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Effect of vitamin D supplementation on insulin resistance in patients with hypothyroidism

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Abstract. ***Background.*** *Over the past decade, numerous non-skeletal diseases have been reported to be associated with vitamin D deficiency, including autoimmune thyroid pathology. Different studies provide evidence that vitamin D may play a functional role in glucose tolerance through its effects on insulin secretion and insulin sensitivity. The effect of vitamin D supplementation on insulin resistance in patients with hypothyroidism has not been investigated. The purpose of the study is to evaluate the effects of vitamin D supplementation on insulin resistance in hypothyroidism.* ***Materials and methods.*** *47 participants, 32–74 years old, including 39 women (82.9 %) and 8 men (17.1 %), took part in the study. Serum thyroid-stimulating hormone, insulin and 25(OH)D concentration were measured, and HOMA-IR was calculated. All measurements were performed at the beginning and the end of the study. Patients with hypothyroidism received 21,000 IU of cholecalciferol orally per week for twelve weeks. The results were analyzed by descriptive tests, and a comparison between variables was made using paired T-tests or Wilcoxon tests, as an appropriate.* ***Results.*** *All of the participants were vitamin D deficient. Mean serum 25(OH)D concentration was 21.72 ± 6.14 ng/ml. The results at baseline and at the end were: for insulin — 19.36 ± 2.39 and 9.92 ± 2.38 mIU/L ($p < 0.05$) and for HOMA-IR — 3.91 ± 0.32 and 2.38 ± 0.17 ($p < 0.05$), respectively.* ***Conclusions.*** *Our data showed significant improvement in serum insulin and in HOMA-IR after treatment with cholecalciferol, suggested that vitamin D supplementation could reduce insulin resistance in hypothyroidism.*

Keywords: *hypothyroidism; insulin resistance; cholecalciferol*

Introduction

Vitamin D insufficiency and deficiency is a global health problem, its role as an immune modulator has been recently emphasized. The evidence is increasingly pointing towards vitamin D significant role in reducing the incidence of autoimmune diseases [1]. Over recent, numerous non-skeletal diseases associated with vitamin D deficiency have been reported including hypothyroidism [2].

Some studies have shown that vitamin D may play a glucose tolerance through its effects on insulin secretion and insulin sensitivity [3].

In comparison to healthy controls, subjects with hypothyroidism have significantly lower circulating concentration of 25(OH)D [4]. Animal studies have shown that vitamin D is a basic factor, necessary for normal insulin secretion [5]. Vitamin D reduces insulin resistance probably through its effect on calcium and phosphorus metabolism and through up regulation of the insulin receptor gene [6].

Considering the discordant results, the direct association between thyroid autoimmunity and newly identified hypothyroidism in the context of type 2 diabetes mellitus [7], and evidence implying a detrimental role for hypothyroidism in insulin sensitivity [8], it could be advocated that the association between insulin resistance and thyroid autoimmunity requires further clarification from both the clinical and research perspectives.

Purpose. We purposed to explore the association between insulin resistance and hypothyroidism focusing on the role of 25(OH)D in an ethnically homogenous population and to evaluate the effects of vitamin D supplementation on insulin resistance in patients with hypothyroidism.

Materials and methods

47 participants, 32–74 years old, including 39 women (82.9 %) and 8 men (17.1 %) took part in the study taking levothyroxine. The patients took part in the study for twelve weeks. We added cholecalciferol to their

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medication and recorded their demographic data and medication before and after supplementation. During the trial, the subjects were instructed not to change dose of levothyroxine. Participants were assessed for weight, height, and BMI. We also measured TSH, serum creatinine, lipid profiles, insulin, calcium, phosphorous. Serum 25(OH)D was measured by radioimmunoassay. HOMA-IR (Hemostatic model assessment-Insulin resistance) was calculated [9].

We also assessed liver function by measuring serum concentration of aspartate aminotransferase and alanine aminotransferase to rule out liver disease and major non alcoholic fatty disease of the liver as exclusion criteria that might affect vitamin D metabolism.

Inclusion criteria were absence of hepatic, renal and bone diseases, malignancy, any history of the use of drugs such as anticonvulsants, calcium, vitamin D.

Written consent was obtained from all participants. After baseline assessment all patients took 21,000 units of cholecalciferol weekly, for 12 weeks. During the treatment, all patients were visited and interviewed about possible side effects, and to determine the degree of compliance. After 12 weeks of treatment, all laboratory tests and clinical evaluations were repeated as per the initial visit.

The Medical Ethics Committee of Bukovinian State Medical University approved the study protocol which complied with the current version of the Declaration of Helsinki.

Statistical analysis was performed using Statistics Package Statistica 10 (StatSoft, Inc., США). The Data were analyzed by descriptive tests such as mean, SD (standard deviation), and SE (Standard Error) and K-S (Kolmogorov-Smirnov) tests were performed to assess the normality of the variables before further statistical analysis. All data in this study are presented as mean ± SD. The effects of Vitamin D supplementation on the variables were analyzed by paired *t* test (for normally distributed) or Wilcoxon test (for non-normally distributed).

Results

The mean age of the participants was 45.2 ± 10.5 years old. The mean weight of the patients at baseline was 72 ± 11 and at the end was 71 ± 8 kg that doesn't have a meaningful differences. All patients were controlled with levothyroxine as monotheraphy. Mean 25(OH)D concentration was 21.72 ± 6.14 ng/ml at baseline and all patients at baseline were vitamin D deficient based on 25(OH)D < 30 ng/ml. TSH before and after treatment was normally distributed, so it was analyzed by paired *t* test. But HOMA-IR and insulin before and treatment were non-normally distributed, so they were analyzed by Wilcoxon test. Insulin concentration decreased significantly after treatment with cholecalciferol ($p < 0.05$). Comparison of mean for HOMA-IR before and after treatment with vitamin D showed a meaningful reduction after supplementation (Table 1).

Twelve weeks of cholecalciferol supplementation did not change lipid profile in patients with hypothyroidism.

Discussion

The main purpose of this study was to investigate the effects of vitamin D supplementation on serum insulin and HOMA-IR in patients with hypothyroisdism. There was an interesting finding. There was an inverse relation between final TSH and basal 25(OH)D concentration. In other words, higher serum basal 25(OH)D led to lower final TSH. This means that who had a higher serum basal 25(OH)D concentration benefited more of vitamin D intake to lowering final TSH. This may be because of non-skeletal effects of vitamin D which appears in higher vitamin D concentration and the effects of lower vitamin D concentration, are limited to the bone and muscle. Our data showed that effects of vitamin D on insulin resistance was significant when vitamin D concentration was 30–50 ng/ml and in lower vitamin D concentration, it didn't affect on insulin resistance.

Effects of vitamin D supplementation on insulin resistance have been shown in numerous studies. Our findings are consistent with results of many other published studies, in which the insulin resistance appears to be decreased in patients with hypothyroidism who had received vitamin D. Von Hurst showed that vitamin D supplementation significantly improved insulin sensitivity and insulin resistance [10].

Monthly supplementation with 120,000 units of vitamin D also improved insulin sensitivity [11]. Although in contrast to some studies, M.D. Witham et al. foundout that vitamin D intake (at different dosage) had no effects on insulin resistance [12]. J. Nagpal et al. reported that vitamin D supplementation had no effect on mean of insulin sensitivity but two years treatment with vitamin D did improve HOMA-IR [13].

There are some mechanisms for the effects of vitamin D: presence of vitamin D receptors on pancreatic β-cells [3]. Vitamin D activating 1α-hydroxylase is expressed in pancreatic β-cells [14], presence of vitamin D response element in the insulin gene, presence of vitamin D receptor in skeletal muscle and the fact that 1,25(OH D increases transcription of insulin receptor genes [6].

It would be useful, though to undertake further studies to discover more about the mechanism and the ef-

Table 1. Comparison of biochemical characteristics (mean ± SD) in patients with hypothyroidism before and after treatment with cholecalciferol for 12 weeks

Variable	Before treatment	After treatment	P-value
TSH, mIU/L	7.8	7.2	> 0.05
Insulin, mIU/L	19.36 ± 2.39	9.92 ± 2.38	< 0.05
HOMA-IR	3.91 ± 0.30	2.38 ± 0.17	< 0.05
25(OH)D, ng/ml	21.72 ± 5.14	38.40 ± 6.23	< 0.05

fect of vitamin D on both alpha and islet beta-cell function and also on the mechanisms determining insulin resistance.

A limitation of our study is that we did not evaluate the effects of placebo on insulin or HOMA-IR. However, there are a few studies that didn't use placebo, evaluated the effects of vitamin D at different doses on insulin resistance [10].

Conclusions

Our data showed significant improvement in serum insulin and in HOMA-IR after treatment with cholecalciferol, suggested that vitamin D supplementation could reduce insulin resistance in hypothyroidism.

Conflicts of interests. Author declares the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

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Вплив додаткового призначення вітаміну D на інсулінорезистентність у хворих на гіпотиреоз

Резюме. ***Актуальність.*** Упродовж останнього десятиліття опубліковані відомості про численні позаскелетні розлади, асоційовані з дефіцитом вітаміну D, включаючи автоімунну патологію щитоподібної залози. Дослідження багатьох авторів підтверджують вагомий вплив вітаміну D на толерантність до глюкози через його дію на секрецію інсуліну й чутливість до інсуліну. Ефективність додаткового призначення вітаміну D на інсулінорезистентність у хворих на гіпотиреоз до цього часу не досліджувалася. ***Мета дослідження***: встановити вплив додаткового призначення холекальциферолу на інсулінорезистентність у хворих на гіпотиреоз. ***Матеріали та методи.*** 47 учасників віком 32–74 роки, у тому числі 39 жінок (82,9 %) і 8 чоловіків (17,1 %), було включено в дослідження. Визначали вміст ТТГ, інсуліну та 25(OH)D у сироватці крові, обчислювали індекс HOMA-IR. Усі дослідження проводили до та після лікування. Пацієнти з гіпотиреозом отримували 21 000 МО холекальциферолу на тиждень перорально упродовж 12 тижнів. Результати проаналізовані методами описової статистики, порівняння між змінними величинами зроблено з використанням парних Т-тестів. ***Результати.*** У всіх учасників дослідження встановлено недостатність і дефіцит вітаміну D. Середній вміст 25(OH)D у сироватці крові становив 21,72 ± 6,14 нг/мл. Показники концентрації інсуліну до та після призначення холекальциферолу дорівнювали 19,36 ± 2,39 і 9,92 ± 2,38 мМО/л ($p < 0,05$), для HOMA-IR — 3,91 ± 0,32 і 2,38 ± 0,17 ($p < 0,05$) відповідно. ***Висновки.*** Отримані результати демонструють вірогідне покращення показників вмісту інсуліну в сироватці крові і HOMA-IR на тлі додаткового призначення холекальциферолу, що вказує на роль вітаміну D у зниженні інсулінорезистентності у хворих на гіпотиреоз.

Ключові слова: гіпотиреоз; інсулінорезистентність; холекальциферол

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Влияние дополнительного назначения витамина D на инсулинорезистентность у больных гипотиреозом

Резюме. ***Актуальность.*** На протяжении последнего десятилетия опубликованы сведения о многочисленных внескелетных расстройствах, ассоциированных с дефицитом витамина D, включая аутоиммунную патологию щитовидной железы. Исследования многих авторов подтверждают весомое влияние витамина D на толерантность к глюкозе из-за его действия на секрецию инсулина и чувствительность к инсулину. Эффективность дополнительного назначения витамина D на инсулинорезистентность у больных гипотиреозом ранее не исследовалась. ***Цель исследования***: установить влияние дополнительного назначения холекальциферола на инсулинорезистентность у больных гипотиреозом. ***Материалы и методы.*** 47 участников в возрасте 32–74 лет, в том числе 39 женщин (82,9 %) и 8 мужчин (17,1 %), были включены в исследование. Определяли содержимое тиреотропного гормона, инсулина и 25(OH)D в сыворотке крови, вычисляли индекс HOMA-IR. Все исследования проводили до и после лечения. Пациенты с гипотиреозом получали 21 000 МЕ холекальциферола в неделю перорально на протяжении 12 недель. Результаты проанализированы методами описательной статистики, сравнения между переменными величинами проведены с использованием парных Т-тестов. ***Результаты.*** У всех участников исследования установлена недостаточность и дефицит витамина D. Среднее содержание 25(OH)D в сыворотке крови составляло 21,72 ± 6,14 нг/мл. Показатели концентрации инсулина до и после назначения холекальциферола составляли 19,36 ± 2,39 и 9,92 ± 2,38 мМЕ/л ($p < 0,05$), для HOMA-IR — 3,91 ± 0,32 и 2,38 ± 0,17 ($p < 0,05$) соответственно. ***Выводы.*** Полученные результаты демонстрируют достоверное улучшение показателей содержания инсулина в сыворотке крови и HOMA-IR на фоне дополнительного назначения холекальциферола, что указывает на роль витамина D в снижении инсулинорезистентности у больных гипотиреозом.

Ключевые слова: гипотиреоз; инсулинорезистентность; холекальциферол