ISSN 2518-1432 (Online); ISSN 2227-4782 (Print) https://doi.org/10.21856/j-PEP.2019.2.07

TYPE 2 DIABETES MELLITUS AND SUBCLINICAL HYPOTHYROIDISM: FOCUSING ON THE ROLE OF CHOLECALCIFEROL*

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Vitamin D insufficiency and deficiency has been associated with both type 2 diabetes mellitus (DM) and different autoimmune disorders [1]. The association between type 2 DM and the presence of thyroid autoimmunity has been a matter of debate [2]. Despite the fact that previous reports dismissed any association between them [3], there is confirmation to suggest an increased frequency of overt and subclinical hypothyroidism in patients with type 2 DM [4].

Considering the discordant results, the direct association between hypothyroidism and type 2 DM, and evidence implying an adverse role for hypothyroidism in insulin sensitivity, it could be supported that the interrelation between type 2 DM and hypothyroidism requires additional explanation from both the clinical and research viewpoint [5].

Created on increasing data from animal and human investigations, vitamin D insufficiency is presently considered as a potential risk factor for type 2 DM [6]. Cholecalciferol is connected with pathogenesis of pancreatic в-cell dysfunction, insulin resistance and systemic inflammation [7]. It is known that these conditions are partly responsible for the development of type 2 DM. Vitamin D can influence on the progress of these disorders directly through the activation of its own receptor, and in an indirect way by the adjustment of calcium homeostasis [8]. Observational researches have reported the intercommunication between vitamin D insufficiency and frequency of type 2 DM [9].

Generally, vitamin D insufficiency and deficiency is considered to be a predisposing

* Роботу виконано відповідно до плану науково-дослідних робіт Українського науково-практичного центру ендокринної хірургії, трансплантації ендокринних органів і тканин МОЗ України в межах НДР «Дослідження пухлин щитоподібної залози у хворих на цукровий діабет» (№ державної реєстрації 0113U006386), а також в рамках планової НДР ВДНЗ України «Буковинський державний медичний університет» «Генетичні, метаболічні аспекти запалення, дисфункція ендотелію та лікування при поєднаній патології внутрішніх органів» (№ державної реєстрації 0112U003546).

Установою, що фінансує дослідження, є МОЗ України.

Автори гарантують колективну відповідальність за все, що опубліковано в статті.

Автори гарантують відсутність конфлікту інтересів та фінансової зацікавленості при виконанні роботи та написанні статті.

Рукопис надійшов до редакції 21.11.2018.

component to both autoimmune pathology and impaired glucose tolerance [10]. These prior results might supply the background to suggest that cholecalciferol could be involved in the supposed relation between type 2 DM and hypothyroidism.

We aimed to explore the association between type 2 DM and subclinical hypothyroidism focusing on the role of cholecalciferol in Ukrainian population, using a cross-sectional study design.

MATERIALS AND METHODS

Subjects with an established diagnosis of type 2 DM and subclinical hypothyroidism (SH) were consecutively recruited from June 2017 to October 2017. A total of 150 participants (65 patients with type 2 DM, 35 patients with type 2 DM and subclinical hypothyroidism, and 50 healthy controls) constituted the study population.

Individuals, in whom normal glycaemia and thyroid functional status were documented by fasting glucose (FPG) and thyroid-stimulating hormone (TSH) levels, were also recruited as controls during the same period.

Current use of corticosteroids served as an exclusion criterion, since this could act as a confounder both at the levels of glucose homeostasis and thyroid autoimmunity. Subjects under vitamin D supplementation were also excluded from the study.

At the day of the recruitment, a structured medical interview and a physical examination were performed in each subject, medical records were retrieved. Informed consent was provided and the study was conducted in accordance with the Declaration of Helsinki. Descriptive characteristics of the study population are summarized in Table 1.

25-hydroxyvitamin D [25(OH)D], TSH, free thyroxine (fT_4), free triiodothyronine (fT_3), serum thyroid peroxidase autoantibody levels (TPOAb) were determined for each subject. Radioimmunoassays were performed according to the manufacturer's instructions for the measurements of serum 25(OH)D and thyroid parameters. 25(OH)D was conducted by immuno hemi luminescent method ECLIA on analyzer Elecsys 2010 (Roche Diagnostics, Germany) with test-system cobas. TSH, fT_4 and fT_3 were measured with DRG (Germany) reagents on automatic analyzer iEMS Reader MF (ThermoLabsystems, Finland), TPOAb — with Immunotech (Chech Republic) reagents.

Data are expressed as mean (standard deviation) or (%). [a]Statistically different vs control; [b]Statistically different vs group with type 2 DM

Subclinical hypothyroidism (SH) was defined as a state of increased serum TSH levels, with circulating fT_4 and fT_3 concentrations within the population reference [11]. Blood concentration of 25(OH)D is employed as a biomarker for overall vitamin D status. It accounts for both dietary and supplemental vitamin D intake as well as endogenous synthesis of vitamin D in the skin. The challenge with the use of this biomarker is that it is also correlated with several factors which themselves are related to numerous health outcomes. Vitamin D

Table 1

Descriptive characteristics of the study population

	Control group	Type 2 DM	Type 2 DM and SH
n	50	65	35
Male / female	21/29	24/41	11/24
Age, years	56.7 (6.2)	61.2 (7.3)	63.1 (7.6)
BMI, kg/m^2	29.1 (4.3)	32.7 (5.1)	33.1 (5.4)
HbA1c,%	–	6.8 (1.6)	7.2 (1.8)
25(OH)D, ng/ml	23.8 (6.2)	19.2 (5.4)[a]	15.1 (4.6)[ab]
TSH, μIU/ml	1.91 (0.72)	2.23 (0.74)	6.72 (1.53)[ab]
Thyroid peroxidase Ab, U/ml	26 (16)	61 (31)[a]	260 (115)[ab]

deficiency was defined as 25(OH)D levels less than 20 ng/ml and vitamin D insufficiency as 20–30 ng/ml [12].

Continuous variables were described as mean (standard deviation) or *n* (%), respectively. Normality assumption was assessed by visual inspection of the distribution as well as the Kolmogorov-Smirnov test. Differences in means were explored using Mann-Whitney and chi-squared tests for continuous and dichotomous variables, respectively. To explore the potential association between 25(OH)D, type 2 DM and SH while controlling for potential confounders, namely, age, gender, body mass index (BMI), and presence of type 2 DM, multivariate logistic regression analyses were undertaken in all study populations. Standardized values (z-scores) of the natural logarithms for all continuous variables were used. Fisher criterion was used to compare variances of the two variational series. Data analyses were performed using SPSS version 8.0 for Windows (SPSS, Chicago, IL, USA).

RESULTS AND DISCUSSION

Patients with type 2 DM and with type 2 and SH had significantly lower 25(OH)D and higher TSH and TPOAb titres compared to controls (Table 1). Prevalence of high TPOAb titres was greater in patients with type 2 DM and type 2 with SH compared to controls.

The great majority of the study population was found to be 25(OH)D deficient or insufficient and the prevalence of vitamin D deficiency/insufficiency was significantly higher in patients with type 2 DM (92.3 %), type 2 and SH (97.1%) compared to controls (86.0 %).

Multivariable logistic regression analyses adjusting for age, gender, and body mass index (BMI) suggested that both the presence of type 2 DM with SH (odds ratio (OR): 3.32, 95 % confidence interval (CI): 1.57–6.91) and 25(OH)D levels (OR: 1.34, 95 % CI: 1.02–1.74) were significantly associated with the presence of type 2 DM and SH (Table 2).

In population of patients with type 2 DM and controls with a high prevalence of vitamin D deficiency/insufficiency, type 2 DM and 25(OH)D levels were significantly associated with SH ($p < 0.005$).

The association between 25(OH)D and SH was noted only in the presence of type 2 DM and it was found to be positive [13]. Conflicting results have been reported in the literature regarding the association between type 2 DM and hypothyroidism [5, 9].

We speculated that this discrepancy might involve a role for cholecalciferol in light of confirmation suggesting its potential link to both thyroid autoimmunity and glucose intolerance individually.

Vitamin D deficiency and insufficiency has been associated with TPOAb titres, serum 25(OH)D levels were found to be significantly lower in patients with SH compared to controls [14], and the severity of 25(OH)D deficiency correlated with thyroid antibody levels in adult and children populations [15].

Similarly, a higher prevalence of vitamin D deficiency has been reported in the presence of type 2 DM [16] and an inverse association between circulating 25(OH)D levels and risk of incident type 2 DM was documented: each 10 ng/ml increment in 25(OH)D levels was associated with a 4% lower risk of type 2 DM [17].

Table 2

Multivariable logistic regression using TPO-Ab titres as the dependent variable

Covariates	Odds ratio	95% CI	P
Type 2 and SH	3.32	1.57–6.91	0.005
25(OH)D	1.34	1.02–1.74	0.038
Age	0.98	0.27–3.35	NS
Gender	0.62	0.31–1.16	NS
Body mass index	1.26	0.87–1.74	NS

CI — confidence interval, NS — non significant.

Patients with type 2 DM without SH have statistically significant higher percentage of TPOAb titres compared to controls (Table 1). All groups have a high prevalence of vitamin D deficiency/insufficiency and the difference between them is statistically significant. Vitamin D is one among many factors that could potentially modify thyroid autoimmunity. This finding should be imputed to the confusing effect of age, body mass index and gender, clearly, all variables used in the multivariable regression analysis. For this reason we took on a regression analysis, adapting for potential confounders.

In our model of regression analysis, both cholecalciferol levels and type 2 DM were included as covariates. The degree of correlation between type 2 DM and 25(OH)D levels in our sample was high as to undermine the analysis.

The study results should not be extrapolated to different persons with different baseline characteristics. Our sample demonstrated significant prevalence of vitamin D deficiency/insufficiency and a higher prevalence of TPOAb in patients with type 2 DM and SH compared to controls.

Preclinical studies of vitamin D action on insulin secretion, insulin action, inflammatory processes, and immune regulation, along with evidence of an increase of hypovitaminosis D worldwide, have prompted several epidemiological, observational, and supplementation clinical studies investigating a potential biological interaction between hypovitaminosis D and DM [18, 19].

The potential confounding effect of seasonal variation in serum 25(OH)D levels is expected to be minimal, since the collection of blood samples was performed during the same season (summer).

Our data and those of others pointing to the involvement of vitamin D in the pathogenesis of SH argue for screening for vitamin D levels in patients with hypothyroidism. Moreover, as treatment with vitamin D is inexpensive and carries minimal side effects, vitamin D supplements may be recommended for type 2 DM and SH patients. Further research is needed to evaluate the beneficial effects of such treatment as well as the optimal doses, including a high-dose regimen of vitamin D recently found to be effective and safe, and to increase compliance in these patients.

CONCLUSIONS

Patients with type 2 DM and with type 2 and SH had significantly lower 25(OH)D and higher TSH and TPOAb titres compared to controls.

The prevalence of vitamin D deficiency/insufficiency was significantly higher in patients with type 2 DM (92.3 %), type 2 and SH (97.1 %) compared to controls (86.0 %).

Multivariable logistic regression analyses adjusting for age, gender, and body mass index suggested that both the presence of type 2 DM with SH and 25(OH)D levels were significantly associated with the presence of type 2 DM and SH.

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TYPE 2 DIABETES MELLITUS AND SUBCLINICAL HYPOTHYROIDISM: FOCUSING ON THE ROLE OF CHOLECALCIFEROL

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Background. Vitamin D deficiency has been associated with both type 2 diabetes mellitus (DM) and thyroid autoimmune disorders. The association of vitamin D with type DM and subclinical hypothyroidism (SH) has not been investigated. **Aim** of the study is to explore the putative association between type 2 DM and SH focusing on the role of 25-hydroxyvitamin D [25(OH)D]. **Materials and methods.** Study population included 65 type 2 DM patients, 35 patients with type 2 DM and SH and 50 healthy controls. To explore the potential association between 25(OH)D and SH while controlling for potential confounders-namely, age, gender, body mass index, and presence of type 2 DM-multivariate logistic regression analyses were undertaken. **Results.** Patients with type 2 DM and with type 2 and SH had significantly lower 25(OH)D and higher TSH and TPOAb titres compared to controls. The prevalence of vitamin D deficiency/insufficiency was significantly higher in patients with type 2 DM (92.3%), type 2 and SH (97.1%) compared to controls (86.0%). Multivariable logistic regression analyses suggested that type 2 DM and 25(OH)D levels were significantly associated with the presence of SH. **Conclusions.** In population of patients with type 2 and SH with a high prevalence of vitamin D deficiency/insufficiency, it was shown that type 2 DM and vitamin D were associated with SH.

Key words: type 2 diabetes mellitus, subclinical hypothyroidism, vitamin D.

ЦУКРОВИЙ ДІАБЕТ 2-ГО ТИПУ І СУБКЛІНІЧНИЙ ГІПОТИРЕОЗ: АКЦЕНТ НА РОЛЬ ХОЛЕКАЛЬЦИФЕРОЛА

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Вступ. З дефіцитом вітаміну D асоційовані як цукровий діабет (ЦД) 2-го типу, так і аутоімунні захворювання щитоподібної залози. Взаємозв'язок вітаміну D і субклінічного гіпотиреозу (СГ) досі детально не вивчався. **Мета дослідження** – встановити можливий взаємозв'язок між типом ЦД 2-го типу і СГ, акцентуючи увагу на ролі 25-гідроксивітаміну D [25(OH)D]. **Матеріали і методи.** Під спостереженням перебувало 65 хворих на ЦД 2-го типу, 35 хворих на ЦД 2-го типу із СГ, а також 50 осіб контрольної групи. Багатофакторний регресійний аналіз проведено для дослідження потенційного зв'язку між вмістом 25(OH)D і СГ, враховуючи вік і стать хворих, індекс маси тіла і наявність ЦД 2-го типу. **Результати.** У хворих на ЦД 2-го типу і СГ встановлено достовірно нижчі рівні 25(OH)D і достовірно вищі титри антитіл до тиреоїдної пероксидази у порівнянні з контрольною групою і хворими на ЦД без СГ. Частота недостатності і дефіциту вітаміну D була значно вищою у хворих на ЦД 2-го типу (92,3%), ЦД 2-го типу із СГ (97,1%) у порівнянні з контрольною групою (86,0%). Багатофакторний регресивний логістичний аналіз вказує на асоціацію ЦД 2-го типу і вмісту 25(OH)D з наявністю СГ. **Висновки.** Серед обстежених осіб з ЦД 2-го типу і СГ встановлена висока частота недостатності і дефіциту вітаміну D, що вказує на їх взаємозв'язок із СГ.

Ключові слова: цукровий діабет 2-го типу, субклінічний гіпотиреоз, вітамін D.

САХАРНЫЙ ДИАБЕТ 2-ГО ТИПА И СУБКЛИНИЧЕСКИЙ ГИПОТИРЕОЗ: АКЦЕНТ НА РОЛЬ ХОЛЕКАЛЬЦИФЕРОЛА

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Вступление. С дефицитом витамина D ассоциируются как сахарный диабет (СД) 2-го типа, так и аутоиммунные заболевание щитовидной железы. Взаимосвязь витамина D и субклинического гипотиреоза (СГ) до сих пор детально не изучалась. **Цель исследования** - установить возможную взаимосвязь между СД 2-го типа и СГ, акцентируя внимание на роли 25-гидроксивитамина D [25(OH) D]. **Материалы и методы.** Под наблюдением находилось 65 больных СД 2-го типа, 35 больных СД 2-го типа из СГ, а также 50 лиц контрольной группы. Многофакторный регрессионный анализ проведен для исследования потенциальной связи между концентрацией 25(OH)D и СГ, учитывая возраст и пол больных, индекс массы тела и наличие СД 2-го типа. **Результаты.** У больных СД 2-го типа и СГ установлены достоверно более низкие уровни 25(OH)D и достоверно более высокие титры антител к тиреоидной пероксидазе в сравнении с контрольной группой и больными СД без СГ. Частота недостаточности и дефицита витамина D была значительно выше у больных СД 2-го типа (92,3%), СД 2-го типа из СГ (97,1%) в сравнении с контрольной группой (86,0%). Многофакторный регрессивный логистический анализ указывает на ассоциацию СД 2-го типа и концентрации 25(OH)D с наличием СГ. **Выводы.** Среди обследованных лиц из СД 2-го типа и СГ установлена высокая частота недостаточности и дефицита витамина D, что указывает на их взаимосвязь из СГ.

Ключевые слова: сахарный диабет 2-го типа, субклинический гипотиреоз, витамин D.