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[Adi Sharabi-Nov](#) , Ekaterina Pundyk Babitzki , [Raed Farhat](#) , Michael Edelstein , [Yaniv Avraham](#) ^{*} , Shlomo Merchavy

Posted Date: 27 May 2025

doi: 10.20944/preprints202505.2085.v1

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Article

The High Prevalence of Thyroid Goiter Between Arab Minorities in Israel—a Possible Hereditary Connection

Adi Sharabi-Nov ^{1,2}, Ekaterina Pundyk Babitzki ³, Raed Farhat ^{3,4}, Michael Edelstein ³, Yaniv Avraham ^{4,*} and Shlomo Merchavy ^{3,4}

¹ Research Wing, Ziv Medical Center, Safed, Israel

² Tel-Hai Academic College, Kiryat Shemona, Israel

³ Ziv Medical Center, Safed, Israel; Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

⁴ Otolaryngology, Head & Neck Surgery department, Ziv Medical Center, Postal code – 13100, Rambam St., Safed, Israel

* Correspondence: yanivavr1@gmail.com; Tel.: +972-4-6828894; Fax: +972-4-6828757

Abstract: Background: Thyroid goiter is endemic in certain world areas, especially with low Iodine supply. Genetic predisposition with the combination of various environmental factors have been suggested as risk factors for thyroid goiter. The exact mechanism causing thyroid goiter is still not clear. Israel has a small geographic area with a diverse non mixed ethnic minorities. All populations share similar environmental conditions. The possibility of an ethnic predisposition for thyroid goiter development in these ethnic populations is yet to be studied. **Methods:** All adult patient with thyroid goiter presented to the head and neck clinic between 2019-2021 were included in the study. Patient files were reviewed retrospectively for demographic data and goiter related symptoms. The overall incidence rate of goiter for each group was calculated. **Results:** A total of 392 patients were included in the study, 235 were Jewish, 123 Arab Druze and 34 Arab Muslims. The overall incidence of thyroid goiter in the Arab Druze group was 6.92% (CI 5.75-8.25) compared to 4.11% in the Jewish (CI 3.60-4.67) group and 7.21% (CI 4.99-10.08) in the Muslim group (34 patients only). The observed number of patients having goiter in comparison with the expected value of Goiter and the Standardized Incidence Ratio (SIR) for the Arab Druze population was 1.41 (1.18-1.67) in comparison to the Jewish population - 0.84 (0.73-0.95). **Conclusions:** Thyroid goiter prevalence in the Arab Druze population was higher compared to the Jewish population with similar environmental conditions. Further studies of possible ethnic genetic influences on goiter development are warranted. A larger study of goiter prevalence in the Arab Muslims group should be considered.

Keywords: thyroid goiter; Arab Muslims; Arab Druze

1. Introduction

Thyroid goiter (TG) is a benign hyperplasia of the thyroid gland. It is classified either as diffuse - with an overall enlargement of the thyroid, or nodular - an irregular cell growth that forms nodules. (1). TG affects approximately 7% of the worldwide general population, being more common in the women population (2) (3). The clinical presenting symptoms associated with TG depends on goiter size and location. A normal sized thyroid gland has a mean sonographic volume of 7 to 10 ml and a weight of 10 to 20 grams (4;5). Most TG are non-visible and asymptomatic, and are usually primarily detected in a routine physical examination of the neck area. A large TG is usually physically visible and in severe cases may cause direct compression of the trachea and/or the esophagus with possible clinical symptoms of dysphagia, positional dyspnea, and dysphonia (6).

The standard work-up of goiter patients includes measuring thyroid stimulating hormone (TSH) and thyroid hormones T3, T4 levels and neck ultrasound examination. In cases of suspected

malignancy, a fine-needle aspiration (FNA) biopsy of the thyroid is warranted (1; 7) according to the American thyroid association (ATA) guidelines. A surgical removal of the thyroid is suggested primarily in cases of suspected malignancy, severe mechanical compression symptoms or for esthetic reasons (8). Other treatment options may include dietary iodine supplementation (in case of iodine deficiency), radioiodine therapy to decrease thyroid mass, and mini-invasive ablation techniques (7).

TG is endemic in certain world areas, with high variability between different populations. Traditionally low dietary iodine intake – usually associated with poor water supply, has been implicated as the main cause for high goiter prevalence in endemic populations (9; 10). In recent years, different studies have suggested that the differences in TG prevalence in between populations in endemic areas is probably resulting from the combination of genetic and environmental factors (11) (12). Various studies have been published supporting this theory (1). A twin study from Denmark (Brix et al, 1999) concluded that the heritability of the predisposition to develop goiters can be accounted for 82% of cases, with only 18% that can be explained by environmental factors (12). A different study in Denmark has found a greater overlap of thyroid volume in twins which was attributed to genetic factors (13). Another study in 2011 has found 4 genetic loci that were associated with thyroid volume (14; 15). A genomic research of a Canadian family with high goiter incidence, has identified a locus on chromosome 14q that can be a possible cause for goiter (16). Targovnik et al. (2010) identified 50 mutations linked with goiter and hypothyroidism or euthyroidism that confirms the allelic heterogeneity of the thyroid gene mutations (17). These studies suggest that the prevalence of TG in different populations, in endemic as well as in non-endemic areas, is more possibly the result of a shared genes pool, rather than environmental factors only (18). The influence of heritability increases with the non-presence of environmental factors as in shared environments and similar living habitats (19).

The possibility of ethnic hereditary being a major factor in the prevalence of TG in specific ethnic groups has almost not been studied, with an exception of a study on the Efe Pygmies from Zaire in 1989 (20), and on Ethiopian origin immigrants in Israel from 1993 (21). TG is considered endemic in these two population groups in comparison to other population groups residing in the same areas. Both studies have concluded that the major factors contributing to the high prevalence of TG in the studied populations were mainly hereditary and not from dietary or environmental causes.

The population of Israel is unique in its diverse ethnic composition: Jews, Arab Muslims, Arab Christians and Arab Druze. These ethnic groups are not mixed for religious, historical and cultural reasons. The Arab Druze are an isolated community from religious reasons, which resides partly in Lebanon, Syria and Israel (22). The Arab Druze strictly close their religion to new adherents. Druze customs strongly favor intermarriage, thus preventing possible mixture with all other ethnic groups in their surroundings (23). The prevalence of TG and the possibility of ethnic hereditary in this ethnic group has yet to be studied.

2. Methods

A retrospective study. All adult patient's files presented with goiter to the head and neck clinic between 2019-2021 were reviewed. To limit possible influences of environmental factors among groups, only patients who reside in the same geographical area with similar water and food supply were included. The Druze group included patients from the 4 villages: Ein Kinia, Masade, Buqata and Majdal Shams. Jewish patients included were from Hatzor Haglilit, Kiryat Shemona, Safed and Katzrin. The Muslim Arab group included patients from Tuba-Zangariya village. All locations are a non- mixed single ethnic group residency (Jewish, Arab-Muslim or Druze). The water sources supplying these locations were comparable in terms of quality and Iodine levels (4-6 µg/L) as reported by the national Israel water authority.

2.1. Patient Data Collection

Patient data collected included: goiter type, Bethesda score of fine needle aspiration cytopathology (FNAC), goiter related symptoms, ethnicity, place of residence, age, gender and family history.

2.2. Demographic Data Collection

Demographic data of all included locations – the number of adult persons living in each location, was obtained from the Israel Population & Immigration Authority,(https://data.gov.il/dataset/residents_in_israel_by_communities_and_age_groups, accessed July 2022).

2.3. Statistical Analysis

In our analysis, continuous data are described using means and standard deviations. Categorical data are described using frequencies and percentages. The comparison of numeric data between groups was performed by an independent sample t test. Relationships between categorical variables and sample groups were examined using Chi-square test or Fisher’s exact test depending on the sample size. Standardized Incidence Ratio higher than 1 was considered higher than expected and a P-value lower than 5% was considered statistically significant. The data were analyzed using the SPSS software, version 25 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 674 Goiter patients’ files were reviewed for their demographic data and other goiter related clinical characteristics. 392 patients met the inclusion criteria and were included in the final analysis (Table 1). Among the included files 235 were Jewish, 123 Druze and 34 Muslims. The total overall mean age was 57.9, with 82.7% of the patients were females (p-value 0.562). The most common type of goiter was MNG type – nontoxic with 54.6% (p-value- 0.324). With the second most common being nodular nontoxic goiter with 40.1 (p-value 0.714). Family history was highest among Muslim patients 17.6 (p-value 0.006). Other variables are presented in Table 1. The overall incidence rate of goiter cases divided by their respective population (residents over the age of 18) x1000 is presented in Table 2. The overall incidence of thyroid goiter in the Arab Druze group was 6.92% (CI 5.75-8.25) compared to 4.11% in the Jewish (CI 3.60-4.67) group and 7.21% (CI 4.99-10.08) in the Muslim group (34 patients only). The observed number of patients having goiter in comparison with the expected value of Goiter and the Standardized Incidence Ratio (SIR) for each group is presented Table 3. A substantial increased in the prevalence of Goiter in the Arab Druze population was observed, with a Standardized Incidence Ratio (SIR) value of 1.41 (1.18-1.67) in comparison to the Jewish population - 0.84 (0.73-0.95).

Table 1. Demographic and clinical characteristics of the study patients stratified by ethnicity groups (#).

Variables	All patients (n=392)	Jewish (n=235)	Druze (n=123)	Muslim (n=34)	P
Age, years (M [95%CI])	57.9 [56.5-59.3]	59.8a [58.0-61.6]	56.5b [54.1-58.8]	49.7c [45.5-53.9]	<0.001*
Gender (n, %)					
Female	324, 82.7	191, 81.3	103, 83.7	30, 88.2	0.562
Male	68, 17.3	44, 18.7	20, 16.3	4, 11.8	
Bethesda score,1-6 (M [95%CI])	2.2 [2.1-2.3]	2.3 [2.1-2.4]	2.1 [2.0-2.2]	2.4 [2.0-2.8]	0.388*
Family history of Goiter (n, %)	23, 5.9	13, 5.5	4, 3.3	6, 17.6	0.006
Surgery (n, %)	65, 16.6	38, 16.2	15, 12.2	12, 35.3	0.006
Diffuse (n, %)	8, 2.0	5, 2.1	2, 1.6	1, 2.9	0.998

Nodular (n, %)	157, 40.1	98, 41.7	46, 37.4	13, 38.2	0.714
Multi-nodular (n, %)	214, 54.6	122, 51.9	74, 60.2	18, 52.9	0.324
Toxic (n, %)	12, 3.1	9, 3.8	1, 0.8	2, 5.9	0.171
Papillary carcinoma (n, %)	16, 4.1	12, 5.1	2, 1.6	2, 5.9	0.241
Difficulty swallowing (n, %)	56, 14.3	31, 13.2	17, 13.8	8, 23.5	0.269
Difficulty breathing (n, %)	54, 13.8	31, 13.2	16, 13.0	7, 20.6	0.483
Aesthetic problems (n, %)	14, 3.6	10, 4.3	2, 1.6	2, 5.9	0.363

* Kruskal-Wallis non-parametric test, # The Jewish group included patients from four towns, the Druze group included patients from four villages, Muslim group included patients only from one village. All are nearby residencies. a-c: different letters represent significant differences between the means.

Table 2. Incidence rate calculations of Goiter stratified by ethnicity.

Ethnic group	Population (§)	Sample		Incidence	
	Residents over the age of 18 (n)	Patients with Goiter (n)	Patients with Goiter (%)	(Goiter cases / population) *1000	95% CI for Rate#
Druze	17,779	123	31.4	6.92	5.75-8.25
Jewish	57,150	235	59.9	4.11	3.60-4.67*
Muslim	4,715	34	8.7	7.21	4.99-10.08
Total	79,644	392	100		

§ updated to December 31st, 2021 according to the Israeli Population and Immigration Authority records. *Significant difference from the Druze group using OpenEpi, Ver. 3.01 with Person-Time=1, *significant differences between the control group and other two groups (p<0.01).

Table 3. Standardized Incidence Ratio (SIR) calculations of Goiter stratified by ethnicity.

Ethnic group:	Number of patients			SIR*	95% CI for SIR
	Observed	Expected‡	Residual		
Druze	123	87.4	35.6	1.41	1.18-1.67
Jewish	235	281.1	-46.1	0.84	0.73-0.95*
Muslim	34	23.5	10.5	1.45	1.02-2.00
Total	392	*p<0.001, $\chi^2_{(2)} = 26.70$			

* The Standardized Incidence Ratio (SIR) = Observe / Expected, *significant differences between the control group and other two groups (p<0.05). ‡ Expected value = 392 * percentage of residents over the age of 18 at each ethnicity group. # Chi-square for goodness of fit.

4. Discussion

This is the first study of goiter prevalence in adult Arab origin populations. Our results show a significantly higher prevalence of TG in the Arab Druze population in comparison to the Jewish population, with similar environmental conditions. Our results could suggest a possible ethnic hereditary predisposition for TG development in the Arab Druze population.

TG is considered as caused by genetic factors interacting with physical and environmental conditions (e.g.: low iodine intake, cigarette smoking, obesity and gender) (24). Multiple previous studies have demonstrated that in areas with adequate iodine intake, a familial genetic predisposition is the major factor for TG development, regardless of the environmental conditions (25). It has already been shown that there is a disproportionate under-recognition on the impact of ethnic hereditary on various health conditions amongst racial and ethnic minorities worldwide (26). The term Ethnic hereditary describes the genetic pooling of a specific ethnic group. An ethnic hereditary predisposition is made possible in small closed societies – either from geographic or ethnic reasons, where the custom of intermarriage is common (27). The Arab Druze population in Israel was estimated at 150,000 persons in 2021 (28) and is distributed mainly in the northern part of Israel (less than 100 Sq. Km.). Druze customs strongly favor marriage within the same village or the same geographical area. This social structure has turned the Druze into a population which remains genetically isolated from their surrounding neighboring communities (29). A previous study of the phylogenetic mitochondrial haplogroup of the Arab Druze in Israel has demonstrated that they are genetically a population isolate (30) (23). Two previous studies support this theory: Schaffer et al. (2017) have found an unusually high prevalence of classical Kaposi's sarcoma in the Arab Druze from Israel (31), while Atzmon et al. (2014) have observed lower cancer rates among Arab Druze in comparison to the non-Druze Arab and Jewish populations in Israel (32). Thus the possibility of an existing ethnic hereditary predisposition for TG in this unique population is highly possible.

All the populations included in this study live in the same geographical area (50 Sq. Km), with similar environmental conditions. The water sources supplying all the included populations are of similar nature, with average Iodine levels of 4-6 µg/L. The possible effect of specific goiterogenic foods effecting goiter development in the study groups can also be excluded. The Arab Druze in Israel leads a modern life style in terms of technology use and academic education. In survey from 2020 of the general Israeli population, no significant differences were found between Arabs – Muslims or Druze and Jewish families in regard to healthy foods consumption or nutritional habits (33). A similar study on the Israeli Ethiopian origin population have shown high TG prevalence regardless if the patients maintained either a modern Israeli diet or the traditional Ethiopian diet (34).

The early detection of TG is of high importance. An enlargement of goiter can result in symptoms related to tracheal or esophageal compression (dyspnea and/or dysphagia). Early detection and proper treatment can prevent possible complication such as progressive enlargement or mediastinal extension (tracheal narrowing, superior vena cava syndrome). Cosmetic discomfort resulting from an enlarged goiter - especially in female patients is of no less importance. Early detection can allow prompt surgery while goiter size is still small (6). Delayed surgical treatment can result in possible surgical complication such as damage to the recurrent laryngeal nerve or hypocalcemia due to a larger goiter size. Our results can point to the benefit of promoting early thyroid screening in the Druze community, especially in women.

We also found a high prevalence of TG in the Muslim population group (SIR 1.44 CI 1.02-2.00). These findings are in line with two studies from Jordan presenting high prevalence of thyroid dysfunction and TG in the Jordanian Arab population (35) (36). The Arab Muslim group in our study was relatively small and included only 34 (8.7%) patients. This low sample size can affect SIR value, and doesn't allow a clear conclusion. Still, these findings are of interest and call for further investigation.

5. Conclusion

The Arab Druze population in Israel has higher TG prevalence in comparison to the Jewish population with similar environmental conditions. Early thyroid screening in the Druze community especially in women should be considered. Further studies of possible genetic factors are warranted. A larger study of goiter prevalence in the Israeli Arab Muslims should also be considered.

This statement is to certify that all authors have seen and approved the final version of this submitted manuscript. We warrant that this article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Authors' contributions: A.S.N.: Conceptualization of study, validation and Formal analysis of manuscript. E.P.B.: Investigation and data curation. R.F.: Resources and visualization of manuscript. ME: supervision and project administration. Y.A.: Conceptualization of study, Writing the Original Draft and the final manuscript. S.M.: Writing - Review & Editing.

Funding statement: No funding was used for this study.

Data availability statement: The data that support the findings of this study is available on request from the corresponding author, [YA]. The data is not publicly available due to ethical restrictions as it contains information that could compromise the privacy of study participants.

Conflict of interest disclosure: No conflict of interest to disclose.

Ethics approval and consent to participate: The study was approved by the Ziv Medical Center human ethics committee. ID:0062-20-ZIV. Due to the retrospective nature of the study, the Ziv Medical Center human ethics committee waived the need of obtaining informed consent. All study methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

Patient consent for study participation: no patient consent was required – a retrospective study.

Consent for publication: not applicable, a retrospective study.

Permission to reproduce material from other sources: not required.

Competing interests: no competing interests to disclose.

Acknowledgments: not applicable.

Abbreviation List

Thyroid goiter (TG), Thyroid Stimulating Hormone (TSH), Fine-Needle Aspiration (FNA), American thyroid association (ATA), Fine-Needle Aspiration Cytology (FNAC).

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