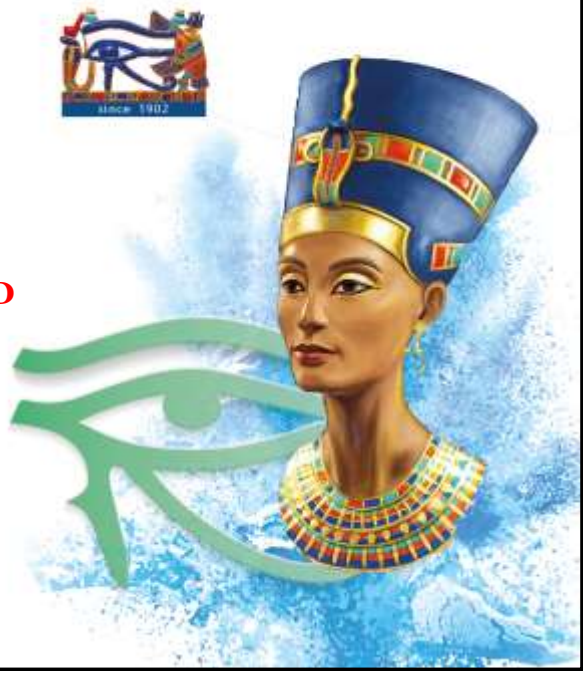
المؤتمر السنوي الدولي للجمعية الرمدية المصرية
INTERNATIONAL CONGRESS OF THE
EGYPTIAN OPHTHALMOLOGICAL SOCIETY
EOS 2023

Thyroid gland dysfunction & vitamin D receptor gene polymorphism in Keratoconus



Eman Azmy Awad, MD
Professor of Ophthalmology
Mansoura University

Introduction

- The exact pathophysiology of KC is not fully explained.
- Various inflammatory mediators (Cytokines) were linked with KC.
- Thyroid gland dysfunctions were reported in KC patients.
- Thyroxin was found to cause biochemical changes in the corneal stroma as a result of thyroxin–receptor interaction

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Introduction

- Vitamin D was found to enhance VDR and activates autophagic lysosomal clearance in oxidatively damaged human corneal epithelial cells.
- Low vitamin D levels were associated with the presence and severity of KC

Aim of the work

To detect the serum level of thyroid hormones, vitamin D and vitamin D receptors (VDR) polymorphism in keratoconus (KC) patients and to identify the association between vitamin D deficiency and thyroid dysfunction in KC.

Patients & Methods

- prospective, observational, cross sectional study
- MOC , Mansoura university
- March 2021 to September 2021.
- **177 KC** patients versus **85** healthy controls.
- IRB code No R.21.01.1157.R1) and (www.clinicaltrials.gov (NCT05073601)

For each patient :

- **Complete ophthalmic examination**
- **Pentacam imaging :**
  - K1,K2,Kmax
  - Corneal pachymetry

For each patient :

- **Blood sample collected**
- **Measurements of:**

1. thyroid stimulating hormone (TSH)
2. free triiodothyronine (FT3)
3. free tetraiodothyronine (FT4)
4. serum 25-OH vitamin D were (ELISA test).
5. VDR polymorphisms were tested including [Taq I , Apa I and Bsm I (PCR-RFLP)

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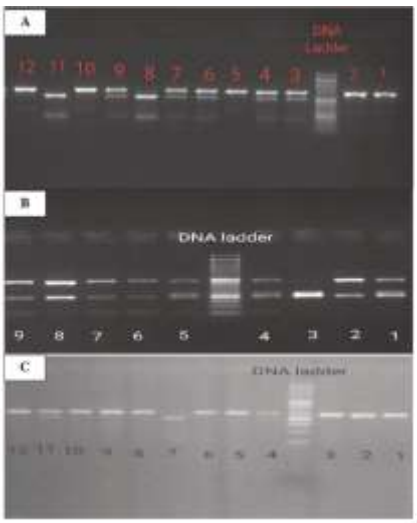
The separation of DNA fragment was done using 2% agarose gel electrophoresis and visualized under UV light

A:Apa1 genotype

B:Taq1genotype

C:Bsm1 genotype



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Results

Table 1. Demographic, topographic, and laboratory data of studied subjects.

		KC group (177 subjects)	Control group (85 subjects)	*P* value
Age		29.7 ± 10.17	31.03 ± 10.12	0.320
Gender (no.): (male/female)		48/93	39/46	0.811
K1 (D)		48.3 (42.8–78.0)	42.3 (41.4–43.5)	**<0.001**
K2 (D)		51.5 (44.4–81.3)	43.1 (42.1–45.0)	**<0.001**
Kmax (D)		57.2 (46.3–89.3)	44.6 (43.1–46.0)	**<0.001**
Pachymetry (μm)		457.0 (211.0–540.0)	514.0 (489.0–560.0)	**<0.001**
TSH (μIU/L)		2.3 (0.04–14.0) (N range 0.4–4Uiu/L)	1.5 (0.08–7.5)	**0.001**
FT4 (ng/dl)		1.43 (0.5–12.0) (N range 0.58–2.46 ng/dl)	1.0 (0.8–1.8)	**<0.001**
FT3 (pg/ml)		2.1 (0.99–11.2) (N range 1.4–4.2 pg/dl)	1.9 (1.2–3.9)	0.831
Thyroid state	euthyroid	138 (78.0%)	81 (95.3%)	**0.004**
	Subclinical hypothyroidism	15 (8.5%)	1 (1.2%)	
	Overt hypothyroidism	3 (1.7%)	0 (0.0%)	
	Subclinical hyperthyroidism	7 (4.0%)	3 (3.5%)	
	Overt hyperthyroidism	14 (7.9%)	0 (0.0%)	
25(OH)vitamin D(ng/ml)	10.6 (6.9–62.0)	31.0 (8.5–61.0)	**<0.001**	
25(OH) vitamin D	Sufficiency (>30 ng/ml)	19 (10.7%)	43 (50.6%)	**<0.001**
	Insufficiency (21–30 ng/ml	95 (53.7%)	31 (36.5%)	
	Deficiency (<20 ng/ml)	63 (35.6%)	11 (12.9%)	

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Results

Table 2. Distribution of VDR genotypes and gene variant alleles in KC patients versus control group.

KC patients (*n* = 177) *n* (%)			Control (*n* = 85) *n* (%)	Relative risk of KC			
				OR		95% CI	*P* value
Taq I	TT	37 (20.9%)	32 (37.6%)	1	-	-	R
	Tt	80 (45.2%)	38 (44.7%)	1.820	0.988	3.353	0.054
	tt	60 (33.9%)	15 (17.6%)	**3.459**	**1.654**	**7.233**	**0.001**
	Tt + tt	140 (79.1%)	53 (62.4%)	**2.284**	**1.293**	**4.035**	**0.004**
	T	154 (43.5%)	102 (60.0%)	**1.948**	**1.343**	**2.825**	**<0.001**
	t	200 (56.5%)	68 (40.0%)				
Apa I	AA	64 (36.2%)	26 (30.6%)	1	-	-	R
	Aa	85 (48.0%)	42 (49.4%)	0.822	0.457	1.478	0.513
	aa	28 (15.8%)	17 (20.0%)	0.669	0.314	1.424	0.297
	Aa + aa	113 (63.8%)	59 (69.4%)	0.778	0.447	1.354	0.374
	A	213 (60.2%)	94 (55.3%)	0.818	0.565	1.185	0.289
	a	141 (39.8%)	76 (44.7%)				
Bsm I	BB	61 (34.5%)	23 (27.1%)	1	-	-	R
	Bb	75 (42.4%)	42 (49.4%)	0.673	0.365	1.239	0.204
	bb	41 (23.1%)	20 (23.5%)	0.773	0.376	1.585	0.482
	BB + bb	116 (65.5%)	62 (72.9%)	0.705	0.398	1.247	0.230
	B	197 (55.6%)	88 (51.8%)	0.855	0.592	1.234	0.403
	b	157 (44.4%)	82 (48.2%)				

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Table 3. Comparison of Vitamin D level among studied VDR genotypes in KC patients.

Parameter		Taq I genotypes			*P* value
		TT (*n* = 37patients)	Tt (*n* = 80 patients)	tt (*n* = 60 patients)	
Vitamin D level (ng/ml)	Median (Min–Max)	19.3 (10.0–62.0)	10.2 (7.6–51.0)	9.5 (6.9–42.0)	<0.001
Vitamin D groups	Sufficiency *n* (%)	10 (27.0%)	5 (6.2%)	4 (6.7%)	<0.001
	Insufficiency *n* (%)	27 (73.0%)	48 (60.0%)	20 (33.3%)	
	Deficiency *n* (%)	0 (0.0%)	27 (33.8%)	36 (60.0%)	
Parameter		**Apa I genotypes**			***P* value**
		AA (*n* = 64)	Aa (*n* = 85)	aa (*n* = 28)	
Vitamin D level (ng/ml)	Median (Min–Max)	12.8 (7.6–62.0)	10.4 (7.5–59.0)	9.9 (6.9–51.0)	0.243
Vitamin D groups	Sufficiency *n* (%)	11 (17.2%)	7 (8.2%)	1 (3.6%)	0.072
	Insufficiency *n* (%)	35 (54.7%)	48 (56.5%)	12 (42.8%)	
	Deficiency *n* (%)	18 (28.1%)	30 (35.3%)	15 (53.6%)	
Parameter		**Bsm I genotypes**			***P* value**
		BB (*n* = 61)	Bb (*n* = 75)	bb (*n* = 41)	
Vitamin D level (ng/ml)	Median (Min–Max)	12.0 (6.9–62.0)	10.0 (7.3–59.0)	12.8 (7.6–42.0)	0.567
Vitamin D groups	Sufficiency *n* (%)	4 (6.6%)	8 (10.7%)	7 (17.1%)	0.441
	Insufficiency *n* (%)	37 (60.7%)	38 (50.7%)	20 (48.8%)	
	Deficiency *n* (%)	20 (32.7%)	29 (38.6%)	14 (34.1%)	

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Table 4. Logistic regression analysis in keratoconus group.

		Multivariate analysis			
		p	OR	95% CI	
TSH		<0.001	2.173	1.603	2.946
T4		<0.001	61.95	24.145	77.06
Thyroid disorder	Hypothyroidism vs normal	0.044	8.474	1.062	67.63
	Hyperthyroidism vs normal	0.086	3.142	0.852	11.58
Vitamin D		<0.001	0.943	0.915	0.917
Vitamin D group	Insufficient vs sufficient	<0.001	5.847	2.936	11.643
	Deficient vs sufficient	<0.001	12.314	5.283	28.704
Taq I	tt vs TT	0.237	1.910	0.654	5.576

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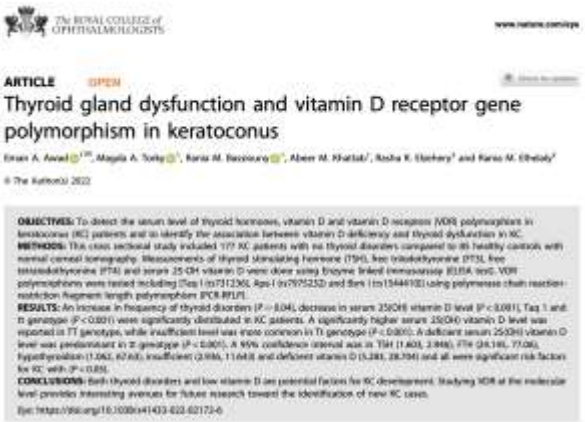
Conclusion

- Both thyroid disorders and low vitamin D are potential risk factors for KC development.
- High serum vitamin D and TT variant are considered protective factors .
- Studying VDR at the molecular level provides interesting avenues for future research toward the identification of new KC case

Acknowledgment

STDF
Egyptian Knowledge Bank
SPRINGER NATURE
OPEN ACCESS AGREEMENT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Thyroid gland dysfunction and vitamin D receptor gene polymorphism in keratoconus

Eman A. Awad, Magda A. Torky, Rania M. Bassiouny, Abeer M. Khattab, Rasha R. Elashery and Rania M. Elhelaly

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OBJECTIVES: To detect the serum level of thyroid hormones, vitamin D and vitamin D receptors (VDR) polymorphism in keratoconus (KC) patients and to identify the association between vitamin D deficiency and thyroid dysfunction in KC.
METHODS: This cross sectional study included 177 KC patients with no thyroid disorders compared to 86 healthy controls with normal corneal tomography. Measurements of thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free tetraiodothyronine (FT4) and serum 25-OH vitamin D were done using Enzyme linked immunoassay (ELISA, test). VDR polymorphisms were tested including (Taq I (rs731236), Bsm I (rs1544410)) using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).
RESULTS: An increase in frequency of thyroid disorders ($P = 0.04$), decrease in serum 25(OH) vitamin D level ($P < 0.001$), Taq I and Bsm genotype ($P < 0.001$) were significantly distributed in KC patients. A significantly higher serum 25(OH) vitamin D level was reported in TT genotype, while insufficient level was more common in Tt genotype ($P < 0.001$). A deficient serum 25(OH) vitamin D level was predominant in tt genotype ($P < 0.001$). A 95% confidence interval was in TSH (1.403, 3.948), FT4 (24.145, 77.04), hypothyroidism (1.042, 67.61), insufficient (2.936, 11.643) and deficient vitamin D (5.283, 28.794) and all were significant risk factors for KC with ($P < 0.05$).
CONCLUSIONS: Both thyroid disorders and low vitamin D are potential factors for KC development. Studying VDR at the molecular level provides interesting avenues for future research toward the identification of new KC cases.

Eye; https://doi.org/10.1038/s41433-022-02172-6

EOS 2023