Pattern of thyroid disorders in black population referred for thyroid scintigraphy at Chris Hani Baragwanath Hospital, South Africa

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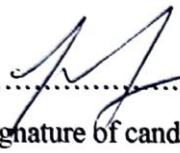
Declaration

I Nadia Zergoug declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Nuclear Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



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Dedication

I would like to thank my family for standing with me through thick and thin.

Abstract

Background: Most endocrine disorders are due to thyroid dysfunction with varying etiologies. Different management protocols exist for the different endocrine disorders, and it is crucial to determine the specific cause due to thyroid dysfunction. This study aimed to describe the spectrum of thyroid diseases in patients who undergo thyroid scintigraphy and to assess the agreement with biochemistry and scintigraphy.

Methods: This was a retrospective study to assess the pattern of thyroid disorders in the patients referred for thyroid scintigraphy at Chris Hani Baragwanath Hospital (CHBAH). All cases diagnosed with thyroid dysfunction based on biochemical results and referred for 99m Tc scintigraphy to nuclear medicine from January 2017 to December 2018 were reviewed. All records reviewed were >18 years of age and were a total of 780.

Results Of the 780 patients reviewed, 631 (80.9%) were black while the remaining 19.1% comprises White, Indian, and Coloured individuals. Among the Blacks, 84% were females and 16% were males. Graves' disease was the commonest thyroid disease diagnosed on scintigraphy in the entire population and among the blacks, constituting 72% (n=454/631) of patients. Other thyroid disorders among the black population include toxic multinodular goitre (13%, n=80/631), non-toxic multinodular goitre (7%, n=45/631), toxic adenoma (3%, n=17/631), and thyroiditis (3%, n=21/631). The black patients' mean age was 47.3 years with a standard deviation (SD) of ±15.1 years. Graves' disease as well as other thyroid disorders affected all age groups but were most prominent in the 40-59 years age group in both females and males. The median thyroid stimulating hormone (TSH) was 0.001 mIU/L while free thyroxine (fT4) ranged from 7.4 – 160 pmol/L in black population diagnosed with hyperthyroidism.

Conclusion: Graves' disease is the commonest cause of thyroid disorders among individuals referred for thyroid scintigraphy, being most prevalent in Black females in the reproductive age group. Thyroid scintigraphy is useful for aetiological diagnosis in patients presenting with thyroid disorders.

Keywords Thyroid disorders, Graves' disease, hyperthyroidism, thyroid function tests, thyroid Scintigraphy.

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I would like to express my heart felt gratitude to my two supervisors without whom I would not have managed to complete this research report.

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Nomenclature/Abbreviation

AACE	American Association of Clinical Endocrinologists
African Population	categorized as Black and Non-Black (whites, Indians and coloureds)
ART	Antiretroviral therapy
CHBAH	Chris Hani Baragwanath Academic Hospital
C5	5th cervical vertebrae
ETA	European Thyroid Association
fT4	free T4
GD	Graves' disease
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
IRIS	Immune reconstitution inflammatory syndrome
IQR	Interquartile range
IRIS-GD	Immune reconstitution inflammatory syndrome- Graves' disease
I-123	Iodine-123
KeV	Kilo electron volt
NIS	Sodium iodide symporter
TA	Toxic adenoma.
TFT	Thyroid function test

TMNG Toxic multinodular goitre

TRH Thyrotropin releasing hormone.

TSH Thyroid Stimulating Hormone

T3 Triiodothyronine

T3RU Triiodothyronine Resin Uptake

$^{99m}Tc0_4^-$ Pertechnetate-99m

UK United Kingdom

USA United States of America

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Thyroid dysfunction with its various etiologies is the commonest endocrine disorder (1). The American Association of Clinical Endocrinologists (AACE) estimates that 4.78% of individuals with thyroid dysfunction remain undiagnosed (1).Thyroid function is very important in regulation of multiple metabolic processes such as lipolysis, gluconeogenesis and oxidative phosphorylation. On the other hand, thyroid dysfunction can lead to significant morbidity and mortality (1-3).A study done by Laulund *et al* aiming at correlating between biochemical thyroid dysfunction and mortality included almost a quarter of a million patients over a period of 7years. It demonstrated increased mortality by 9% and 12% for hyper and sub clinically hyperthyroidism respectively. Additionally, it demonstrated an increase in mortality of 7% in patient with hypothyroidism(2). In a large study conducted by the United States (US) National Health and Nutrition Examination Survey involving 13,344 individuals with unknown thyroid function status, hypothyroidism was the most commonly encountered thyroid disorder affecting 4.6% of the population, followed by hyperthyroidism in 1.3% (1).

The prevalence of hyperthyroidism in Europe is between 0.5 - 2% (1). It is more frequent in females. The most common cause of hyperthyroidism is Graves' disease, followed by toxic multinodular goitre. Less frequent causes include thyroid adenoma and thyroiditis (3). However, these vary significantly between different races and ethnic groups (4). However, in South Africa, there is paucity of literature describing thyroid disease patterns in the Black and Non-black South African population.

1.1 Thyroid gland

The thyroid is a butterfly-shaped gland located in the neck. It is composed of right and left lobes and connected in the midline by the isthmus inferior to the larynx, at the level of C5 to T1 vertebrae (5). The main function of the thyroid gland is the production, storage, and release of thyroid hormones triiodothyronine (T3) and thyroxine (T4). These hormones are synthesized using iodine. The thyroid hormones are produced by the thyroid gland to regulate several metabolic functions in the human body. The production of thyroid hormones is regulated by thyroid stimulating hormone (TSH), a hormone released from the anterior pituitary in response

to low circulating levels of T3 and T4 through negative feedback. Thyroid stimulating hormone (TSH) is the primary screening test for thyroid dysfunction.

Early diagnosis of thyroid dysfunction using the correct laboratory tests is key for timeous treatment (6). Investigations complementary to laboratory tests include neck ultrasonography and thyroid scintigraphy. The use of biochemistry tests and thyroid scintigraphy can be sufficient to differentiate between different causes of thyroid dysfunction for implementation of a rapid, accurate diagnosis and treatment (7).

1.2 Thyroid dysfunction

Thyroid disorders include hyperthyroidism, hypothyroidism and euthyroid goitre. Hyperthyroidism is due to inappropriate high synthesis and secretion of thyroid hormones by the thyroid gland (8). The commonest encountered aetiologies of hyperthyroidism are Graves' disease, toxic multinodular goitre and thyroid adenoma (6). Patients can present with a hypermetabolic state with clinical manifestations such as heat intolerance, weight loss, diarrhoea and tachycardia (6). However, symptoms may be non-specific or may be absent. Primary hypothyroidism occurs when there is low production of thyroid hormones with compensatory high TSH. It is essential to distinguish between thyroiditis and congenital hypothyroidism (6). Thyroiditis is an inflammation of the thyroid gland caused by a viral upper respiratory infection that causes an increase in the release of preformed thyroid hormone. On the other hand, congenital hypothyroidism is defined as a lack of thyroid hormone at birth. Thyroid gland hypofunction typically results in low T4 and T3 levels, with elevated TSH and TRH levels due to a feedback mechanism to the hypothalamus and pituitary gland. It is also important to determine the degree of function of a palpable thyroid nodule with scintigraphy (9).

Thyroid function tests play an important role in the diagnosis of thyroid disorders. The initial investigations are thyroid function tests (TFTs); a series of blood tests that is used to measure how well the thyroid gland is working. Available tests include T3, freeT4 and the determination of thyroid stimulating hormone (TSH) (9). TSH is the primary biomarker for the diagnosis of thyroid dysfunction and for guiding treatment of thyroid disease. Monitoring TSH levels is essential. Following a thyroid function test, patients can then be referred for thyroid scintigraphy to identify the underlying cause.

Thyroid scintigraphy is a nuclear medicine study that visualizes the thyroid gland and gives an indication of the function of the thyroid gland with selective uptake of radionuclides (10).

1.3 Radiopharmaceuticals

Pertechnetate ($^{99m}Tc0_4^-$) is the radioisotope mostly used for thyroid scintigraphy. It is eluted from the molybdenum-99m/Tc-99 generator, in the metastable or exited state. It decays by isometric transition to reach the stable state. With a half-life of 6 hours, energy of 140 kilo electron volt (KeV) using gamma photons, it is appropriate for use in gamma camera (11). $^{99m}Tc0_4^-$ is an analogue of iodine. It is trapped by the epithelial cells of the thyroid gland which is facilitated through the sodium iodide symporter (NIS) (6). It is not organified or incorporated into the gland, therefore it is quickly eliminated and seen in the normal biodistribution of the radiopharmaceutical. After intravenous injection, it reaches its maximum uptake by 15 minutes (9).

1.4 Thyroid scintigraphy/interpretation

Thyroid scintigraphy can help to identify the cause of thyroid dysfunction by demonstrating the distribution of the radiotracer in functional thyroid tissue (12). In other words, it can differentiate productive (hyperthyroidism) from destructive thyrotoxicosis (acute and sub-acute thyroiditis), and focal from diffuse activity of the thyroid gland (12). There are two forms of hyperthyroidism including productive thyrotoxicosis where there is excessive production of thyroid hormones and destructive thyrotoxicosis (inflammation of thyroid follicular cells), where there is increased release of preformed thyroid hormones. In both types, TSH is supressed while serum T4 is high (12).

Thyroid scintigraphy is performed with intravenous injection of radioactive I-123 or Pertechnetate-99m ($^{99m}Tc0_4^-$). Thyroid scintigraphy with $^{99m}Tc0_4^-$ is the most commonly used and the preferred technique because, it is readily available, lower cost, lower radiation exposure for the patient and shorter acquisition or scanning time (13). Thyroid scintigraphy is performed using gamma camera that images gamma rays emitted from the body of the patient following the injection of $^{99m}Tc0_4^-$. The thyroid gland is imaged 5-30 minutes after intravenous injection of 2-10 mCi (74-370MBq) of $^{99m}Tc0_4^-$ preferably with a pinhole and low energy parallel collimator. Anterior as well as right and left anterior oblique images of the thyroid gland are then obtained for 100,000-250,000 counts (or 5 minutes) each with the patient in supine position with the neck extended forward.

The pitfalls of thyroid scintigraphy include oesophageal activity as this may may mimic ectopic thyroid tissue and poor image quality when the tracer uptake is low (13). The use of thyroid scintigraphy is not appropriate in the case of hypothyroidism and euthyroid condition with no goitre (7). Perchlorate, propylthiouracil and other medications will interfere with radiotracer uptake by inhibiting the trapping of iodine and organification by the thyroid gland and therefore their discontinuation is mandatory to increase the accuracy of thyroid scintigraphy .

Biochemistry (TSH, T4) results are required when reporting thyroid scintigraphy. Productive thyrotoxicosis on scintigraphy has three distinct patterns. The first pattern demonstrates homogeneous increased uptake of tracer with increased thyroid to background ratio consistent with Graves' disease. The second pattern is the identification of prominent hot nodule(s) suppressing the rest of the thyroid gland consistent with toxic adenoma. Finally, it can present as mixed areas of increased and decreased uptake, consistent with toxic multinodular goitre. In contrast the destructive thyroiditis will show decreased or absent uptake.

Thyroid dysfunction continues to be underdiagnosed in Africa, as shown by Ogbera *et al* in their study wherein the prevalence rate of Grave's disease was between 1.2-9.9% (14). In CHBAH, South Africa, a retrospective analysis of thyroid disease in 58 pregnant women showed a prevalence of hyperthyroidism of 68%, of which Graves' Disease was 83%, gestational hyperthyroid 16%, hypothyroid 26% and euthyroid colloid goitre 8% (10). These two studies were done by compared biochemistry findings to the clinical findings. No study compared biochemistry and scintigraphy findings.

1.5 Study Aim and Objectives

This study aimed to describe the patterns of thyroid disorders in the African population referred for thyroid scintigraphy at Chris Hani Baragwanath Academic Hospital, South Africa. It aimed to describe the comparison between biochemistry and scintigraphy using Technetium-99m (Tc-99m) for thyroid dysfunction in this population. The findings of the current study provide data on thyroid disorders in a referral hospital setting in South Africa.

Objectives

1. Primary objective: To determine the relationship between biochemistry and thyroid scintigraphy for patients referred to nuclear medicine at Chris Hani Baragwanath Academic Hospital.
2. Secondary objective: Description of the spectrum of thyroid diseases diagnosed with thyroid scintigraphy in patients.

CHAPTER 2

METHODOLOGY

2.1 Study design

This was a cross-sectional study of African population with thyroid dysfunction referred for thyroid scintigraphy at Nuclear Medicine department, CHBAH between January 2017 and December 2018. Information of patients with thyroid dysfunction referred to the department was extracted from Nuclear Medicine electronic database. A total of 780 records were reviewed. Two classes of Ethnicity were labelled for the African population and included the black and non-black (Whites, Indians and Coloured, these all formed a minority group).

2.2 Study site

The Nuclear medicine department at Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, South Africa. The hospital is a catchment area for referral hospitals (it includes Sebokeng, Northwest etc) and clinics based in Soweto. Nuclear medicine department often get requests from endocrinologists for thyroid scintigraphy for inpatients and outpatients at the hospital. It uses $^{99m}Tc0_4^-$ thyroid scintigraphy for further investigation of thyroid dysfunction. In a month approximately 35 patients are referred for thyroid scintigraphy.

2.3 Study population

All records of patients who had thyroid scintigraphy between January 2017 and December 2018 were retrieved. We included 780 patients with no history of thyroid cancer.

2.4 Selection Criteria

2.4.1 Inclusion criteria

1. Patients referred to nuclear medicine department of CHBAH for thyroid scintigraphy from January 2017 to December 2018
2. Patients ≥18 years of age

2.4.2 Exclusion criteria

1. Patients with a clinical diagnosis of thyroid cancer

2. Patients with more than 10% incomplete or missing medical information.

2.5 Data Collection

A standardized data collection sheet was used. Data was extracted from records of all patients with thyroid dysfunction who were referred for thyroid scintigraphy. Patients' demographics, thyroid function test results and scintigraphy results were recorded as de-identified data.

2.6 Statistical Analysis

All data was analysed using STATA statistical software (version 15). Categorical data such as scintigraphy results with race was analysed using Pearson's Chi-Square test. Median and interquartile range was calculated for continuous variables such as fT4 and TSH. Where the mean or median and their distribution were same, the minimum and maximum values for continuous variables were used. A P value of < 0.05 was considered statistically significant. Kruskal-Wallis test with Benjamin Hocherberg adjustment was used for comparing continuous and categorical variables.

2.7 Ethics clearance

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC), with ethics clearance number M190211. Permission to access patients' medical records was also obtained from the Chief Executive Officer, CHBAH.

CHAPTER 3

RESULTS

3.1 Socio-demographic characteristics

During the period under review (January 2017 - December 2018), there were 780 patients referred for thyroid scintigraphy on account of thyroid dysfunction. Most of the patients (81%, n=631) were Black, and were predominantly females (79%, n=616). The age range for this patient cohort was 18-78 years while the median age was 48.2 years and IQR of 47.2-49.3) years as shown in Table *1*.

Table 1 Socio-demographic characteristics

Variable	Total
Age (Median (IQR))	48.2(47.2-49.3)
Age category N (%)	
18-29	86(11)
30-39	149(19)
40-49	205(26)
50-59	160(21)
60-69	103(13)
70+	77(10)
Sex N (%)	
Female	616(79)
Male	164(21)
Ethnicity N (%)	
Black	631(81)
Non-black	149(19)
TSH-T4 (Median (IQR))	0.81(0.5-1.1)
T4 (Median (IQR))	39.1(37.1-41.2)
Scan results N (%)	
Graves	535(69)
Toxic multinodular	106(14)
Nontoxic multinodular	63(8)
Toxic adenoma	23(3)
Thyroiditis	32(4)
Normal scan	8(1)

Other	13(2)

For both female and male gender in the black population, Graves' disease was the commonest among the younger and middle age groups as shown in Figure *1*

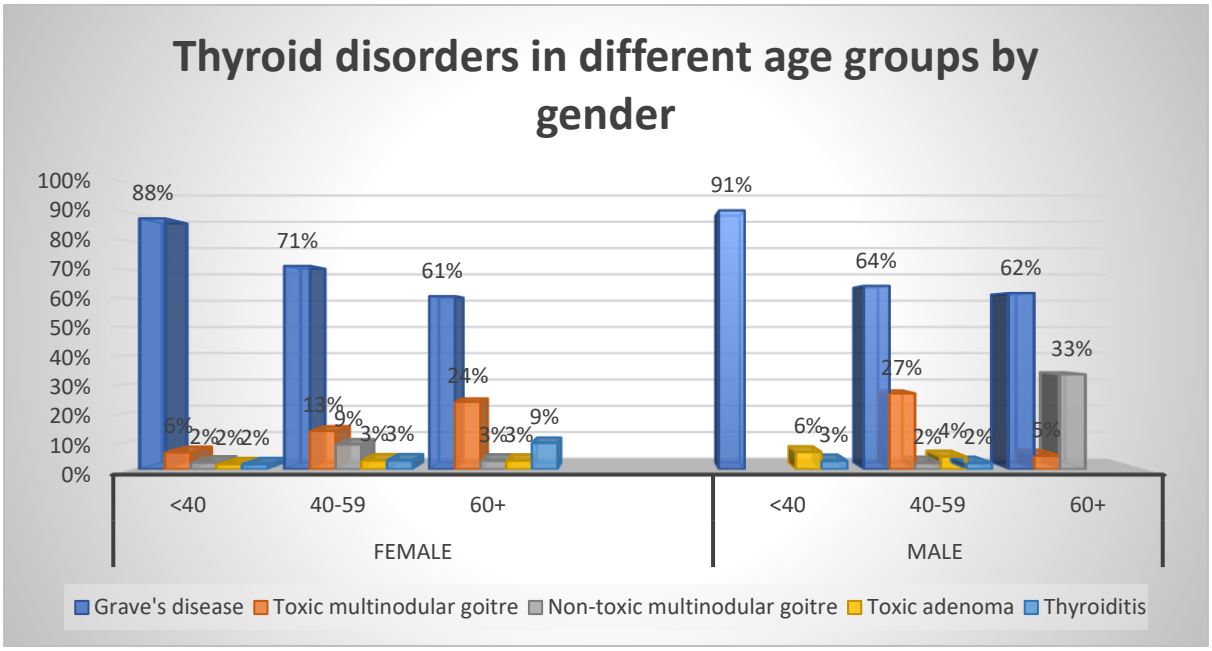

Figure 1 Thyroid disorders on scintigraphy in various age groups and gender

3.2 Scintigraphy characteristics

The majority (59%) of the black patients were between ages 18-49 years while the non- Black patients for the same age range constitute 42%. Most (57%) of the non- Black patients were 50 years. The patients in the 40-49 years age category (26%, n=205) constitute the highest with thyroid dysfunction for both males and females.

On scintigraphy, the most predominant thyroid disorder in the entire cohort was Graves' disease (69%, n=535) followed by Toxic Multinodular Goitre (14%, n=106), Non-toxic Multinodular Goitre (8%, n=63), Thyroiditis (4%, n=32) and Toxic Adenoma (3%, n=23). Similar trend of pathology on scintigraphy was also seen among the black population which constitute the majority, Graves' disease (72%) being the commonest and Toxic Adenoma (3%), the least common. Some patients also had normal thyroid scan features as shown in Table *2*.

Most of the patients with scintigraphy findings of Graves' disease, Toxic Multinodular Goitre and Toxic Adenoma had median TSH value of 0.001mIU/L (well suppressed), while for Non-Toxic Multinodular Goitre, median TSH was 0.74 mIU/L and for thyroiditis, 0.02 mIU/L in black patients. Graves' disease has the widest variation in TSH (0.0-12.9 mIU/L) level as well as the fT4 (7.4 - 160.0 pmol/L) level which is more prominent in Black patient cohort compared to non- Black as shown in Table *1*.

Table 2 Diagnosis on scintigraphy and Ethnicity

Variable	Black N (%)	Non-Black N(%)	P value
Scintigraphy results			
Graves' disease	454(72)	81(54)	0.003
Toxic multinodular Goitre	80(13)	26(17)	
Non-toxic multinodular Goitre	45(7)	18(12)	
Toxic adenoma	17(3)	6(4)	
Thyroiditis	21(3)	11(7)	
Hypothyroidism	9(1)	4(3)	
Normal thyroid	5(1)	3(2)	
Age category			
18-29	72(11)	14(9)	0.003
30-39	128(20)	21(14)	
40-49	176(28)	29(19)	
50-59	125(20)	35(23)	
60-69	78(12)	25(17)	
70+	52(8)	25(17)	
Sex			
Female	529(84)	87(58)	<0.0001
Male	102(16)	62(42)	

Table 3 Median and IQR of fT4 levels in the various thyroid scintigraphy diagnoses

Diagnosis	Black	Non-Black
Graves' disease	34.0 (20.8 - 61.4)	40.0 (24.0 - 65.6)
Toxic multinodular	27.3 (18.0 - 40.1)	25.5 (16.4 - 35.1)
Nontoxic multinodular	16.2 (13.3 - 19.6)	15.5 (10.2 - 16.8)
Toxic adenoma	26.2 (20.0 - 32.7)	27.5 (24.0-36.6)
Thyroiditis	25.8 (20.8 - 37.5)	24.0 (20.1 - 36.0)
Normal thyroid	13.5 (13.5-17.1)	10.9 (5.9 - 14.0)

Table 4 Median fT4 level in thyroid disorders black population

	Female	Male
Graves' disease	33.5 (20.8 – 62.0)	33.5 (20.7 - 54.4)
Toxic multinodular Goitre	26.0 (17.1 - 40.6)	34.1 (28.3 - 37.3)
Non-toxic multinodular Goitre	16.1 (12.0-19.3)	14.5 (13.3-17.5)
Toxic adenoma	28.6 (20.0-39.9)	22.8 (20.0-27.8)
Thyroiditis	25.8 (17.4 - 38.2)	22.6 (21.0 - 24.1)

The TSH levels were 6.92 times higher for toxic adenoma compared to nontoxic multinodular goitre as shown in Figure *2*. Thyroiditis TSH levels was 4.07 times higher compared to nontoxic multinodular goitre.

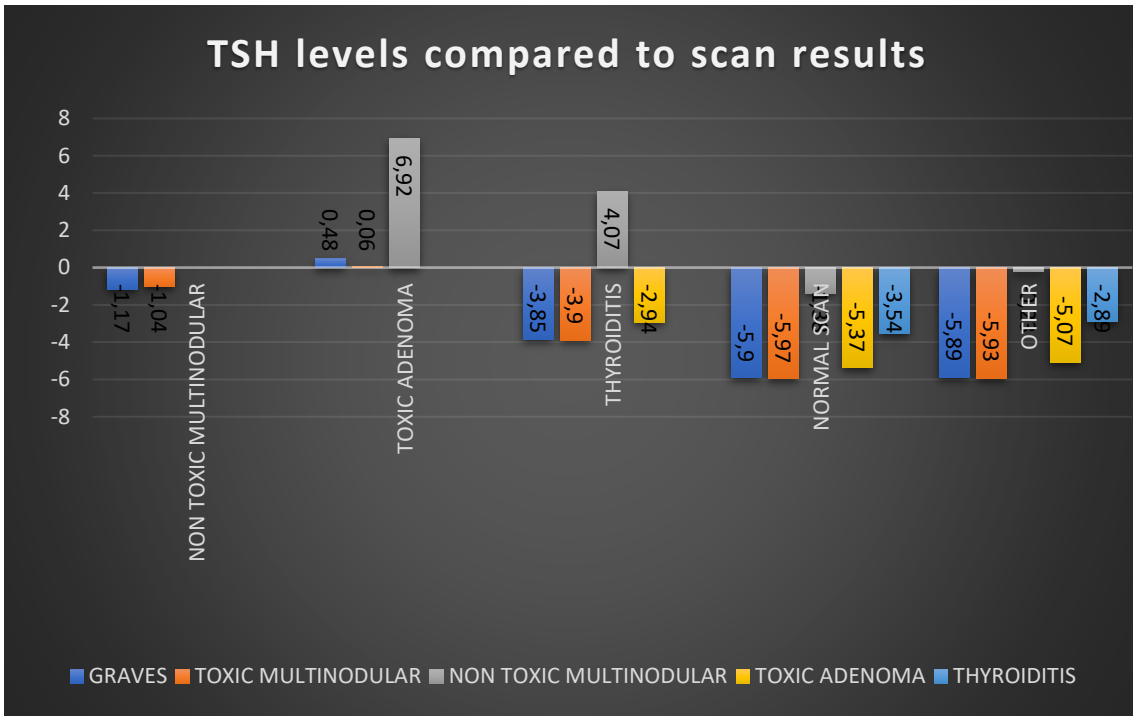

Figure 2 Comaprison of TSH levels and scan results

The T4 levels for grave disease were 9.67 times higher compared to non-toxic multinodular goitre. Thyroiditis T4 levels were 5.97 times higher than nontoxic multinodular goitre.

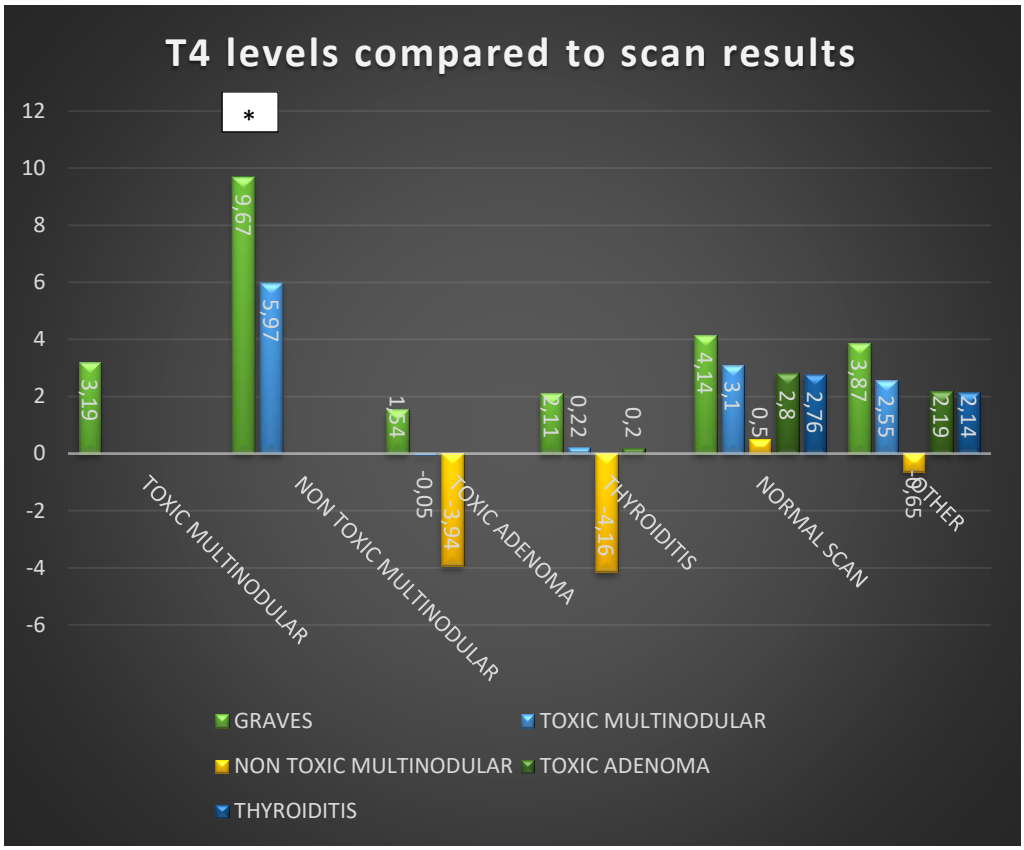

Figure 3 Comparison of T4 levels with scan results

CHAPTER 4

DISCUSSION

In this retrospective study at a tertiary (referral) hospital in Johannesburg, we set out to determine the patterns of thyroid dysfunction among patients referred for thyroid scintigraphy in South Africa. To the best of our knowledge, this study is the first to assess the relationship between thyroid biochemistry and scintigraphy for thyroid dysfunction in patients referred for scintigraphy.

The most common endocrine conditions are benign thyroid abnormalities, especially hyper- and hypothyroidism. The most common aetiologies of hyperthyroidism are autoimmune hyperthyroidism (Graves' disease, GD), toxic multinodular goitre (TMNG), and toxic adenoma (TA). Less common aetiologies include destructive thyroiditis. Most of the black population in our study cohort were females (84%) and over five times more than the male (16%) counterpart. Graves' disease was the most common thyroid disorder diagnosed on scintigraphy, comprises 73% of the total black population in our study. Our study is similar to that by Alswat et al. (2020) which also found that female prevalence with Graves' disease was five times higher than males, accounting for 75% of their study population (7).
In a study in Brazil, by Olmos RD et al. (2015), black ethnicity was identified as a risk for developing overt hyperthyroidism. Using white race as the reference hypothyroidism was commoner in whites as compared to individual blacks (21).

Our data showed that Graves' disease affect all age groups with females in the reproductive age group more commonly affected. Graves' disease was also the commonest in males, predominantly among young and middle-aged men.
Nodular goitre was the second commonest cause of thyroid disease. Toxic multinodular goitre was seen in all age groups in Black females while in the males, it was only prominent among age group 40-59 years. Non-toxic multinodular goitre was commoner among females 40 years and above while in males it was only prominent in the age group 60 years and above. Our study finding is similar to a local study in Polokwane, Limpopo province in 2015 which also showed that most of the patients (predominantly females) that presented with nodular goitres were from ages 41-60 years. Toxic adenoma is likewise commoner in the female population, across all

age groups and highest among patients aged 40-60 years. Toxic adenoma was not recorded in any male patient aged 60^{+} years in the entire study population, this shows that toxic adenoma is far uncommon in elderly males unlike in elderly females due to our study only having 21% males compared to 79% females. This show the imbalance in the different thyroid dysfunctions between males and females. Our findings also showed that thyroiditis is commoner among females and that it is increasingly common with advancing age, however, it was uncommon among elderly males.

Serum TSH measurement plays a critical role in the diagnosis of thyroid disease and is one of the most frequently requested tests in clinical medicine. This is mainly due to its wide availability, low cost, and high sensitivity. It is a good screening tool and valid indicator of thyroid function status due to TSH secretion being extremely sensitive to plasma concentrations of free thyroid hormones. TSH is a sensitive marker of thyroid dysfunction since minor changes in fT4 result in substantial changes in TSH, hence it may be most practical to measure both at once (one step approach). In a study by Vadiveloo T et al. they looked at the challenges in interpreting thyroid stimulating hormones (TSH) results. The study was done with 150,000 patients with no serum thyroid antibodies and no previous thyroid treatment. They found that TSH increased with age in both men and women, and they noticed TSH level increased from 3.98 mIU/L at age 31-40 years to 5.94 mIU/L at age above 90 years (15). The TSH levels were higher in women compared to men (15). They suggested the use of age–specific reference intervals for TSH, especially in individuals over 70 years old would result in reclassification of many TSH results from "abnormal" to "normal" [within the 95^{th} centile reference interval].

Regarding thyroid function (TSH and fT4) results for the black population in our study, the most common biochemical profile was undetectable TSH levels and high fT4 in Graves' disease [TSH: 0.01 - 9.9 mIU/L, T4: 20.8 - 61.4 pmol/L] and toxic adenoma [TSH: 0.0-0.11mIU/L, T4: 20.9 - 32.7 pmol/L]. Non-toxic multinodular goitre in the black population showed lower values of TSH as compared with non- Blacks. In contrast, for toxic multinodular goitre in the black population, TSH levels were much higher, than in the non- Blacks. Overall, in the four thyroid abnormalities (Graves' disease, toxic multinodular goitre, toxic adenoma and thyroiditis) causing hyperthyroidism, fT4 levels in the black population were higher than non- Blacks. As at the time thyroid scintigraphy was done, about 15% (n=95) of the black patients were already in subclinical hyperthyroidism (TSH < 0.27 mIU/L, T4: 12.0 - 22.0

pmol/L), most likely due to the use of anti-thyroid drugs, (following overt hyperthyroidism) and in a few others with thyroiditis. In this group of patients, Graves' disease and multinodular goitre were the top two culprits. The European Thyroid Association (ETA) recommends that definitive treatment be given to these patients especially the elderly who are at increased risk of adverse cardiac events.

The overall mean age for black patients in our study was 47.3 years compared to non-blacks which was 52.2 years. This again confirms younger age groups at diagnosis in Black patients (7). Razvi et al. 2019 found that demographic, diagnostic, and disease related factors, such as age, sex, ethnicity, medications and mineral supplements influence the TSH level and should be considered when making the diagnosis of thyroid disorders (15). The use of automated immunoassays should be standardized across different laboratories so that there is comparison and standard for fT4 and TSH and again this was demonstrated in the same study by Razvi et al. 2019 (15). If different methods are used this may in turn affect the quality of comparisons of the TSH and fT4.

A study by Nicolaou et al. 2017, retrospectively looked at thyroid disorders in pregnancy among blacks attending the Antenatal Endocrine Clinic during a 4 year period at Chris Hani Baragwanath Academic Hospital Johannesburg (10). The sample size was 58 patients and showed a prevalence of hyperthyroidism of 68%, of which Graves' Disease was 83%, (10). In the other study by Alswat et al. 2020, prevalence of GD was more than 40% and about 67% of GD patients comprises female and their mean age at diagnosis was 32 ± 0.9 years **.** A study by Malabu et al. 2008 demonstrated the mean age of patients with Grave's disease was 32 years ±0.9 (16). Poor nutrition and poverty in Sub-Saharan Africa may have contributed to increasing thyroid dysfunction in the form of hyperthyroidism, autoimmune hypothyroidism, and thyroid cancer (17). Mc Leold et al. 2015, confirmed the prevalence of hyperthyroidism (thyrotoxicosis) was nearly three times more likely in non-Hispanic Black subjects compared with non-Hispanic whites in young population (18)**.** These results suggest there are racial differences in the prevalence of thyroid disorder (thyrotoxicosis) and other contributing factors include immunological factors, environmental exposures, or a combination of both (18). The spectrum of changes in thyroid function test is related to both the severity and stage of thyroid illness (19).

The relationship between TSH and scan results after adjusting with Benjamin-Hocherberg test showed the magnitude in which each dysfunction differs from the other. Non-toxic nodular goitre and toxic adenoma had a difference of 6.85 times for TSH level, this shows that patients with non-toxic multinodular goitre were 6.85 times less likely to have elevated TSH compared to toxic adenoma patients from our study. In our study, the TSH level in toxic multinodular goitre was lower compared to the non-toxic multinodular goitre. The level of T4 was 9.46 times more in GD patients compared to non-toxic multinodular goitre patients. Patients with thyroiditis had T4 levels that were 4.1 times higher than patients with non-toxic multinodular goitre. Patients in the 70^{+} age group were 4.39 times more likely to have elevated TSH compared to the 30-39 age group. This is similar to a retrospective study over a period of ~ 6 years, a general population without thyroid disorder in Scotland done by Vadiveloo et al. 2013, in which they observed increased level of TSH in elderly women over 90 years**.** This is probably related to increased production of TSH during circadian rhythm at night, in older subjects and different according to ethnicity (20). The 60-69 age group had 3.95 times elevated T4 compared to 18-29 age group considering that the percentages of these groups were almost the same 11% and 13% respectively.

CHAPTER 5

CONCLUSION

Graves' disease is the commonest cause of hyperthyroidism in the black population in South Africa, and predominantly affecting females in the reproductive age group. However, age group 40 - 59 years is most affected by thyroid disorders in both females and males, and scintigraphy is useful for aetiological diagnosis. TSH levels were inversely related to free T4 levels and there was good correlation between biochemistry and scintigraphy outcome for the various thyroid disorders.

Limitations

The first limitation is that it is a retrospective single centre study. Data on patients' co-morbidities especially autoimmune conditions as well as HIV status were not documented by the referring clinicians. The increased incidence of these underlying conditions in the South African population and their impact on thyroid function could not be ascertained. The second limitation relates to the thyroid function tests results that were analysed not only at the study site laboratory but also the various laboratories under NHLS in the peripheral hospitals where a significant number of the patients were referred for thyroid scintigraphy. Despite these limitations, this study adds significant information on the patterns of thyroid disorders diagnosed with biochemistry and scintigraphy techniques in an African population.

Recommendations

Based on our results, clinical characteristics of patients (Neomecarazole, smoking habits, metformin drugs, supplements and others) and the different normal range of T4 and TSH from different laboratories were not assessed, more detailed clinical information and using a single laboratory in future studies are needed to improve our study. Targeted investigation to definitively exclude assay interference may require specialist laboratory input.

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Appendices

Appendix 1 **Ethics clearance certificate**

Appendix 2 Plagiarism/turn-it-in report cover page.

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CHAPTER 1 INTRODUCTION AND LITERATURE REVIEW 1.0 Introduction Thyroid dysfunction with its various aetiologies is the commonest endocrine disorder (1). The American association of Clinical Endocrinologist (AACE) estimates that 4.78% of individuals with thyroid dysfunction remain undiagnosed (1). Thyroid function is very important in regulation of multiple metabolic processes such as lipolysis, gluconeogenesis and oxidative phosphorylation. On the other hand, thyroid dysfunction can lead to significant morbidity and mortality (1-3). A study by Laulund et al. aimed at correlating biochemical thyroid dysfunction with mortality, included almost a quarter of a million patients over a period of 7 years. The study demonstrated increased mortality by 9% and 12% for hyper and subclinical hyperthyroidism respectively. In addition, the study demonstrated an increase in mortality by 7% in patients with hypothyroidism (2).. In a large study conducted by the United States (US) National Health and Nutrition Examination Survey that looked at 13,344 individuals with unknown thyroid function status, hypothyroidism was the most commonly encountered thyroid disorder affecting 4.6 % of the population, followed by hyperthyroidism in 1.3% (1). The prevalence of hyperthyroidism in Europe is between

Appendix 3 **CHBAH CEO Permission letter**

GAUTENG PROVINCE

REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 22nd January 2019

TITLE OF PROJECT: Pattern of thyroid disorders in the Black Population referred for thyroid scintigraphy at Chris Hani Baragwanth Hospital, South Africa.

JNIVERSITY: Witwatersrand

Principal Investigator: Dr Nadia Zergoug

Department: Nuclear Medicine

Supervisor : Prof MDTHW Vangu

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 22/01/2019

Approved/Not Approved
Hospital Management
Date: 22 01 2019

Data Collection sheet

Biodata

1. Code:
2. Age:
3. Gender:
4. Race: Please cross (*x*) appropriate box

Black	
White	
Indian	
Colored	
Other	

Indication for study:

Biochemistry:

- TSH (mIU/L)
- T4 (pmol/L)

Ultrasound of the neck	Yes		No	

If yes – findings?

Date and Thyroid Scintigraphy findings: