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Original Article

Vitamin D Level and its Relation with the Newly Diagnosed Diabetic Neuropathy in Women with Hypothyroidism

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Abstract

Diabetic nephropathy has an important role in the kidneys' function to remove extra fluid and waste products from the body. One way to avoid this disease is the treatment of other diseases, such as diabetes, thyroid gland diseases, and high blood pressure, in addition to maintaining a healthy lifestyle. This study aimed to find the relationship of thyroid hormone, blood biochemical parameters, and anthropometric measurement with the newly diagnosed diabetic neuropathy in women with hypothyroidism. In total, 90 women (with an age range of 35-55 years) were selected, 45 of whom were diagnosed with diabetic neuropathy and had hypothyroidism, and the other 45 were healthy women recruited as the control group. The following parameters were determined: serum triiodothyronine, thyroxine, thyroid stimulating hormone (TSH), 1,25-Dihydroxyvitamin D3 (DHVD3) activities, anthropometric measurement, fasting blood sugar (FBS), hemoglobin A1C (HbA1C), urea, creatinine, and lipid profile. The results showed a significant increase in the body mass index, blood pressure, TSH, FSB, HbA1C, urea, creatinine, and triglycerides of women with newly diagnosed diabetic neuropathy and hypothyroidism, compared to that in the control group ($P \leq 0.05$). A significant decrease was also observed in the high-density lipoprotein cholesterol, DHVD3, total triiodothyronine, and total thyroxine of women with newly diagnosed diabetic neuropathy and hypothyroidism, compared to that in the control group ($P \leq 0.05$). There was a correlation between vitamin D3 deficiency (VDD) and thyroid dysfunction in women with the newly diagnosed diabetic neuropathy, which indicated VDD is related to thyroid dysfunction and influences newly diagnosed diabetic neuropathy in women.

Keywords: 1,25-Dihydroxyvitamin D3, Glutathione reductase hyperthyroidism, Hypothyroidism

1. Introduction

Diabetic nephropathy is a significant long-term consequence of diabetes that affects around 30% of individuals with type 1 diabetes (T1D) and 40% of patients with type 2 diabetes (T2D) (1). It is now the primary reason for end-stage kidney disease (ESKD) globally with almost 40% of new patients in need of renal replacement therapy (2). Epidemiological studies have underlined the complication's distinctive heterogeneity prompting the term "diabetic kidney disease" (DKD) to be used to refer to all types of renal impairment happening in diabetic individuals (3).

In addition to the classical albuminuric phenotype, dual new phenotypes have also appeared, namely "non-albuminuric renal impairment" and "progressive renal decline", suggesting that DKD progression toward ESKD may occur via dual-distinctive pathways in both T1D and T2D, as indicated by progressive albuminuria and the decline in the glomerular filtration rate (GFR), respectively. Additionally, over the last two decades, the therapy of hyperglycemia has changed dramatically in T2D patients with reduced renal function, as some

new anti-hyperglycemic medications have become available and the lowest GFR safety limits have been reconsidered for several older treatments (4).

Hypothyroidism has been linked to diabetes mellitus. A meta-analysis found that thyroid dysfunction occurs at a rate of 11% in patients with diabetes mellitus[6]. Autoimmunity has been implicated as the primary etiology of diabetes mellitus linked with thyroid dysfunction (5). Uncontrolled T1D and T2D can result in a "low triiodothyronine (T3) state" defined by low serum total and free T3 levels, a rise in reverse T3 levels, but near normal serum thyroxine (T4) and thyroid stimulating hormone (TSH) levels (6, 7). The relationship between T2D mellitus (T2DM) and thyroid dysfunction has received little attention, although it may hold the key to understanding numerous aspects of metabolic syndromes, such as atherosclerosis, hypertension, and other related cardiovascular diseases. In T2DM, the decreased insulin secretion results in a variety of metabolic abnormalities, including hyperglycemia, due to the reduced insulin-stimulated absorption, the increased hepatic glucose synthesis, as well as dyslipidemia, which includes altered fatty acid, triglyceride, and lipoprotein homeostasis (7).

Type 2 diabetes is related to several components of metabolic syndrome, including obesity, hypertension, and dyslipidemia. Secondary dyslipidemia is a consequence of hypothyroidism as well (8). Statins and fibrates, which are used to treat dyslipidemia, produce myalgia, myopathy, and rhabdomyolysis with renal damage, particularly in the existence of hypothyroidism. The following case report describes the aforementioned issues in a patient with diabetes who also has primary hypothyroidism, as well as the renal response to thyroxine supplementation (9).

The most common thyroid metabolic abnormality in hemodialysis patients may be euthyroid ill syndrome. According to the findings of previous research, it has affected about 70% of patients with end-stage renal disease (10). Vitamin D is critical for skeletal health and may also affect non-skeletal health, as evidenced by its relationship with autoimmune diseases (11, 12).

Based on the findings of previous studies, there is a correlation between thyroid autoimmunity and 25-hydroxyvitamin D (25-OHD) autoimmunity (13).

Vitamin D deficiency (VDD) continues to be a significant public health problem. It has garnered increased attention in recent years due to its significant prevalence and potential role in the development of several chronic disorders. The significant frequency of VDD in the general population demonstrates how prevalent it is in chronic conditions, such as diabetes mellitus. In developed and emerging countries, the primary dangers are T2D and hypothyroidism (14).

The T2DM significantly increases the likelihood of thyroid dysfunction with time (15). In the majority of high-income and developing nations, T2DM and hypothyroidism are the leading causes of death and morbidity (15). Several investigations, however, have revealed a higher prevalence of hypothyroidism in T2DM patients (16). Additionally, favorable connections between VDD and hypothyroidism have been seen in T2DM patients (17). The 25-OHD has been found to affect the thyroid gland through immune-mediated mechanisms by directly reducing thyrotropin-stimulated iodide uptake. Additionally, a high level of 25-OHD is related to low levels of (18).

This study hypothesizes that subclinical thyroid abnormalities are related to particular cardiovascular events and death in patients undergoing dialysis. Therefore, TSH, free T3, and free T4 were assessed in 1,255 patients with T2DM receiving maintenance hemodialysis in 4D (Die Deutsche Diabetes Dialyse Studie), and thyroid status was compared to clinical consequences. The present study evaluated the association between blood TSH levels and vitamin D status in patients with T2DM.

2. Materials and Methods

2.1. Study Population

This study was performed on 90 women aged 35 to 55 years, from September 2019 to December 2020. The study groups included 45 women with hypothyroidism

having the newly diagnosed diabetic neuropathy and 45 healthy women in the control group.

2.2. Anthropometric Measurements

All patients' data were collected, including their age, disease duration, measured blood pressure, and body mass index (BMI), which was determined by their body weight in kilograms divided by their body height in meters squared (kg/m^2).

2.3. Hormone and Biochemical Measurements

Venous blood samples were collected from fasting participants for estimating serum total triiodothyronine (TT3), total tetraiodothyronine (TT4), thyroid stimulating hormone (TSH), and vitamin D3, which were measured by Mini Vida's with Biomerix Kits (Biomerieux Corporate, France). While fasting blood sugar (FBS), hemoglobin A1C (HbA1C), lipid profile, including triglycerides (TG) and high-density lipoprotein (HDL), blood urea, as well as serum creatinine, were measured by using an automated analyzer (BIOLABO Kenza 240 TX).

2.4. Statistical Analysis

Microsoft Excel 2010 was used to conduct the statistical analysis. Means and standard deviations of the anthropometric and biochemical measurements were used to express data (SPSS, version 20). A *P*-value of less than 0.05 was considered significant, and a *P*-value of less than 0.01 was considered highly significant.

3. Results and Discussion

Table 1 illustrates the results of anthropometric measurement between hypothyroidism women with diabetic neuropathy and the control group. There have been statistically significant differences between hypothyroidism women with diabetic neuropathy and the control subjects in their BMI ($P \leq 0.05$) and hypertension ($P \leq 0.01$); however, there were no significant differences between them in their age and height ($P \leq 0.05$) (Table 2).

Table 1. Anthropometric measurement between hypothyroidism women with diabetic neuropathy and the control group

Parameters	Hypothyroidism Women with Diabetic Neuropathy No (45)	Control No (45)	*P*-value
	Mean±SD	Mean±SD	
Age (Years)	45.25±6.05	42.95±6.50	0.110
Height (cm)	187.77±5.02	175.93±2.56	0.126
Weight (Kg)	90.01±2.19	78.34±2.10	0.05*
BMI (Kg/m^2)	30.25±3.59	22.20±3.11	0.05*
SBP (mmHg)	165±5.00	130.50±5.00	0.001**
DBP (mmHg)	90.0±5.50	70.2±5.00	0.001**

P<0.05 is significant, and *P*<0.01 is highly significant
BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure
There are significant differences between * and **

Table 2. Comparison of fasting blood sugar, hemoglobin A1C, lipid profile, urea, creatinine, and vitamin D3 between hypothyroidism women with diabetic neuropathy and the control group

Parameters	Hypothyroidism Women with Diabetic Neuropathy No (45)	Control No (45)	*P*-value
	Mean±SD	Mean±SD	
FBS (mg/dl)	213±10.32	74±5.00	0.001**
HbA1C (%)	8.00±1.23	4.14±1.03	0.05*
TG (mg/dl)	216.00±10.91	114.02±9.37	0.01**
HDL-c (mg/dl)	36.19±5.18	55.41±3.13	0.05*
Urea (mg/dl)	35.57±4.44	28.17±2.19	0.05*
Creatinine (mg/dl)	1.18±0.49	0.65±0.31	0.05*
D3 (ng/ml)	12.53±2.01	35.92±2.51	0.001**

P<0.05 is significant, and *P*<0.01 is highly significant
FSB: Fasting blood sugar, TG: Triglyceride, HbAC1: Hemoglobin AC1, HDL: High-density lipoprotein
There are significant differences between * and **

Diabetic nephropathy, as one of the consequences of diabetes, has been linked to diabetic patients' health and longevity. A gold standard for diagnosing DKD has been kidney biopsy, which is a challenging task in large population samples. Research has shown that the morning urine albumin-creatinine ratio (UACR) is an important risk factor for diabetic nephropathy and renal events that can make prognostic information available (19, 20). It is a simple technique for collecting information similar to 24-h urine collection, which is the gold standard (21).

Both hypothyroidism and hyperthyroidism have been shown to impair kidney function directly through their effects on renal blood flow, GFR, tubular function, electrolyte balance, electrolyte pump function, as well as kidney structure (22) (Table 3).

Reduced free T3 (FT3) and T3 levels have been associated with an increased risk of decreased estimated glomerular filtration rate (eGFR) and an increased UACR. Additionally, while the AUROC of FT3 for these three patterns of kidney disorders was significantly greater than that of any other thyroid hormone, the AUROC of FT3 and T3 for reduced eGFR in each participant suggested that decreased T3 has been consistently identified as the most common disturbance in patients with kidney disorders and that stands for an independent analyst of survival. Differences in results are due to the time following exposure. To begin with, it is widely accepted that thyroid hormone levels fluctuate over time and are subject to a variety of variables, including cardiovascular disease, diabetes, anemia, and malnutrition (23).

Therefore, it seems that in an individual patient, there is a full disconnection between biochemical hypothyroidism and tissue hypothyroidism in peripheral target organs. Hypolipidemic agents do not cause rhabdomyolysis in all hypothyroid patients (9).

The GFR decreases in hypothyroid patients for a variety of reasons, including decreased renal blood flow (24), increased peripheral vascular resistance, and intrarenal vasoconstriction because of decreased renal responsiveness to vasodilators (25). Additionally, renal vasodilators, such as vascular endothelial growth factor and insulin-like growth factor-1 expression, decreased (26).

Furthermore, decreased renin release and the altered renin angiotensin aldosterone system activity contribute to decreased GFR56. There has been a decrease in tubular creatinine secretion, a mechanism regulated by thyroid hormones through the Na+/Ca2+ exchanger and the Na+/K+ATPase activity, which contributes to the increase in serum creatinine (27).

Hypothyroidism results in alterations comparable to those seen in early diabetic nephropathy, such as the thickening of the glomerular and tubular basement membranes and the expansion of the mesangial matrix, which contributes to the glomerular protein leakage (28) (Table 4).

Table 3. Hormone profile measurement between hypothyroidism women with diabetic neuropathy and the control group

Parameters	Hypothyroidism Women with metabolic syndrome No (45)	Control No (45)	*P*-value
	Mean±SD	Mean±SD	
TT3 (mMole/L)	0.6.32±0.30	1.3±0.93	0.05
TT4 (mMole/L)	46.11±8.44	88.14±10.41	0.001
TSH (mIU/ml)	23.45±3.62	3.43±1.52	0.001

P<0.05 is significant, and *P*<0.01 is highly significant
TT3: serum total triiodothyronine, TT4: total tetraiodothyronine, TSH: Thyroid stimulating hormone

Table 4. The correlation coefficient of vitamin D3 levels in hypothyroidism women with diabetic neuropathy

Hypothyroidism Women with Diabetic Neuropathy	Correlation coefficient (r)
D3 vs. Age	0.012
D3 vs. SBP	0.301*
D3 vs. DBP	0.223*
D3 vs. BMI	0.591**
D3 vs. FBS	0.696**
D3 vs. HbA1C (%)	0.363*
D3 vs. TG	-0.351**
D3 vs. HDL-C	0.423**
D3 vs. urea	0.145
D3 vs. creatinine	0.109
D3 vs. TT3	0.120
D3 vs. TT4	0.320*
D3 vs. TSH	-0.520**

P<0.05 is significant, and *P*<0.01 is highly significant
SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, FBS: Fasting blood sugar, HbA1C: Hemoglobin A1C, TG: Triglyceride, HDL: High-density lipoprotein**,** TT3: Serum total triiodothyronine, TT4: Total tetraiodothyronine, TSH: Thyroid stimulating hormone
There are significant differences between * and **

Few previous studies have investigated the association between VDD and the newly diagnosed diabetic neuropathy in women with hypothyroidism on a global scale. Vitamin D deficiency was shown to be more prevalent in T2DM patients than in the control subjects. The VDD has long been recognized as a major public health hazard on a global scale. Vitamin D deficiency was shown to be associated with low thyroid hormone levels in the patients group, which is consistent with previous research findings of those of adult (29, 30) and pediatric populations (31). Additionally, VDD and the newly diagnosed diabetic neuropathy are frequently recognized as a risk factor for thyroid illness and a consequence. Therefore, efficient vitamin D and T2DM regulation are critical for reducing the prevalence of thyroid disorders in the middle-aged population and they may affect their overall quality of life. Indeed, T2DM and thyroid diseases (15, 32) are significantly interrelated as the two most frequently encountered endocrinological disorders associated with VDD in general clinical practice (11, 12, 16, 17). Additionally, various studies have demonstrated a correlation between thyroid volume and a range of risk factors, including iodine shortage and supply, BMI, age, gender, smoking status, hereditary variables, impaired fasting glucose, as well as diabetes mellitus (31, 33). Moreover, a study examined the influence of environmental and lifestyle variables. It is worth noting that VDD may play a role in the pathophysiology of both diabetes mellitus and thyroid illness. Vitamin D insufficiency may even be the secondary cause of many disorders. In addition, thyroid dysfunction may have affect vitamin D consumption, absorption, and metabolism.

Findings of the present study corroborated earlier research findings, specifically that VDD was correlated with a raised risk of thyroid diseases in patients with T2D (34).

The correlation of vitamin D3 deficiency with thyroid dysfunction and newly diagnosed diabetic neuropathy women indicated the relationship between VDD and thyroid dysfunction and identified vitamin D3 as an influential factor in women with newly diagnosed diabetic neuropathy.

Authors' Contribution

Study concept and design: N. K. S.
Acquisition of data: H. S. J.
Analysis and interpretation of data: E. A. A. A.
Drafting of the manuscript: E. A. A. A.
Critical revision of the manuscript for important intellectual content:
Statistical analysis:
Administrative, technical, and material support:

Ethics

This study has the approval of the Ethics Committee of the National Diabetes Center (Mustansiriyah University, Baghdad, Iraq) and all participants signed a consent form before the study.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017;12(12):2032-45.
2. Ritz E, Zeng XX, Rychlik I. Clinical manifestation and natural history of diabetic nephropathy. Contrib Nephrol. 2011;170:19-27.
3. Doshi SM, Friedman AN. Diagnosis and Management of Type 2 Diabetic Kidney Disease. Clin J Am Soc Nephrol. 2017;12(8):1366-73.
4. Pugliese G. Updating the natural history of diabetic nephropathy. Acta Diabetol. 2014;51(6):905-15.
5. Kordonouri O, Maguire AM, Knip M, Schober E, Lorini R, Holl RW, et al. Other complications and associated conditions with diabetes in children and adolescents. Pediatr Diabetes. 2009;10 (12):204-10.
6. Barker JM, Yu J, Yu L, Wang J, Miao D, Bao F, et al. Autoantibody "subspecificity" in type 1 diabetes: risk for organ-specific autoimmunity clusters in distinct groups. Diabetes Care. 2005;28(4):850-5.
7. Baxter JD, Webb P. Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. Nat Rev Drug Discov. 2009;8(4):308-20.
8. Diekman T, Lansberg PJ, Kastelein JJ, Wiersinga WM. Prevalence and correction of hypothyroidism in a large cohort of patients referred for dyslipidemia. Arch Intern Med. 1995;155(14):1490-5.
9. Tokinaga K, Oeda T, Suzuki Y, Matsushima Y. HMG-CoA reductase inhibitors (statins) might cause high elevations of creatine phosphokinase (CK) in patients with unnoticed hypothyroidism. Endocr J. 2006;53(3):401-5.
10. Song SH, Kwak IS, Lee DW, Kang YH, Seong EY, Park JS. The prevalence of low triiodothyronine according to the stage of chronic kidney disease in subjects with a normal thyroid-stimulating hormone. Nephrol Dial Transplant. 2009;24(5):1534-8.
11. Van Belle TL, Gysemans C, Mathieu C. Vitamin D in autoimmune, infectious and allergic diseases: a vital player? Best Pract Res Clin Endocrinol Metab. 2011;25(4):617-32.
12. Van Belle TL, Gysemans C, Mathieu C. Vitamin D and diabetes: the odd couple. Trends Endocrinol Metab. 2013;24(11):561-8.
13. Tamer G, Arik S, Tamer I, Coksert D. Relative vitamin D insufficiency in Hashimoto's thyroiditis. Thyroid. 2011;21(8):891-6.
14. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5.
15. Papazafiropoulou A, Sotiropoulos A, Kokolaki A, Kardara M, Stamataki P, Pappas S. Prevalence of thyroid dysfunction among greek type 2 diabetic patients attending an outpatient clinic. J Clin Med Res. 2010;2(2):75-8.
16. Kim D. Low vitamin D status is associated with hypothyroid Hashimoto's thyroiditis. Hormones. 2016;15(3):385-93.
17. Bozkurt NC, Karbek B, Ucan B, Sahin M, Cakal E, Ozbek M, et al. The association between severity of vitamin D deficiency and Hashimoto's thyroiditis. Endocr Pract. 2013;19(3):479-84.
18. Chailurkit LO, Aekplakorn W, Ongphiphadhanakul B. High vitamin D status in younger individuals is associated with low circulating thyrotropin. Thyroid. 2013;23(1):25-30.
19. Wanner C, Krane V, Marz W, Olschewski M, Asmus HG, Kramer W, et al. Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis (4D study): demographic and baseline characteristics. Kidney Blood Press Res. 2004;27(4):259-66.
20. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238-48.
21. Franczyk-Skora B, Gluba A, Banach M, Kozlowski D, Malyszko J, Rysz J. Prevention of sudden cardiac death in patients with chronic kidney disease. BMC Nephrol. 2012;13:162.
22. Kaptein EM, Wilcox RB, Nelson JC. Assessing thyroid hormone status in a patient with thyroid disease and renal failure: from theory to practice. Thyroid. 2004;14(5):397-400.
23. Meuwese CL, Dekker FW, Lindholm B, Qureshi AR, Heimburger O, Barany P, et al. Baseline levels and trimestral variation of triiodothyronine and thyroxine and their association with mortality in maintenance hemodialysis patients. Clin J Am Soc Nephrol. 2012;7(1):131-8.
24. Crowley WF, Jr., Ridgway EC, Bough EW, Francis GS, Daniels GH, Kourides IA, et al. Noninvasive

evaluation of cardiac function in hypothyroidism. Response to gradual thyroxine replacement. N Engl J Med. 1977;296(1):1-6.
25. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med. 2001;344(7):501-9.
26. Schmid C, Brandle M, Zwimpfer C, Zapf J, Wiesli P. Effect of thyroxine replacement on creatinine, insulin-like growth factor 1, acid-labile subunit, and vascular endothelial growth factor. Clin Chem. 2004;50(1):228-31.
27. McDonough AA, Brown TA, Horowitz B, Chiu R, Schlotterbeck J, Bowen J, et al. Thyroid hormone coordinately regulates Na+-K+-ATPase alpha- and beta-subunit mRNA levels in kidney. Am J Physiol. 1988;254(2 Pt 1):C323-9.
28. Wheatley T, Edwards OM. Mild hypothyroidism and oedema: evidence for increased capillary permeability to protein. Clin Endocrinol. 1983;18(6):627-35.
29. Bener A, Al-Hamaq AO, Kurtulus EM, Abdullatef WK, Zirie M. The role of vitamin D, obesity and physical exercise in regulation of glycemia in Type 2 Diabetes Mellitus patients. Diabetes Metab Syndr. 2016;10(4):198-204.
30. Bener A, Ozdenkaya Y, Al-Hamaq A, Barisik CC, Ozturk M. Low Vitamin D Deficiency Associated With Thyroid Disease Among Type 2 Diabetic Mellitus Patients. J Clin Med Res. 2018;10(9):707-14.
31. Welsh KJ, Soldin SJ. DIAGNOSIS OF ENDOCRINE DISEASE: How reliable are free thyroid and total T3 hormone assays? Eur J Endocrinol. 2016;175(6):R255-R63.
32. Akbar DH, Ahmed MM, Al-Mughales J. Thyroid dysfunction and thyroid autoimmunity in Saudi type 2 diabetics. Acta Diabetol. 2006;43(1):14-8.
33. Palma CC, Pavesi M, Nogueira VG, Clemente EL, Vasconcellos Mde F, Pereira LCJ, et al. Prevalence of thyroid dysfunction in patients with diabetes mellitus. Diabetol Metab Syndr. 2013;5(1):58.
34. Toulis K, Tsekmekidou X, Potolidis E, Didangelos T, Gotzamani-Psarrakou A, Zebekakis P, et al. Thyroid Autoimmunity in the Context of Type 2 Diabetes Mellitus: Implications for Vitamin D. Int J Endocrinol. 2015;2015:710363.