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Vitamin D Deficiency and Microalbuminuria in Patients with Diabetes Mellitus

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ABSTRACT

Aim: As diabetes mellitus and its complications become more prevalent in the world, it is becoming an important public health problem. Previous studies have investigated vitamin D in the context of diabetes mellitus and its complications.. Microalbuminuria is important as the initial level of diabetic nephropathy. In this context, we aimed to investigate the level and deficiency of vitamin D in diabetic patients with microalbuminuria.

Material and Methods: 52 type 1 (20.1%) and 206 (79.9%) type 2 diabetes patients who applied to the outpatient Endocrinology and Metabolic Diseases clinic between April 2019 and December 2020 were included in the study. Patients were classified according to microalbuminuria. Fasting glucose, HbA1c, duration of diabetes, and 25 (OH) Vitamin D levels and mean waist circumference were compared between the groups. Finally, the groups were compared according to diabetes type and microalbuminuria.

Results: Urinary albumin/creatinine rates (UAC) in 159 (42.7%) diabetic patients were in normal range, and 65 (17.5%) diabetics had UAC between 30-300 mcg. 12 (3.2%) had UAC >300 mcg. 22 (5.9%) had chronic renal failure. Vitamin D deficiency was 61.6% and vitamin D insufficiency was 28.6% in all study groups. Median GFR was 98 (38-136) ml/dk and median 25 (OH) D level was 17.1 (5.0-44.2)mg/dl. 25 (OH) Vitamin D levels and GFR were found to be significantly lower in the microalbuminuria group ($p<0.01$). 25 (OH) D levels were found to be low in both type 1 and type 2 diabetes patients with the complication of microalbuminuria, however only in type 1 diabetes patients low vitamin D this was found significant ($p=0.01$)

Conclusion: 25 (OH) vitamin D deficiency and insufficiency were found to be more common in patients with diabetes. with microalbuminuria, which was more significant in type 1 diabetes patients The underlying mechanisms and potential therapeutic effect of vitamin D should be further investigated.

Keywords: *Diabetes, Microalbuminuria, Vitamin D*

Diabetes Mellituslu Hastalarda Mikroalbuminüri ve D Vitamini

ÖZ

Amaç: Dünyada giderek artan sıklığı ile diyabet, komplikasyonları yolu ile önemli bir halk sağlığı sorunu olarak karşımıza çıkmaktadır. Önceki çalışmalar vitamin D için hem diyabet hem de komplikasyonları ile ilişkili olarak değerlendirmiştir. Mikroalbuminüri diyabetik nefropatinin başlangıç düzeyi olarak önem arz etmektedir. Bu bağlamda mikroalbuminürisi olan diyabetik hastalarda D vitamini düzeyini ve eksikliğini araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmaya Nisan 2019 ve Aralık 2020 tarihleri arasında Endokrinoloji ve Metabolizma Hastalıkları polikliniğine başvuran 52 tip 1 (%20,1) ve 206 (%79,9) tip 2 diyabet hastası dahil edildi. Hastalar mikroalbüminüriye göre sınıflandırıldı. Açlık glikozu, HbA1c, diyabet süresi, 25 (OH) Vitamin D düzeyleri ve ortalama bel çevresi gruplar arasında karşılaştırıldı. Son olarak gruplar diyabet tipi ve mikroalbüminüriye göre karşılaştırıldı.

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Bulgular: 159 (%42,7) hastada normal idrar albümin / kreatinin oranı (UAC) vardı. 65 (%17,5) hastada 30-300 mcg arasında UAC vardı. 12 (%3,2) UAC> 300 mcg'ye sahipti. 22'sinde (%5,9) kronik böbrek yetmezliği vardı. Tüm çalışma gruplarında D vitamini eksikliği %61,6, D vitamini yetmezliği %28.6 olarak bulundu. Mikroalbüminüri grubunda ortanca GFR 98 (38-136) ml/dk)idi ve ortanca 25 (OH) D düzeyi 17.1 (5,0-44,2)mg/dl idi. GFR ve 25 (OH) D düzeyleri anlamlı olarak düşük bulundu (p<0,01). 25 (OH) D seviyeleri hem tip 1 hem de tip 2 diyabet hastalarında düşük saptandı. Ancak bu düşüklük sadece tip 1 diyabet hastaları için anlamlı bulundu. (p=0,01)

Sonuç: 25 (OH) D vitamini eksikliği ve yetersizliği, özellikle tip 1 diyabette daha belirgin olmak üzere diyabet ve mikroalbüminürili hastalarda daha yaygın olarak saptandı. Komplikasyonların gelişmesinde D vitamininin diyabet tiplerine göre etki mekanizması ve potansiyel terapötik etkisi daha kapsamlı bir şekilde araştırılmalıdır.

Anahtar Sözcükler: *Diyabet, Mikroalbuminüri, D vitamini*

INTRODUCTION

Diabetic nephropathy (DN) is a long-term microvascular complication of both type 1 and type 2 diabetes that can progress to end stage renal disease and is one of the most important complications leading to higher morbidity and mortality. DN can be detected early by urinary microalbumin as recommended bythe American Diabetes Associaton (ADA) (1).

Microalbuminuria is not only an important sign of diabetic nephropathy, but also contributes to cardiovascular mortality in diabetes (2,3). Its frequency in type 1 diabetic patients was 15% and in type 2 diabetic patients ranged from 25.6 -29.7% according to previous studies (4-6).

In recent years, there have been significant advances in the understanding of 25 (OH) vitamin D and its effects beyond its known role in bone and mineral metabolism. Preliminary studies demonstrated 25 (OH) vitamin D deficiency in the pathogenesis of diabetes (7). In addition, vitamin D supplementation has been shown to increase insulin sensitivity and secretion (8,9).

There are some studies that have investigated the effect of vitamin D on glomerular function. Vitamin D decreased podocyte loss and albuminuria in rat models, with active Vitamine D treatment fewer signs of podocyte injury and podocyte hypertrophy reversal were observed in subtotally nephrectomized rats (10). In animal studies, active Vitamin D slowed down mesangial proliferation and negatively affected RAAS activation and Vitamin D receptor null mice were shown to have several fold elevated renin expression and angiotensin 2 production (11).

Therefore, we aimed to investigate the association between 25 (OH) vitamin D levels and microalbuminuria in patients with type 1 and type 2 diabetes mellitus. Our study was unique that it compared relationship between 25(OH) Vitamin D deficiency and microalbuminuria according to types of diabetes.

MATERIALS and METHODS

52 type 1 (20.1%) and 206 (79.9%) type 2 diabetes patients, aged between 18-70 patients were enrolled in the study. All patients were regularly followed up by Endocrinology and Metabolism department between April 2019 and December 2020. Age smaller than <18, pregnancy, liver disease, active infection, use of any medications, or any illness that affects 25(OH) vitamin d levels were exclusion criteria. Weight (kg) and height (m) were measured using standard methods. The waist circumference (WC) was measured at the midpoint between the underside of the chest and the uppermost edge of the iliac crest in the standing position.

All the laboratory analyses were studied in the same laboratory. Serum creatinine (Cre) was measured by enzyme-linked immunosorbent assay (ELISA) and glomerular filtration rate (GFR) was measured by CKD- EPI method (ml/dk/1,75m^2) Urine microalbuminuria was measured by ımmunoturbidometric method. Microalbuminuria was defined as urine albumin 30-300 mg/g, macroalbuminuria was defined as urine albumin > 300mg/g (12). 25 (OH) Vitamin D was measured by high-performance liquid chromatography. Patients were divided into type 1 and type 2 according to previous records. Vitamin D deficiency was defined as 25 (OH) Vitamin D <20 ng/ml, Vitamin D insufficiency was defined as 25 (OH) Vitamin D between.21-29 ng/ml (13).

Ethical approvation was taken from Istanbul Research and Educational Hospital (2021/2784).

Statistics

Statistical evaluations were performed using IBM SPSS 22.0 (Statistical Package for the Social Sciences software version 22.0). Descriptive analyses were expressed as median (min-max) or mean±standard deviation (SD) and percentages (%), Shapiro-Wilk test was used for normality. The Chi-square test or Fisher's exact test, where appropriate, was used for categorical variables. Student's t-test was

used for comparison of normality distributed continuous variables of two groups. The Mann-Whitney U-test was used for comparisons of continuous variables that were not normally distributed between two groups.

Logarithmic transformation was used to continuous variables that were not normally distributed.

RESULTS

Totally 258 diabetes patients were included in the study. The median age was 54 years (min 21-max 70). 50 patients were type 1 diabetes patients, 208 patients were type 2 diabetes patients, mean glucose level was 198 ±73.75, mean body mass index was 32.16±6.74 kg/m^2. Median urine albumin/creatinine level was 14.0 mg/g (1.3-633. The general physical and biochemical properties of the groups were given in Table 1.

159 (42.7%) patients had normal urine albumine/creatinine ratio (<30 mcg) (UAC). 65 (17.5%) patients had UAC between 30-300mcg. 12 (3.2%) had UAC >300 mcg. 22 (5.9%) had chronic renal failure. General characteristics acccording to microalbuminuria were presented in Table 2.

Vitamin D deficiency was found 61.6%, vitamin D insufficiency was found 28.6% in all study groups. GFR and mean 25 (OH) D level were found significantly lower in the microalbuminuria group. (p=0.01) (Table 2, 3).

25 (OH) D levels were lower in both type 1 and type 2 diabetes microalbuminuria patients. The p-value of 25 (OH) D in microalbuminuria patients was lower in type 1 diabetes patients.(p=0.01) (Table 4)

Table 1: General characteristics of the patients.

Characteristics	Findings
Age [years, median (min-max)]	54 (21-70)
Gender [Female / Male (%)]	48.1 / 51.9
Diabetes Duration [years, median (min-max)]	11 (1-30)
HbA1c [%, median (min-max)]	8.8 (5.6-15.3)
WC (cm±SS)	104.6 ±16.4
Serum Creatinine (mg/dl±SS)	0.8 (0.4-1.97)
GFR [ml/min/1.73 m^2, median (min-max)]	98 (38-136)
25 (OH) Vitamin D [mg/dl, median (min-max)]	17.1 (5.0-44.2)

Median (min-max), mean±standard deviation for WC, **WC:** Waist circumference, **GFR:** Glomerular filtration rate.

Table 2: General characteristics according to microalbuminuria.

Parameters	MAU<30 mg/g (n=155)	MAU>30 mg/g (n=98)	p
Age [years, median (min-max)]	53.5 (21-70)	55 (24-67)	0.06
Gender [Female, n (%)]	75 (48.4)	53 (54.1)	0.38
Diabetes Duration [years, median (min-max)]	10 (1-30)	12 (2-30)	0.68
Glucose levels (mg/dl±SS)	215.2±102.6	207.3±90.6	0.55
HbA1c [%, median (min-max)]	8.1 (5.6-15.3)	8.9 (5.6-14.7)	0.51
WC (cm±SS)	105.0±15.3	110.5 ±15.9	**0.02**
Creatinine (mg/dl±SS)	0.7 (0.4-1.2)	0.9 (0.5-1.97)	**<0.01**
GFR [ml/min/1.73 m^2, median (min-max)]	100 (59-137)	87 (32-117)	**0.01**
25(OH) D [mg/dl, median (min-max)]	20.0 (8.4-44.0)	15.2 (7.0-29.0)	**0.01**

Median (min-max), mean±standard deviation for Glucose and WC, Mann-Whitney U Test. Chi-Square test for gender, student's t test for Glucose and WC, **MAU:** Microalbumin, **WC:** Waist circumference, **GFR:** Glomerular Filtration Rate, **25 (OH) D:** 25 (OH) Vitamin, D, significant p values were given as bold.

Table 3: Status of vitamin D levels according to microalbuminuria.

Status of Vitamin D Levels	Cases with MAU >30 mg/g, n (%)	Cases with MAU>300 mg/g, n (%)
Normal 25(OH) D (n=20)	5 (25)	0 (0)
25(OH) D Insufficiency (n=59)	16 (27.11)	1 (1.6)
25(OH) D Deficiency (n=127)	57 (45.2)	10 (7.9)
p	**0.027**	0.084

Chi-square test, **MAU:** Microalbumin/creatinine, significant p values were given as bold.

Table 4: Results of groups according to diabetes type and microalbuminuria.

Parameters	T1D with MAU (+) (n=12)	T1D with MAU (-) (n=30)	p*	T2D with MAU (+) (n=69)	T2D with MAU (-) (n=97)	p**
Serum Creatinine [mg/dl, median (min-max)]	1.0 (0.6-1.3)	0.8 (0.5-1.3)	0.8	0.7 (0.4-1.4)	0.9 (0.5-1.97)	0.03
GFR [ml/min/1.73 m^2, median (min-max)]	89 (69-137)	104 (54-128)	0.7	87 (32-137)	101 (39-137)	**0.01**
Diabetes Duration [years, median (min-max)]	12 (1-34)	14 (0.3-35)	0.48	10 (1-30)	11 (2-33)	0.86
WC (cm±SS)	96.43±11.52	81.8±9.83	**0.12**	107.49±15.34	112.88±13.88	**0.02**
25 (OH) D [mg/dl, median (min-max)]	10 .0 (5.0-22.1)	18.0 (9.1-44.2)	**0.01**	16.0 (7.0-24.6)	18.0 (8.4-30.0)	**0.09**

Median (min-max), mean±standard deviation for WC, Mann Whitney U Test, student's t test for WC Creatinine: Cre, **MAU:** Microalbumin, **WC:** Waist circumference, **GFR:** Glomerular Filtration Rate, **25 (OH) D:** 25 (OH) Vitamin, D, significant p values were given as bold.
T1D with MAU (+): Type 1 Diabetes with Microalbuminuria

DISCUSSION

The results of the current study showed that microalbuminuria was more frequent in patients with 25 (OH) Vitamin D deficiency and the mean 25(OH) Vitamin D levels were lower in the microalbuminuria group.

All study groups had a high proportion of vitamin D deficiency and/or insufficiency in the study (90.2%). This was consistent with other prevalence studies. In a study from Turkey with 4860 outpatients, 25 (OH) vitamin D deficiency and insufficiency were found in 91.1% (14). In another study with 209 adults from the Aegean region of Turkey, 88.7% were found to have 25 (OH) vitamin D deficiency and insufficiency (15).

The current study showed that Vitamin D deficiency and insufficiency were observed in higher HbA1c values. This could be explained by possible several mechanisms. Vitamin D has been found to regulate insulin secretion from pancreatic beta cells (16,17), also it has been demonstrated that vitamin D coordinates epigenetic, redox control, mitochondrial function which results in reduced oxidative stress and defends tissues from toxins (18,19). Additionally; Vitamin D and its analogs prevent beta-cell degeneration from immune attack by several mechanisms, which is crucial for type 1 diabetes mechanism (20,21).

Analysis of results of the current study showed that higher urine albumin/ creatinine ratio is associated together with low 25 (OH) Vitamin D. Previously; Levine et al. demonstrated low 1.25 (OH) D with high albumin/ creatinine ratio in patients with chronic renal failure (22). Low Vitamin D had been shown to be associated with high angiotensin II levels which were increased in DN patients (23). In another study; paricalcitol administration of CRF patients has resulted in decreased proteinuria (24). A study from Iran also has pointed that treatment with Vitamin D decreased proteinuria in 60 patients with type 2 diabetes (25).

Current study demonstrated that the association of vitamin D deficiency with microalbuminuria was higher in type 1 diabetes patients (p=0.01). Therefore Vitamin D's effects on different mechanisms responsible for progression of diabetic complications according to diabetes type should be more extensively investigated.

Limitations of these studies were its cross-sectional design, it reflects the findings of single-center experience, however, The sample size was much larger than was previously used in similar studies that will add new data to the literature

In conclusion, 25 (OH) Vitamin D deficiency and insufficiency were found to be higher in patients with diabetes and microalbuminuria. Vitamin D deficiency was more pronounced especially in type 1 diabetes patients with microalbuminuria. Underlying mechanisms and the potential therapeutic effect of Vitamin D should be investigated more thoroughly.

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Authorship Contributions

Concept: **Savaş Karataş,** Design: **Savaş Karataş,** Data Collection or Processing: **Savaş Karataş, Yalçın Hacıoğlu,** Analysis or Interpretation: **Savaş Karataş, Şennur Köse,** Literature Search: **Savaş Karataş, Yalçın Hacıoğlu, Şennur Köse,** Writing: **Savaş Karataş, Yalçın Hacıoğlu, Şennur Köse.**

Conflicts of Interest

The authors declare that they have no competing interest.

Financial Disclosure

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Ethical Approval

The study was conducted with the written approval of the Ethics Board of a research and education hospital (2021/2784).

Peer Review Process

Extremely peer reviewed and accepted.

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