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The Factors that Affect Thyroid Hormone Replacement Adherence in Patients with Differentiated Thyroid Carcinoma in South Africa

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THE FACTORS THAT AFFECT THYROID HORMONE REPLACEMENT ADHERENCE IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA IN SOUTH AFRICA



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Degree: Master of Medicine (Nuclear Medicine)

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment of the requirements for the degree of Master of Medicine

Johannesburg, 2024

DECLARATION

I, Peggy Serote, declare that this Research Report is my own work. It is being submitted for the Degree of Master of Medicine (Nuclear Medicine) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



15th July 2024 at WITS, Parktown, Johannesburg, South Africa.

DEDICATION

I would like to thank all the people who are dear and matter the most in my life, especially Mongane Wally Serote. Your support and encouragement have been invaluable to me, and I truly appreciate everything you have done, and I couldn't have done it without you. To my sons, may you be inspired by mummy to achieve your greatest dreams. Once again, thank you for your kindness and generosity!

ABSTRACT

Background: Thyroid cancer has become the most common endocrine malignancy, accounting for 1-2% of all malignant tumors worldwide. Most thyroid cancers have an excellent prognosis with 20-year survival rates of more than 95%, however, recurrence and persistent rates are high. Poor adherence to the thyroid replacement hormone jeopardizes any effort to obtain positive outcomes in thyroid cancer patients.

Aim: This study aimed to explore and evaluate the most common factors contributing to non-adherence in patients with DTC at CMJAH.

Methods: Data from participants with histologically proven DTC, they were patients with previous thyroidectomy with or without lymph node dissection who received therapeutic doses of radioactive iodine. The study was conducted between 01 August and 31 December 2022 at the Department of Nuclear Medicine at the CMJAH. Proportions and percentages were used to summarize categorical variables. Differences were analyzed using the chi-squared test or Fisher's exact test where appropriate. Continuous variables with a normal distribution were reported using the mean and standard deviation; variables with a skewed distribution were reported using the median with interquartile ranges (IQR). P-values less than 0.05 were considered statistically significant. Stata version 17 (StataCorp) 2021, College Station, TX: StataCorp LLC was used to analyze the de-identified data.

Results: Only twenty-one percent of participants were classified as non-adherent to THR, while 79% of the participants were adherent. The majority of the participants, about 89% were female. The most adherent participants were between the ages of 40-59 and were married. Awareness of long-term use of THR as well as self-administration showed an increased adherence. Among the participants who had only one chronic illness, 37 out of 72 were found to be adherent. Long-term use of THR correlated to adherence in 31 participants. Most participants (101) and their families (107) were literate about THR, with 62 and 59 adhering to THR. The majority (120) were informed about THR by the doctors at the clinic.

Conclusion: Results were comparable to reported rates in studies conducted in some high-income countries, with the majority of the participants adherent. Self-sufficiency, health literacy, family support, and trusting relationships with health providers contribute the most.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS AND SYMBOLS

CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CT	Computed tomography
DTC	Differentiated thyroid carcinomas
HRQL	Health-related quality of life
IQR	Interquartile ranges
MMAS-8	Morisky Medication Adherence Scale
MRI	Magnetic resonance imaging
NCR	National Cancer Registry
QOL	Quality of life
REDCap	Research Electronic Data Capture
T4	Tetraiodothyronine
THR	Thyroid hormone replacement
TSH	Thyrotropin
T3	Triiodothyronine
WHO	World Health Organisation
WITS	University of the Witwatersrand

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CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Thyroid cancer is the most common endocrine malignancy worldwide, accounting for 1-2% of all malignant tumors (Chagi et al., 2019; Pellegriti et al., 2013). The cancer growth of cells starts in the thyroid, a part of the endocrine system which is located at the base of the neck. The thyroid produces hormones that regulate the metabolism, heart rate, blood pressure, body temperature, and weight (Shahid et al., 2023). Worldwide, an estimated 586,202 people were diagnosed with thyroid cancer in 2020 (Thyroid Cancer - Statistics, 2012). In the U.S., thyroid cancer is estimated to be the 13th most commonly diagnosed cancer (Siegel et al., 2022), accounting for nearly 44,000 new cancer diagnoses in 2022 (2.3% of the total), and the 6th most commonly diagnosed cancer among women (Avram et al., 2019). According to the South African National Cancer Registry, 728 patients were diagnosed with thyroid cancer in 2019, with 3 times more females (1.28%) than males (0.40%) (National Cancer Registry (NCR), 2019). Most thyroid cancers show a biologically indolent phenotype and have an excellent prognosis with 20-year survival rates of more than 95%, however, recurrence and persistent rates are high (Haugen et al., 2016).

1.2 Literature review

1.2.1 Pathophysiology

Thyroid cancer starts when cancer cells begin to grow out of control in the thyroid gland. There are two main types of cells in the thyroid gland: the follicular cells and the supporting cells (also called the *C cells*) located within the thyroid parenchyma (Cote et al., 2015). The follicular cells are the major cell type in the thyroid gland and they are derivates of the endoderm which secretes the thyroid hormone (Khan & Farhana, 2023). The circulating form of this hormone is thyroxine, which is tetraiodothyronine (T4) along with a small quantity of triiodothyronine (T3) (Khan & Farhana, 2023; Shahid et al., 2023). The follicular cells form the single layer of cuboidal epithelium that makes up the outer structure of the almost spherical thyroid follicle. Follicular cells absorb the amino acids and iodide from the blood circulation on the basolateral side,

synthesize thyroperoxidase and thyroglobulin from amino acids, and secrete these into the thyroid follicles together with iodide (Shahid et al., 2023). These cells take up iodinated thyroglobulin from the follicles by endocytosis, extract thyroid hormones using proteases, and subsequently release thyroid hormones into the blood (Shahid et al., 2023). The thyroid hormones are transported in every part of the body where they control metabolism and other bodily functions.

Papillary and follicular thyroid carcinoma, comprising more than 90% of all thyroid malignancies, arise from follicular epithelial thyroid cells involved in iodine metabolism (Haugen et al., 2016; Pstrąg et al., 2018). Cancers derived from papillary and follicular cells are generally differentiated thyroid carcinomas (DTC) and they are the most common types (Shah, 2015). These cancers are not usually aggressive, they are similar to normal thyroid tissue, however, they do become more aggressive variants through mutations (Shah, 2015). Thyroid malignancies have become more prevalent, especially among women (Pstrąg et al., 2018)

1.2.2 Symptoms and etiology

Most thyroid cancers don't cause any symptoms early in the disease. It is not clear why some cells become cancerous and aggressively infiltrate the thyroid because they resemble normal thyroid tissue when viewed in the laboratory. Nevertheless, as thyroid cancer grows, symptoms such as difficulty in swallowing or breathing or a lump that can be felt through the skin on the neck become noticeable. Some risk factors of DTC are iodine deficiency, exposure to radiation, gene mutations, an enlarged thyroid, family history, and obesity (Kruger et al., 2022; Reiners & Drozd, 2021).

1.2.3 Diagnosis and Treatment of DTC

DTC is diagnosed after intrathyroid nodules are discovered through neck physical examination, imaging such as neck ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) (Hoang et al., 2013). DTC usually presents as a thyroid nodule, the treatment is total thyroidectomy, with or without cervical lymph node dissection (Schmidbauer et al., 2017). Post-surgery, at some centers like ours, patients are referred to the nuclear medicine department for ablation of remnant thyroid tissue, adjuvant therapy, or treatment of known metastatic disease with radioactive iodine (Mizrachi & Shaha, 2017; Schmidbauer et al., 2017). This is followed

by the standard treatment consisting of lifelong supplementation with thyroid hormone replacement (THR) at a dose titrated to suppress thyrotropin (TSH) levels close to the detection level (Hannoush & Weiss, 2016). The prescribed THR restores the body's physiological need for thyroid hormone, rectifying post-surgical hypothyroidism and preventing tumor growth by negative feedback on pituitary TSH secretion (Hannoush & Weiss, 2016). DTC expresses the TSH receptor on the cell membrane and responds to TSH stimulation by increasing the expression of several thyroid-specific proteins (thyroglobulin, sodium-iodide symporter) (Hannoush & Weiss, 2016). The resultant effect is increasing tumor cell growth rates. Thyroid hormone replacement is a synthetic version of the secreted thyroid hormone that completely mimics all its physiologic effects (Gluvic et al., 2021). Levothyroxine is the commonly preferred and reliable prescribed THR (Eghtedari & Correa, 2023; Hannoush & Weiss, 2016). Administered orally, it dissolves in the stomach at low pH, and absorption from the gastrointestinal tract mainly occurs in the small intestine rather than the stomach (Hays, 1988, 1991). Food, supplements, and some drugs can decrease the possible 70 - 80% absorption of oral TSH, reducing bioavailability (Lipp, 2021).

Sadly, the suppressive doses of THR potentially have numerous side effects ranging from anxiety, insomnia, sweating, palpitations, and osteoporosis to more serious ones such as fractures, atrial fibrillation, and cerebrovascular accidents (Gluvic et al., 2021). Conversely, THR withdrawal with the resultant hypothyroidism has a negative impact on the patient's health-related quality of life (HRQL) (Bărbuş et al., 2017). It leads to fatigue, decreased appetite, constipation, impaired motor skills, and fluid retention. The World Health Organisation (WHO) defines adherence as the extent to which a person's behavior corresponds with agreed recommendations from a health care provider (De Geest & Sabaté, 2003). In high-income countries, such as the United States of America, up to 50% of patients with chronic diseases adhere to treatment recommendations (De Geest & Sabaté, 2003). Whereas, in medium- to low-income countries, when combined with substandard access to health care, lack of appropriate diagnosis, and limited access to medicines, poor adherence jeopardizes any effort to deal with chronic conditions (De Geest & Sabaté, 2003). Elevated TSH levels are associated with advanced tumor stage, adherence alleviates the adverse outcomes.The implication of low adherence translates into adverse outcomes, such

as increased morbidity, e.g. weight gain, lethargy, mood disorders, and mortality (Walsh et al., 2019a, 2019b).

Five interacting dimensions that affect medication adherence are mentioned, ranging from sociodemographic factors, including gender, age, marital and socioeconomic status, to cultural belief systems (Chaudri, 2004; De Geest & Sabaté, 2003). Patient psychosocial factors include low health literacy, self-efficacy, poor social support, and forgetfulness; condition-related factors, such as duration since starting treatment and comorbidities; treatment factors such as side effects and lastly health system/provider factors such as provider-patient communication (De Geest & Sabaté, 2003). The aim of oncology patient care is primarily cure and tumor control. However, increasingly, it is recognized that cancer management can significantly affect every aspect of the patient's quality of life (QOL) (Shrestha et al., 2019; Tan et al., 2007). The importance of adherence to interventions has a far superior impact on the overall patient's QOL than any improvement in specific medical treatments (De Geest & Sabaté, 2003). Consequential to a high survival rate and long-term follow-up, DTC needs special consideration regarding THR adherence, particularly in developing countries.

1.3 Aim

The aim of this study focused on adherence, as well as the factors affecting adherence in DTC patients treated with radioactive iodine post thyroidectomy at the Nuclear Medicine Clinical Department at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

1.4 Objective

To explore and evaluate the most common factors contributing to non-adherence in patients with DTC at CMJAH.

CHAPTER 2: METHODOLOGY

Ethics clearance for this observational study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (WITS), (Ethics No. M220386) **Appendix I**, to prospectively collect data from participants with histologically proven DTC. These were patients with previous thyroidectomy with or without lymph node dissection who received therapeutic doses of radioactive iodine. The study was conducted between 01 August and 31 December 2022 in the Department of Nuclear Medicine at the CMJAH, a quaternary-level state-owned facility. The CMJAH is in Johannesburg, healthcare services are free for unemployed patients and those on a social grant with some referral hospitals more than 100 km away.

2.1 Sample Size and Sampling Method

The study population included histologically diagnosed DTC patients who had previous thyroidectomy with or without lymph node dissection and had received therapeutic doses of radioactive iodine. A participant information sheet, **Appendix II**, detailing the research, was provided to the participants. The participants did not need to sign any consent forms as they completed the questionnaire/forms themselves, which implies consent. Study data were collected and managed using Research Electronic Data Capture (REDCap) hosted at the Faculty of Health Sciences, WITS. The participants were selected from the patients who are routinely followed up weekly at the thyroid cancer clinic in the Department of Nuclear Medicine at CMJAH within five years (2014 - 2022).

Data was collected using a well-designed, self-reported questionnaire, **Appendix III**. Demographic data, including age, gender, education, relationship, employment, and social grant status, distance traveled to the hospital, and the associated cost constituted the initial section of the questionnaire. The second section included questions about self-sufficiency, social support, health education, comorbidities, polypharmacy, and provider relations.

There is no gold standard tool for evaluating adherence (Morisky et al., 2008). Therefore, the questionnaire was adapted from the Morisky Medication Adherence Scale (MMAS-8) and modified to suit the study. The modification was based on the

type of treatment prescribed. The quality of the MMAS-8 in assessing adherence in hypertensive patients has been validated in the USA (Morisky et al., 2008). The tool uses a series of short behavioral questions geared in such a way as to avoid the 'yes-saying' bias commonly seen with chronic care patients (Morisky et al., 2008). Adherence to medication in our study referred to participants taking THR as prescribed. According to the manufacturer's recommendations, THR should ideally be taken orally 30 minutes to 1 hour before eating breakfast and at the same time, with water. Self-reporting was chosen due to its simplicity, inexpensive, convenience, and high specificity for non-adherence. The limitations of self-adherence are social desirability and reporting biases with modest sensitivity for non-adherence (Tedla & Bautista, 2017).

2.2 Inclusion criteria

Patients who are 18 years or older who had been prescribed THR for more than six months were eligible for inclusion in the study.

2.3 Exclusion criteria

Patients younger than 18 years old, newly diagnosed patients, and individuals who declined to participate were excluded from the study.

2.4 Data analysis

Proportions and percentages were used to summarise categorical variables. Differences were analyzed using the chi-squared test or Fisher's exact test where appropriate. Continuous variables with a normal were reported using the mean and standard deviation; variables with a skewed distribution were reported using the median with interquartile ranges (IQR). P-values less than 0.05 were considered statistically significant. Stata version 17 (StataCorp) 2021, College Station, TX: StataCorp LLC was used to analyze the de-identified data. The scores for adherence were calculated from seven key questions**,** with 0 as non adherence and 1 as adherence. The median was determined from these scores. Anything from the median and above was considered good adherence, and anything below was considered non-adherent.

CHAPTER 3: RESULTS

The average patient population seen in the Nuclear Medicine Clinical Department at the CMJAH clinic over six months is 150. One hundred and twenty-three participants were recruited, representing 82% of the eligible patient population seen at the clinic in six months. Sixty six (54%) participants were found to adhere to THR, while the non-adherent participants were 57 (46%). No statistical significance was found between the demographics and the comparison for adherence for our study population. Most participants, n = 64 were between 40 and 59 years old and had the highest frequency of adherence, with a mean age of 49.7 years (SD 14.3), **Table 1**.

Table 1. Demographic profile and comparison of adherence

Variable	Total	Non-adherent	Adherent	p-value
Total number of participants		57 (46%)	66 (54%)	
Mean Age	49.7 (14.3)	51.5 (13.9)	48.1 (14.6)	0.1943
Age category				0.520
<30	12 (10%)	3 (5%)	9 (14%)	
30-39	16 (13%)	8 (14%)	8 (12%)	
40-49	32 (26%)	13 (23%)	19 (29%)	
50-59	32 (26%)	18 (32%)	14 (21%)	
60-69	20 (16%)	9 (16%)	11 (17%)	
>70	11 (9%)	6 (10%)	5 (7%)	
Gender				0.781
Female	109 (89%)	51 (89%)	58 (88%)	
Male	14 (11%)	6 (11%)	8 (12%)	
Marital status				0.071
Divorced	10 (8%)	7 (12%)	3 (5%)	
Married	43 (35%)	13 (23%)	30 (45%)	
Partner	9 (7%)	5 (9%)	4 (6%)	
Single	48 (39%)	24 (42%)	24 (36%)	
Widowed	13 (11%)	8 (14%)	5 (8%)	
Education				0.062
Graduate	15 (12%)	3 (5%)	12 (18%)	
Did not attend school	2 (2%)	1 (2%)	1 (2%)	
Postgraduate	2 (2%)	2 (3%)	0	
Primary	21 (17%)	10 (18%)	11 (17%)	
Secondary with grade 12	42 (34%)	17 (30%)	25 (38%)	
Secondary without grade 12	41 (33%)	24 (42%)	17 (25%)	
Employment				0.871
Currently employed	51 (41%)	25 (44%)	26 (39%)	
Employed previously	39 (32%)	17 (30%)	22 (33%)	
Never been employed	33 (27%)	18 (26%)	18 (28%)	
Social grant				0.333
No	81 (66%)	35 (61%)	46 (70%)	
Yes	42 (34%)	22 (39%)	20 (30%)	
Type of housing				0.165
Backroom	18 (15%)	10 (18%)	8 (12%)	
Flat/apartment	15 (12%)	6 (10%)	9 (14%)	

House **Shack**	74 (60%) 16 (13%)	30 (53%) 11 (19%)	44 (67%) 5 (7%)	
Distance to CMJAH **<5 km** **5-10 km** **11-20 km** **>20 km**	 6 (5%) 10 (8%) 30 (24%) 77 (63%)	 4 (7%) 7(12%) 13 (23%) 33 (58%)	 2 (3%) 3 (5%) 17 (26%) 44 (66%)	0.302
Cost of transport **<R50** **R50-R99** **+R100**	 19 (15%) 69 (56%) 35 (29%)	 9 (16%) 29 (51)% 19 (33%)	 10 (15%) 40 (61%) 16 (24%)	0.494

Females comprised 109 (89%) of the participants and the males were (14) 11%. About 58 (88%) of females were adherent, while 8 (57%) of males were found to be adherent. Forty-three participants were married, with 30 (45%) adhering to THR, compared to 24 of the 48 single participants. Eighty-three participants attended school with or without graduation from secondary school. Seventy-seven (63%) of the participants traveled more than 20 km to the hospital. Sixty-nine (56%) participants paid between R 50. 00 and R 99.00 to visit the hospital.

Table 2. Evaluation of adherence

	Variable	**Total**
1.	Do you sometimes forget to take THR Never/rarely Once in a while Sometimes Usually	 100 (81%) 12 (10%) 9 (7%) 2 (2%)
2.	Do you feel hassled about sticking to THR All the time Never/rarely Once in a while Sometimes	 3 (2%) 98 (80%) 6 (5%) 16 (13%)
3.	If you feel that THR is not working, do you stop All the time Never/rarely Once in a while Sometimes	 3 (2%) 116 (95%) 1 (1%) 3 (2%)
4.	Time for THR administration Evening Morning	 2 (2%) 121 (98%)
5.	Do you take THR with food? No Yes	 116 (94%) 7 (6%)
6.	Do you take THR with tea/coffee? No Yes	 106 (86%) 17 (14%)
7.	How long before eating/drinking <30 minutes 30-60minutes >60 minutes	 14 (11%) 56 (46%) 53 (43%)

Out of 77 (63%) participants who traveled more than 20 km, 44 were adherent, and out of six who traveled the least distance, only two were adherent. Forty out of 69 respondents were adherent and spent R 50-99 to visit the hospital. Thirty-five respondents spent more than R 100 to travel to the hospital, and only 16 were adherent. Evaluation of adherence, **Table 2 and Figure 1**, demonstrated that 100 (81%) rarely forgot to take THR, 80% felt pressured to persevere with THR, and 95% never considered stopping treatment. Most participants (98%) took the THR in the morning, 94% took it on an empty stomach, and 89% took it more than 30 minutes before eating food.

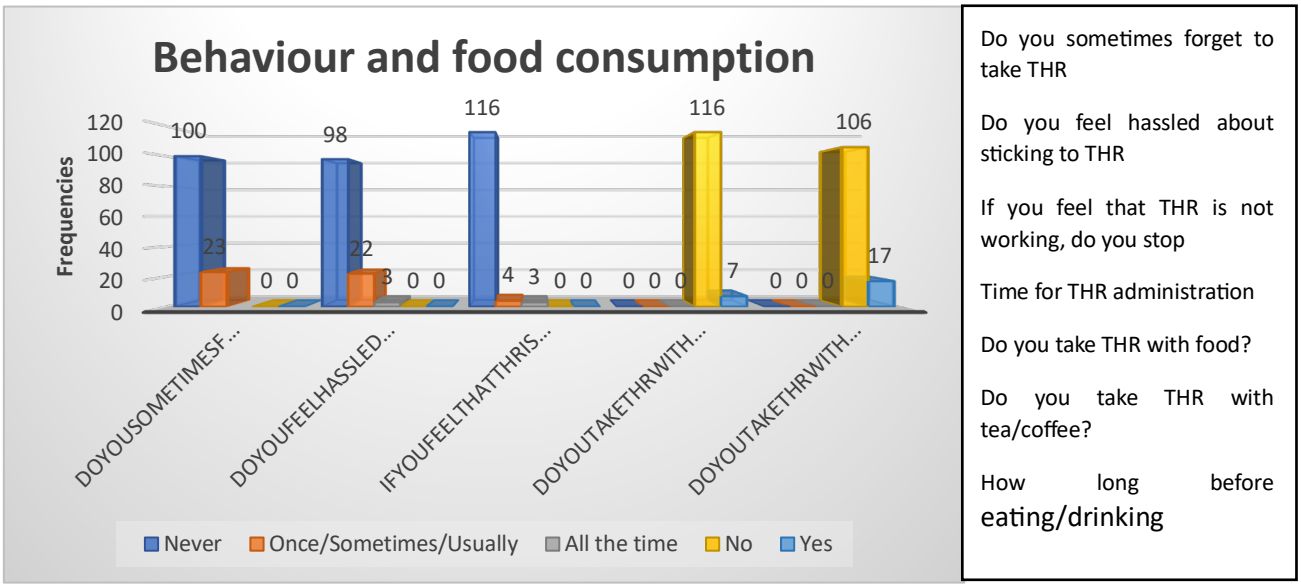


Figure 1. Behavior and food consumption of the participants

Those participants who took medication in the mornings were found to be 100% adherent compared to the participants who took medication in the evenings, **Figure 2**.

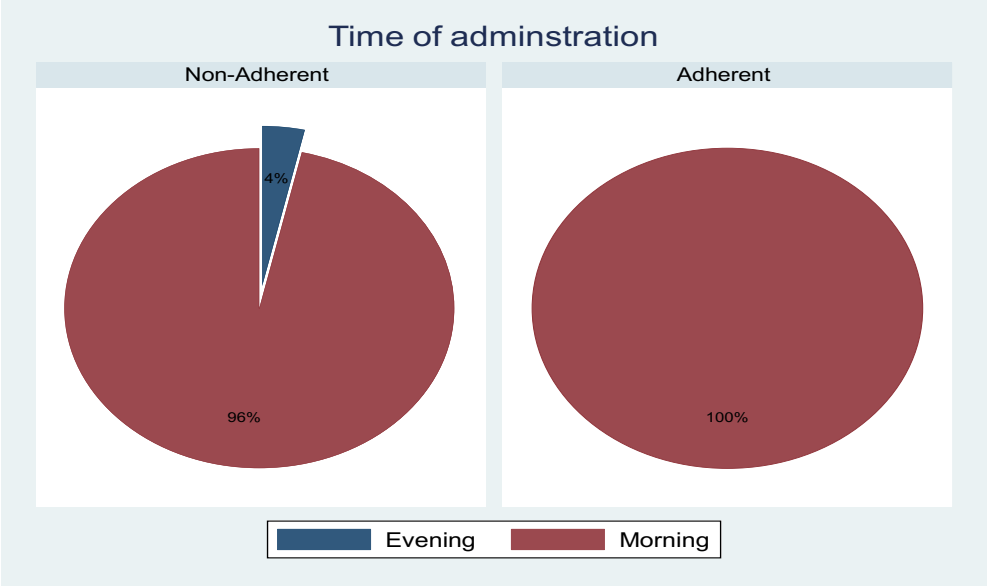


Figure 2. Time of medication administration

Eighty-six percent of participants did not take thyroid hormone replacement with tea or coffee (**Table 2**).**Table 3** lists the psychosocial factors associated with adherence and non-adherence. About three-quarters of the participants (91) were expected to be on THR for over five years, and 49 were adherent. One hundred and nine respondents self-administered their THR, and 62 were adherent. Of the 14 respondents who were assisted, only four were adherent. Of the 72 participants with one chronic illness, 37 were adherent. The six participants, with four to five conditions, were found to be non-adherent. Sixty-five participants took THR for over five years, and 31 were adherent. One hundred and eleven of the participants understood why they were taking THR, and 62 were adherent. One hundred seven participants had family members who understood why they were on THR, and 59 were adherent. An equal number of participants (2%) always experienced heart palpitations in both groups.

Table 3. Psychosocial factors

Variable	Total	Non-adherent	Adherent	p-value
Mode of THR administration				0.052
Assisted	14 (11%)	10 (18%)	4 (6%)	
Self	109 (89%)	47 (82%)	62 (94%)	
Number of daily medications				0.988
Five or more	9 (7%)	5 (9%)	4 (6%)	
Four	6 (5%)	3 (5%)	3 (5%)	
Three	7 (6%)	3 (5%)	4 (6%)	
Two	29 (24%)	13 (23%)	16 (24%)	
One	57 (46%)	27 (47%)	30 (45%)	
None	15 (12%)	6 (11%)	19 (14%)	
Number of chronic diseases				0.092

Five or more	3 (2%)	3 (5%)	0	
Four	3 (2%)	3 (5%)	0	
Three	5 (4%)	2 (4%)	3 (5%)	
Two	25 (21%)	8 (14%)	17 (25%)	
One	72 (59%)	35 (61%)	37 (56%)	
None	15 (12%)	6 (11%)	9 (14%)	
Duration of taking THR				0.490
<1	10 (8%)	3 (5%)	7 (11%)	
1-1.99 years	23 (19%)	9 (16%)	14 (21%)	
2-4	25 (20%)	11 (19%)	14 (21%)	
5+	65 (53%)	34 (60%)	31 (47%)	
Do you understand why you are taking THR				0.222
No	12 (10%)	8 (14%)	4 (6%)	
Yes	111 (90%)	49 (86%)	62 (94%)	
Family members understand why the participant is on THR				0.394
No	16 (13%)	9 (16%)	7 (11%)	
Yes	107 (87%)	48 (84%)	59 (89%)	
Palpitations				0.847
Always	4 (3%)	2 (3%)	2 (3%)	
Never	76 (62%)	33 (58%)	43 (65%)	
Rarely	12 (9%)	5 (9%)	7 (11%)	
Sometimes	26 (21%)	14 (25%)	12 (18%)	
Very often	5 (4%)	3 (5%)	2 (3%)	

While the adherence score was 7 for the majority, the rest of the participants scored 5 and 6, while the least number was 3 and 4. **Figure 3** there were insignificant differences between participants who were adherent and whose family members were understanding of them taking medication and those who were non-adherent and whose family members were not understanding. They were 89% and 80% respectively. **Table 4** lists the health system/provider factors and shows that the information about THR was found at the doctor or clinic, as reported by 120 participants, and sixty-three were adherent.

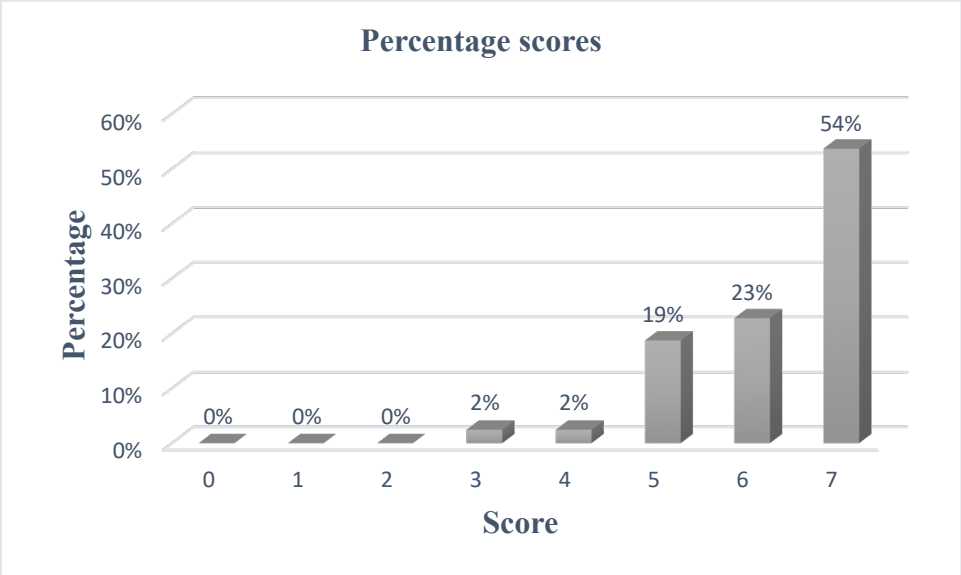


Figure 3. Percentage scores for adherence

The majority of the participants in both the adherent and non-adherent groups knew the reason for taking the medication.

Table 4. Health system/provider factors

Variable	Total	Non-adherent	Adherent	p-value
Where do you find information on THR **Doctor/Clinic** **Family/friend** **Internet**	 120 (98%) 1 (1%) 2 (1%)	 57 (100%) 0 0	 63 (95%) 1 (2%) 2 (3%)	0.499
Did the Doctors explain why you take THR **No** **Yes**	 6 (5%) 117 (95%)	 4 (7%) 53 (93%)	 2 (3%) 64 (97%)	0.414
Did Doctors give you time to ask why you take THR **No** **Yes**	 14 (11%) 109 (89%)	 9 (16%) 48 (84)%	 5 (8%) 61 (92%)	0.168

Participants who adhered to taking medication have an equal number of participants who took medication within 30 – 60 minutes before eating/drinking and those who took medication more than 60 minutes before having a meal/drinking, **Figure 4**. Whereas with non-adherent participants, only 40% took medication within 30 -60 minutes before eating, 35% took more than 60 minutes before eating/drinking, and 25% took less than 30 minutes before eating/drinking.

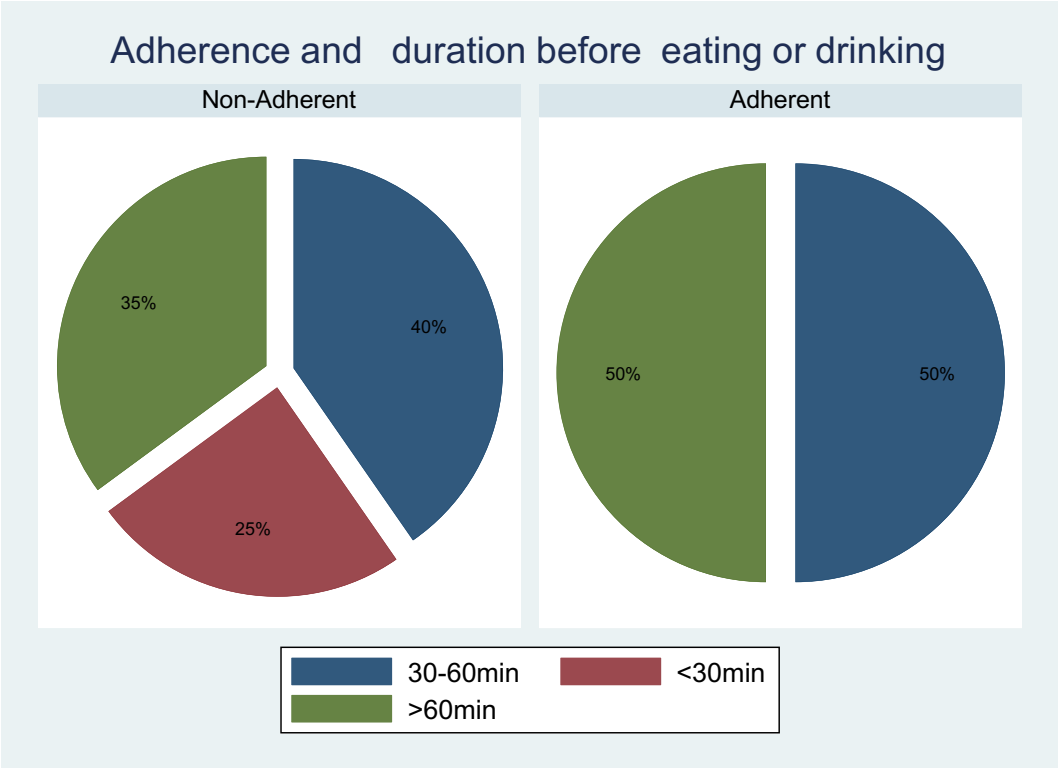


Figure 4. Adherence and duration before eating or drinking

Fifteen percent of participants who had been on one chronic medication for 1 – 1.99 years as well as those who were on chronic medication for more than 5 years found it easier to adhere to cancer medication i.e. THR. While 25% of study participants who have been on one chronic medication for more than 5 years were not adherent to the cancer medication.

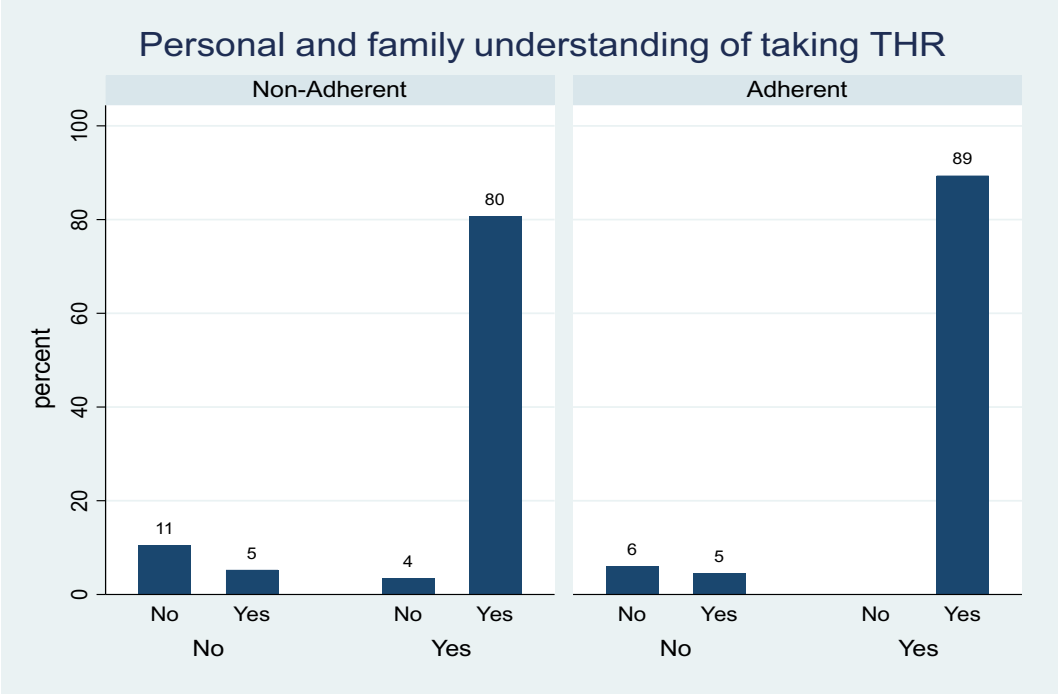


Figure 5. Personal and family understanding of taking THR

In both groups of participants; the adherent and non-adherent, individuals who adhered to taking THR had an understanding of taking THR as well as their family members, **Figure 5**. The younger age group was more likely to be adherent to the THR medication compared to the older participants as shown in the boxplot in **Figure 6**, the age difference between the 2 groups was not statistical significant.



Figure 6. Age and adherence

CHAPTER 4: DISCUSSION

Treatment adherence is of importance in thyroid cancer and requires ongoing care and management which is largely influenced by the socioeconomic status of the patients. This study has demonstrated satisfactory long-term adherence to THR with 54% adherence in our study population. However there was no statistical significance found when analysing the demographic profile of the participants in relation to their adherence to medication. Adherence was mostly apparent in the middle-aged group as well as those individuals who were married. These findings suggest that gender may influence the medication adherence process. Notably, the ratio of women to men in our study was 8:1 this observation may be due to women's health-seeking behavior (Asch et al., 2006; Vaidya et al., 2012), furthermore, thyroid cancer affects more women than men (Rahbari et al., 2010). A study examining gender differences for thyroid preparations found that females showed greater use of THR, consistent with a higher prevalence of thyroid disease in females compared to males (Orlando et al., 2020). These results were comparable to findings in a 2002 study by Hassen and colleagues (Hassen et al., 2022). However, another study found significant disparities between women and men in medication usage, with women less likely to adhere to chronic medications and less likely to receive the medication treatment and monitoring recommended by clinical guidelines (Manteuffel et al., 2014). In a study by Manteuffel et al. (2014), women were prescribed more medication than men (Manteuffel et al., 2014). Other studies have also shown the significant impact the socio-psychological support that marital status provides influences the cancer treatment and survival (Ai et al., 2021; Aizer et al., 2013). The social support associated with a relationship such as marriage may influence medication adherence, as described in the 2015 study by Martos-Méndez (Martos-Méndez, 2015). This may indicate the importance of documenting a patient's relationship status to identify those at high risk of poorer outcomes due to non-adherence to TRH. Medication-related financial burdens and the cost of medicines have been listed as significant barriers to adherence to medication by previous studies (De Geest & Sabaté, 2003; Dillon et al., 2018). In South Africa, difficulties traveling to the center were significant. Most participants traveled more than 20 km for treatment, and the cost factor was associated with the travel to the hospital. Traveling more than 20 km meant spending the whole day at the hospital. Nonetheless, this finding did not affect adherence. The cost of travel findings raises

awareness of the need to support community-level clinics and hospitals in playing a role in the management of these patients. We found that 89% of the participants self-administered their THR, fulfilling their medical recommendations regarding medication. In our study, 90% of the participants were literate regarding THR, compared to 87.2% in Italy, a high-income country (Cappelli et al., 2018). Social support has a decisive influence on medication adherence(Gast & Mathes, 2019). We found that 87% of the participants had social support, with their family members knowledgeable about their treatment. The younger participants had a higher prevalence of medication adherence than the older group. Similar findings were observed in a study by Semrad et al younger patients with DTC in California are more likely to be female and with papillary histology (Semrad et al., 2015).

Multiple diseases, the complexity of polypharmacy, and detailed dosing schedules (THR taken 30-60 minutes before meals) can impact adherence negatively over a long time. Our findings contradicted a prior study on adherence to adjuvant hormone therapy among women with breast cancer who used one or more medications before hormone therapy (Neugut et al., 2016). Seventy-four percent of participants with an expectation of long-life THR use were adherent, likely due to the time spent in the treatment program. Forty-seven percent of participants with long-term use of THR, beyond five years, were adherent. Our finding may have been related to the time or duration for the participants to eventually gather information about their treatment from forming successful doctor-patient relationships. This point was noted in the study done in rural-urban China by *Xu* et al.(Xu et al., 2021).

Highlighting the importance of education on individual adherence to THR becomes more relevant. Regarding health literacy, we found that almost all (98%) of our participants found out about THR at our center. There was less use of alternative information sources such as the Internet, contrary to a 2016 study in Italy that found nearly 60% of the respondents used the Internet for information (Lombardo & Cosentino, 2016). The study participants who had education were likely to adhere to medication compared to individuals who did not complete secondary education. The role of education in promoting change in behavior as the lack of knowledge hinders effective treatment. Study participants who understood the disease course and why they had to take THR adhered to treatment, a finding supported by previous

observations in a South African study (Chauke et al., 2022). Some participants reported gaps in knowledge due to a lack of health provider-patient interaction time. This is an opportunity missed in transmitting and coaching by medical providers. This result was also reflected by Xu and colleagues (2021)(Xu et al., 2021). Experience with the provider and a trusting relationship was crucial to medication adherence.

Self-reporting rather than objective adherence measures was a limitation. The biological markers were not recorded in this study because the participants had only missed treatment for two weeks or less. For the biological markers to be detectable, they must have missed their treatment for at least a month. Future studies looking at adherence can take this further by assessing biological markers and pharmacy records and comparing the different levels of adherence. Another limitation was that we didn't elicit the contribution of African traditional medicine use to adherence, considering the study location. African traditional medicine use is prevalent, persistent, and will keep growing (Xaba et al., 2022).

CHAPTER 5: CONCLUSIONS

Adherence is essential for preventing adverse outcomes and achieving therapeutic targets in chronic diseases. The financial status of patients and limited access to healthcare facilities affect adherence. Self-sufficiency, health literacy, family support, and a trusting relationship with health providers contributed to high adherence rates to THR comparable to high-income countries. An essential and ongoing priority is improving patient education during follow-up care and building better experiences and trusting relationships with patients. Opportunities for policy reforms and involvement in community-level clinics and hospitals were highlighted.

5.1 Limitations

Self-reporting rather than objective adherence measures was a limitation. The biological markers were not recorded in this study because the participants had only missed treatment for two weeks or less. Another limitation was that we didn't elicit the contribution of African traditional medicine use to adherence, considering the study location. African traditional medicine use is prevalent, persistent, and will keep growing (Xaba et al., 2022). Lastly, the study was performed in Gauteng, a metropolis, and the surrounding areas, so it might only represent a small percentage of the South African population.

5.2 Recommendations

Future studies looking at adherence can take this further by assessing biological markers and pharmacy records and comparing the different levels of adherence. Collaborations with other tertiary institutions as well as research institutes to do a bigger study to reach the whole South African population. Training provided to clinical staff on how to provide culturally sensitive care to their patients.

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APPENDIX I: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr P Serote

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220386

NAME: (Principal Investigator)	Dr P Serote
DEPARTMENT:	School of Clinical Medicine Department of Radiation Sciences Division of Nuclear Medicine Medical School University
PROJECT TITLE:	*The factors that affect thyroid hormone replacement adherence in patients with differentiated thyroid carcinoma in South Africa*
DATE CONSIDERED:	2022/03/25
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor MDT Vangu; Drs S Dhoodhat and D Mpanya
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/08/01

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **March** and therefore reports and re-certification will be due in the month of **March** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

APPENDIX II: STUDY INFORMATION SHEET

Study title: The factors affecting thyroid hormone replacement adherence in patients with differentiated thyroid carcinoma in a South African population.

Good day,

I am Dr Peggy Serote and I work in the Department of Nuclear medicine.

I would like to invite you to take part in this research to help us understand some of the factors that affect thyroid hormone replacement adherence in patients with your condition (differentiated thyroid carcinoma). I am hoping you can help us learn more about why some patients take (adhere to) their medication in the right way and at the right time, whilst others do not. By sharing your views and experiences with us, we will gain more understanding, and this might assist in providing some important answers about treatment adherence.
If you agree to participate, I will ask you to sign a form called a consent form. This will show that you are comfortable with what has been explained and that you are happy to participate.

You will be asked to complete a paper-based questionnaire, which will take about 15 - 20 minutes to complete. This will take place privately to ensure confidentiality.
The types of questions that you will be asked are will be basic ones about age; education; employment etc. Others will be about the medication as this can influence our study.
This is not part of routine care.
Participating in the research is not anticipated to cause any disadvantage or discomfort.

There is no direct benefit to you. The longer-term objective is the possibility of better treatment for subsequent patients.

Participation is voluntary. Refusal to participate will involve no penalty or loss of benefits to which the Participant is otherwise entitled. Participant may discontinue participation at any time without penalty, or loss of benefits to which the Participant is otherwise entitled. There is no requirement to provide a reason for withdrawing and any data collected will in default be destroyed, unless the Participant specifically consents to its retention.

There will be no cost to you by participating in this research.
The research is completely confidential and anonymous. The concerned form will be locked away and will only be accessible by the researchers.

Contact details of researchers:
Prof MDTH Vangu
Department of Nuclear Medicine, Charlotte Maxeke Johannesburg Academic Hospital & University of the Witwatersrand, Johannesburg, South Africa.
Tel: +27 (0)11 488 3500, email: mboyo-di-tamba.vangu@wits.ac.za

Dr. P Serote, Department of Nuclear Medicine, Charlotte Maxeke Johannesburg Academic Hospital & University of the Witwatersrand, Johannesburg, South Africa.
Tel: +27 (0)11 488 3560, email: pserote@gmail.com

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.
If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet

APPENDIX III: MORISKY MEDICATION ADHERENCE SCALE (MMAS-8)

Participant number:

1. **Age:**

2. **Gender:**

   Male ☐ Female ☐

3. **Relationship status:**

   Single ☐ Married ☐ Partner ☐ Divorced/separated ☐ Widowed ☐

4. **Level of education:**

   Never ☐ Primary ☐ Secondary without matric ☐ Secondary with matric ☐

   Graduate ☐ Post-graduate ☐

5. **Employment:**

   Currently employed ☐ Never been employed ☐

6. **Social grant:**

   Yes ☐ No ☐

7. **Type of housing:**

   House ☐ Flat/apartment ☐ Backroom ☐ Shack ☐

8. **Distance to Charlotte Maxeke Johannesburg Academic Hospital:**

   Less than five kilometres (km) ☐ 5-10km ☐ 10-20km ☐ more than 20 km ☐

9. **Cost of transport:**

   Less than R50 ☐ More than R50 but less than R100 ☐ More than R100 ☐

10. **Mode of administration of thyroid hormone replacement (THR):**

    Self-administration ☐ Assisted by a family member or domestic helper ☐

11. **Number of daily medications (are you taking other medicines other than THR):**

    One ☐ Two ☐ Three ☐ Four ☐ Five or more ☐

12. **Number of other chronic diseases: (non-communicable - diabetes, hypertension, cardiovascular or communicable – HIV, TB)**

    One ☐ Two ☐ Three ☐ Four ☐ Five or more ☐

13. **Duration of taking THR:**

    Less than 1 year ☐ More than 1 but less than 2 years ☐

    More than 2 but less than 5 years ☐ More than 5 years ☐

14. **Do you understand why you are taking THR:**

    Yes ☐ No ☐

15. **Does your family members understand why you are taking THR:**

    Yes ☐ No ☐

16. **How you sometimes forget to take THR for more than 2 weeks?**

    Never/rarely ☐ Once in a while ☐ Sometimes ☐ Usually ☐ All the time ☐

17. **Taking THR exactly as prescribed is a real inconvenience for some people. Do feel hassled about sticking to THR?**

    Never/rarely ☐ Once in a while ☐ Sometimes ☐ Usually ☐ All the time ☐

18. **If you feel that THR is not working, do you sometimes stop taking it?**

    Never/rarely ☐ Once in a while ☐ Sometimes ☐ Usually ☐ All the time ☐

19. **When do you take your THR?**

    Morning ☐ Noon ☐ Evening ☐

20. **Do you take THR with food?**

    Yes ☐ No ☐

21. **Do you take THR with coffee or tea?**

Yes ☐ No ☐

22. **How long do you wait before eating or drinking coffee after taking THR?**

Less than 30 minutes ☐ 30-60 minutes ☐ More than 1 hour ☐

23. **Do you have symptoms, like palpitations, when taking THR?**

Very often ☐ Always ☐ Sometimes ☐ Rarely ☐ Never ☐

24. **How long will you be taking THR?**

Less than 6 months ☐ More than 6 months but less than a year ☐ More than a year but less than 5 years ☐ More than 5 years ☐

25. **Where did you find the information on THR?**

Doctor/clinic ☐ Internet ☐ From reading magazines ☐ TV ☐

Family/Friends ☐ Support group/NGO ☐

26. **Did the doctors at the thyroid cancer clinic explain why you should take THR?**

Yes ☐ No ☐

27. **Do you think the doctors gave you time to ask why you should take THR?**

Yes ☐ No ☐

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ORIGINALITY REPORT

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