mL^{-1}	15–65	50.7	5.6	8.3

25-OH-D: 25-hydroxyvitamin D; 1,25-$(OH)_2$-D: 1,25-dihydroxyvitamin D (calcitriol); PTH: parathyroid hormone.

Medical University of Graz (Graz, Austria) for evaluation of metabolic syndrome before bariatric surgery. Severe vitamin D deficiency was noted during the routine laboratory tests, and the patient received an oral loading dose of 180,000 IU cholecalciferol followed by 2,000 IU daily.

6 weeks later, the patient was sent to the nephrology outpatient clinic for evaluation of asymptomatic hypercalcaemia and hypercalciuria. Laboratory investigation demonstrated an increased 1,25-dihydroxyvitamin D (1,25-$(OH)_2$-D) and suppressed parathyroid hormone (PTH) level (table 1).

During the ensuing work-up, stage I sarcoidosis was diagnosed by chest radiography, with bilateral hilar lymphadenopathy. High angiotensin-converting enzyme levels (176.7 U·L^{-1}; normal range 20–70 U·L^{-1}) and cytological samples from bronchoscopy with typical histopathological findings confirmed the diagnosis of sarcoidosis. 5 weeks after the initial diagnosis of hypercalcaemia and withdrawal of oral cholecalciferol, calcium levels had normalised (ionised calcium 1.26 M) and the 25-hydroxyvitamin D (25-OH-D) level was in the upper normal range, whereas levels of 1,25-$(OH)_2$-D were still elevated and of PTH remained suppressed (table 1).

Vitamin D deficiency is highly prevalent, especially in obese individuals [4], but also in respiratory disease [5, 6]. Although vitamin D has a low-risk profile and a broad therapeutic window, we suggest that the use of vitamin D in healthy individuals outside of clear indications or clinical trials should be questioned for two reasons: first, there are currently no large prospective randomised controlled trials showing that vitamin D supplementation leads to beneficial outcomes; and, secondly, because of the potential risk of calcitriol-mediated hypercalcaemia that may arise from a variety of potentially unrecognised or asymptomatic conditions, as in the present patient. Asymptomatic sarcoidosis, especially in stage I, is not uncommon [7]. Vitamin D and calcium metabolism is abnormal in sarcoidosis. A Japanese group reported hypercalcaemia in 7% of newly diagnosed patients [8], whereas, in the ACCESS (A Case Control Etiologic Study of Sarcoidosis) cohort, hypercalcaemia and/or hypercalciuria were found in 4% of recently diagnosed patients [9] even without concomitant vitamin D therapy. Calcitriol-induced hypercalcaemia can occur in sarcoidosis when macrophages are challenged with sudden availability of the substrate 25-OH-D because pulmonary alveolar macrophages possess a 1α-hydroxylase and are able to produce 1,25-$(OH)_2$-D. Furthermore, the feedback mechanism seems to be less effective [6].

Although vitamin D is an important immunomodulator that may have a positive effect in patients with sarcoidosis [10], vitamin D loading doses are not recommended and vitamin D repletion must be undertaken with great care [6].

We think it is important to carefully weigh the risk/benefit ratio and consider the risk of hypercalcaemia in apparently healthy patients on vitamin D therapy. Therefore, calcium levels should be checked regularly when administering vitamin D, since hypercalcaemia is often asymptomatic.

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