

Dedication

To the souls of my parents

To my wife (Ghada) & our kids

(Hiba, Esra, & Abdelrahman)

Acknowledgements

In the name of Allah, the beneficent, the merciful, praise is to our God, Allah, the Lord of the World, who made me strong and gave me the health to do this work.

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Abstract

The objective of this study was to investigate some immunogenetic aspects of thyroid diseases and the possible association with HLA Class-II loci and their frequencies in Sudanese patients. The function of the thyroid gland is to produce the thyroid hormones T₃ and T₄, which regulate gene transcription throughout the body. In medical practice, the thyroid becomes an issue when its size or shape becomes abnormal or when it produces too much or too little hormone. Thus, we typically think of the thyroid with reference to the clinical states of goiter, hyper- or hypothyroidism.

Among the 208 thyroid disease patients, 67 diagnosed as hypothyroidism, 57 hyperthyroidism, 56 goiters, 18 Graves' disease, and 3 Hashimoto's thyroiditis. Forty blood specimens collected in EDTA containers from the patients with Graves' disease, Hashimoto's thyroiditis, and non-autoimmune thyroid diseases (n= 19) to be used for HLA typing by PCR-SSP technique. Another 20 blood specimens collected from normal Sudanese individuals with no family history of thyroid disease and matching ethnicity and sex, also typed for HLA -DR and DQ genes.

All blood specimens from thyroid disease patients (n=208), and control group (n=60) were tested for anti thyroid (anti-TPO, and anti-Tg) antibodies by ELISA. Thyroid function tested by measurement of serum TSH, T₄, and T₃ hormones by immulite autoanalyzer. The result of anti-TPO antibody of thyroid disease patients and control group was positive in 21.2% (44/208) and 5% (3/60) respectively, p. value (0.011). But 66.7% (12/18) of Graves' disease patients were give positive result of anti-TPO antibody, which is highly significant (0.000) when compared to control group. Anti-Tg antibody result showed no significant difference between thyroid disease patients and control group, p. value (0.528). Anti-Tg antibody was positive in 27.8%, and in 10% of patients and control group respectively, P. value 0.041.

HLA-class II, DR and DQ alleles were typed from the DNA samples of forty thyroid disease patients and twenty normal individuals. HLA-DRB1*0301 found to be carried by 50% of Graves' disease patients and by 15% of control group, P.value (0.020) and relative risk (5.7). HLA-DQB1*0201 allele carried by 55.6 % of Sudanese patients with Graves' disease, and in 20 % of control group, p. value (0.023), relative risk (5.0). In contrast, the allele DQB1*0601 found in 27.8 % of patients with Graves' disease, and in 60 % of control group, p. value (0.046).

□□□□□□□□

هدفت هذه الدراسة الى معرفة بعض أوجه مرض الغدة الدرقية من حيث المسببات الجينية المناعية و امكانية ربط ذلك مع وجود جينات النوع الثانى لمستضدات خلايا الدم البيض البشرية عند مرضى سودانيين. الوظيفة الرئيسية للغدة الدرقية هى تصنيع وافراز هرمونى الثايروكسين رباعى اليود (T₄) و الثايرونين ثلاثى اليود (T₃) التى تعمل على تنظيم ترجمة الجينات الى بروتينات معينة يحتاجها كل جسم الانسان. عندما يتغير شكل أو حجم الغدة الدرقية أو حين تقوم بافراز هرمونات بمعدل يختلف عن الطبيعى, بذلك تكون الغدة الدرقية موضوع للدراسة و يأتى التفكير فى وضعيتها الوظيفية من حيث زيادة أو نقص افراز الهرمونات.

من بين المائتين و ثمانية (208) مريض بالغدة الدرقية الذين أدرجوا فى هذه الدراسة , 67 منهم تم تشخيصهم حاملى الغدة , 57 افراط نشاط الغدة, 56 تورم الغدة, 18 مرضى Graves" و 3 مرضى Hashimoto. تم أخذ 40 عينة دم وريدى فى حاوية بها مادة مانعة للتجلط (EDTA) من مرضى الغدة الدرقية بالمناعة الذاتية (عدد = 21) واخرين لأسباب غير مناعية (عدد = 19) و التى تم استخلاص ال DNA منها ومن ثم استخدامها فى تحديد نوع جينات مستضدات خلايا الدم البيض البشرية (-HLA DR/DQ) عن طريق تقنية PCR-SSP , و لنفس الغرض تم جمع 20 عينة دم وريدى أخرى من سودانيين أصحاء ليست لديهم خلفية وراثية لمرض الغدة الدرقية و مشابهيين للمرضى من حيث العرق و النوع.

كل عينات مصل الدم التى تم جمعها بدون مادة مانعة للتجلط من مرضى الغدة الدرقية (عدد = 208) والأصحاء (عدد = 60) تم تحليلها لمعرفة تركيز الأجسام المضادة للغدة الدرقية من نوع anti-TPO و anti-Tg باستخدام تقنية ELISA. أظهرت النتائج وجود الأجسام المضادة من النوع anti-TPO بتركيز ايجابى عند 21.2% من مرضى الغدة الدرقية و 5% من الأصحاء بقيمة احتمالية 0.011 فى حين أن 66.7% من مرضى Graves" لديهم تركيز ايجابى لهذه الأجسام المضادة بقيمة احتمالية 0.000 عند المقارنة مع الأصحاء. كذلك أظهرت النتائج وجود الأجسام المضادة من النوع anti-Tg عند المرضى بنسبة تزيد قليلا عن ما هو عند الأصحاء بقيمة معنوية 0.528

ولكن الفرق كان واضحا عند مقارنة نتائج مرضى Graves مع الأصحاء حيث جاءت نتائجهم بنسبة 27.8% و 10% على التوالي ب قيمة احتمالية تساوى 0.041 ل قد تم اختبار وظيفة الغدة الدرقية فى مصل الدم عند المرضى والأصحاء ب قياس ثلاثة هرمونات هي T3, T4, TSH باستخدام جهاز التشغيل الذاتى Immulite Autoanalyzer و قد كانت الفروقات واضحة فى نشاطات الهرمون المحفز للغدة الدرقية TSH بين الأنواع المختلفة لمرض الغدة الدرقية.

عندما تم تحليل نتائج جينات النوع الثانى DR/DQ لمستضدات خلايا الدم البيض البشرية من عينات DNA لبعض المرضى و الأصحاء. وجد أن 50% من مرضى Graves يحملون الجين DRB1*0301 مقارنة مع 15% من الأصحاء يحملون نفس الجين ب قيمة احتمالية تساوى 0.020 و معدل خطورة 5.7 كذلك الجين DQB1*0201 وجد عند 55.6% من مرضى Graves و 20% من الأصحاء ب قيمة معنوية 0.023 و معدل خطورة 5.0 و على العكس مما سبق فان الجين DQB1*0601 وجد عند 27.8% من مرضى Graves و 60% من الأصحاء ب قيمة معنوية تساوى 0.046

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Abbreviations

T ₄ :	Thyroxine
T ₃ :	Triiodothyronine
rT ₃ :	reverse Triiodothyronine
TSH:	Thyroid-Stimulating Hormone
TRH:	Thyrotropin Releasing Hormone
TRAb:	Thyrotropin Receptor Antibody
TPO:	Thyroid Peroxidase
TPOAb:	Thyroid Peroxidase Antibody
Tg:	Thyroglobulin
TgAb:	Thyroglobulin Antibody
ATA:	Anti Thyroglobulin Antibody
AMA:	Anti Microsomal Antibody
AID:	Autoimmune Disease
AITD:	Autoimmune Thyroid Disease
GD:	Grave's Disease
HT:	Hashimoto's thyroiditis
AH:	Autoimmune Hypothyroidism
IDD:	Iodine Deficiency Disorder
WHO:	World Health Organization
MHC:	Major Histocompatibility Complex
HLA:	Human Leukocyte Antigen
TSHR:	Thyroid Stimulating Hormone Receptor
CTLA 4:	Cytotoxic T-Lymphocyte-Associated antigen 4
MIT:	Monoiodotyrosine

DIT: Diiodotyrosine

H₂O₂: Hydrogen Peroxidase

MZ: Monozygotic

DZ: Dizygotic

APC: Antigen Presenting Cell

RR: Relative risk

OR: Odd ratio

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