A descriptive analysis of children and adolescents with Graves disease attending the paediatric endocrinology services of the Red Cross War Memorial Children's Hospital and Groote Schuur Hospital over 20 years.

Degree:

Master of Philosophy in the Sub-specialty of Paediatric Endocrinology (minor dissertation)

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DECLARATION

I, Jacqueline Faria Mendes, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ACKNOWLEDGEMENTS

I would like to take this opportunity to thank my supervisor Dr Michelle Carrihill for her assistance in the development of this study and her invaluable guidance throughout the process.

I would like to thank Mrs Miriam Petersen and Ms Felicia Nojekwa. Honestly, this study would not have been possible without your tenacity and persistence in tracing and tracking down patient records. Nothing was ever too difficult for you.

My sincerest gratitude to Dr Wisdom Baseru for his careful consideration of the statistical analyses.

DEDICATION

Professor Lungile Pepeta

16 July 1974 - 07 August 2020

"If I have seen further it is by standing on the shoulders of giants."

Isaac Newton

ABSTRACT

Background

Hyperthyroidism occurs in about 1 per 5000 children and adolescents. Graves disease (GD) is the most common cause of hyperthyroidism in children and adolescents. The treatments that are currently available for children with GD include Carbimazole (CMZ), radioactive iodine (RAI) therapy and surgery. The paucity of GD data in children from the sub-Saharan African region, challenge the physician in identifying the best suited diagnostic and treatment strategies for the patient population in their setting.

Objective

The aim was to describe the population group attending the Paediatric and Adolescent Endocrinology Services (PAES) at Red Cross War Memorial Children's Hospital (RCCH) and Groote Schuur Hospital (GSH) in Cape Town, Western Cape. This study hoped to contribute information to the body of evidence concerning GD in the paediatric population of South Africa.

Methods

This was a retrospective folder review of all children and adolescents diagnosed with GD, attending the PAES in the previous two decades. Their demographic profile, clinical and laboratory findings and the treatment modalities utilised were described. All patients diagnosed with GD between the ages of 1 and 20 years old were included. Data were described as proportions and percentages. The measures of central tendency were described by median, and inter-quartile range (IQR).

Results

Thirty-one patients were included in the study. Twenty-six patients were female. The median age at presentation was 10.1 years (IQR: 8.9; 11.7). All patients were initially treated medically with Carbimazole (CMZ). Two patients experienced mild adverse reactions attributed to CMZ. Twelve (39%) patients went into remission after a single course of CMZ, after a median of 16.3 months (IQR: 8.6; 35.1). At the study's conclusion, nine (29%) patients were in remission, nine (29%) remained on CMZ therapy, ten (32%) underwent RAI and three (10%) relapsed before GD remission was achieved. One-quarter of the patients (n=8) were known with Down syndrome (DS). These patients presented at a significantly younger age than those without DS.

Conclusion

The children and adolescents diagnosed with GD managed in the PAES were similar in sex distribution, slightly younger in age and tolerated CMZ better than reported in literature. This study demonstrated the importance of considering prolonging CMZ therapy in patients not yet in remission and as a viable retreatment option in patients that relapse.

ABBREVIATIONS

Anti-Tg	Antithyroglobulin antibodies
ATD	Antithyroid drug
Anti-TPO	Antithyroid peroxidase antibodies
BB	Beta blockade
BMI	Body mass index
BR	Block and replace
CMZ	Carbimazole
DRC	Departmental research committee
DS	Down syndrome
fT3	Free triiodothyronine
fT4	Free thyroxine
GD	Graves disease
GSH	Groote Schuur Hospital
HPT	Hypertension
IQR	Interquartile range
mmHg	Millimetres of Mercury
RCCH	Red Cross War Memorial Children's Hospital
MCC	Medicine control council
MMI	Methimazole
RAI	Radioactive iodine
PAES	Paediatric and Adolescent Endocrine Services
PTU	Propylthiouracil
SAHPRA	South African Health Products Regulatory Authority
T1DM	Type 1 diabetes mellitus
TF	Thyroid function
TFT	Thyroid function test
TG	Thyroglobulin
TPO	Thyroid peroxidase
TRAbs	Thyrotropin receptor antibodies
TS	Thyroid scintigraphy
TSH	Thyroid Stimulating Hormone
TSHR	Thyrotropin Receptor
US	Ultrasound

PUBLICATION FORMAT

CHAPTER 1: INTRODUCTION

1.1 Context

This chapter initially explored the rationale for this study and explored the medical literature that pertained to the research question. The chapter concluded with clarification of the methodology and the ethical considerations.

1.1.1 Rationale for the study

The Paediatric and Adolescent Endocrine Services (PAES) has managed children and adolescents at Red Cross War Memorial Children's Hospital (RCCH) and Groote Schuur Hospital (GSH) for more than two decades. The PAES physicians had begun to raise questions about the characteristics and the clinical outcomes of the patients with Graves disease (GD). International guidelines and consensus statements contribute evidence to PAES management. This recent description of the population and patient outcomes informed the service about previous and current practices and possible future treatment strategies.

1.1.2. Background

Epidemiology

Hyperthyroidism occurs in about 1 per 5000 children and adolescents.[1] GD is the most common cause for thyrotoxicosis in children and adolescents. The incidence of GD in children is currently estimated to be increasing worldwide, also reported in a South African GD study conducted in adults.[2, 3] Majority of the incidence data arise from international studies. In Denmark the incidence rates range from 0.79 per 100,000 person-years.[4, 5] Léger reported incidence rates of 0.1per 100,000 person-years in young children and 3 per 100,000 person-

years in adolescents in other Northern European countries.[6] In Hong Kong, a rate of up to 6.5 per 100,000 person-years has been stated.[7] Data from France reported incidence of GD to be 4.8 per 100,000 in those younger than 15 years.[2] Adult data from South Africa described an average annual incidence for females as 8,75 per 100,000 and for males 0,70 per 100,000.[3]A female predominance is well described in literature.[5-7]

The incidence rate of GD increases with age, approximately 80 percent of paediatric cases occur after 11 years of age. Hence, it is seen more often in adolescence. Two sub-Saharan studies investigating hyperthyroidism in children were identified in the literature. One study from Senegal reported that the average age for presentation was younger than 10.9 years.[8]The other, a Malian based study, reported an average age of 12.5 (SD ± 3.34-year).[9] Prepubertal children may have more severe disease, evidenced by longer duration of medical therapy, and lower rates of remission compared to their post pubertal counterparts.[10] It was important to consider whether prepubertal children were more common in other African settings. GD is a polygenic disease where multiple factors (genetic, immunologic, and environmental factors) may interact with one another to cause disease and influence its severity. The data describing GD in children and adolescents from sub-Saharan Africa are potentially limited to two studies. Therefore, the epidemiological data that are available will often refer to adult patients with thyroid disease.[11]

Autoimmunity & comorbidities

Autoimmune thyroid disease occurs when autoantibodies are directed against various proteins in thyroid tissue such as thyroglobulin, thyroid peroxidase, and the sodium-iodide cotransporter.[12] However in GD, the vast majority of patients produce thyroid stimulating hormone receptor antibodies (TRAbs).[2] Stozek et al demonstrated that 88.7% of patients with GD were positive for TRAbs.[13] The incidence of GD is known to be higher in children with other autoimmune diseases like coeliac disease and type 1 diabetes (T1DM), and those children at risk for autoimmune diseases, for example Turner, Di George and Down syndromes.[14] A

study conducted among patients with T1DM in Durban found a high prevalence of coexistent autoimmune thyroid disease and the prevalence of GD was 1.5%.[15]

1.1.3. Diagnosis & workup

Clinical findings

Children with GD may present with non-specific symptoms often delaying the diagnosis.[2] These may be behavioural changes like schooling problems, irritability, emotional lability, nervousness and insomnia. Care givers and patients may complain of physical ailments that include weight loss despite an increased appetite, tremors, palpitations and chest pain.[2] Health care providers may identify tachycardia, hypertension, and an acceleration in the linear growth, with or without a concurrent advancement in bone age.[16] A diffuse symmetrical goitre may also be evident.[2] The increase in blood flow through the gland may result in a palpable thrill or an audible bruit.[17] Children present with milder thyroid eye disease than adults, eye lid retraction, proptosis soft tissue involvement and true exophthalmos is rare.[18, 19] Extra-thyroidal manifestations like thyroid dermopathy, pretibial myxoedema, and acropachy are rare in children.[17, 20]

Laboratory findings

The laboratory findings in patients with GD demonstrate serum thyroid stimulating hormone (TSH) concentrations below the normal range with an elevated serum free thyroxine (fT4) and free triiodothyronine (fT3) concentrations above the normal reference range. However, in triiodothyronine (T3) toxicosis an elevated fT3 concentration occurs with a normal fT4 concentration.[21] Serum TRAb titres are almost always elevated and higher titre levels have been shown to be associated with increasing disease severity and risk of relapse. At diagnosis TRAbs have been found to be markedly higher in younger patients compared to older patients.[22] Patients with GD may also have antibodies against thyroglobulin (TG) and thyroid peroxidase (TPO) which can assist to confirm autoimmune thyroid disease.[22] Similarly,

Hashitoxicosis can mirror GD in clinical presentation and positive serum antibodies to TG and TPO, but the great majority are negative for TRAbs.[23, 24]

Thyroid imaging

The types of thyroid imaging modalities available for GD diagnosis include ultrasound (US) and thyroid scintigraphy (TS). Ultrasound has replaced radioisotope imaging methods for the diagnosis of GD.[2] The gland may be found to be diffusely, often homogeneous enlarged. The echogenicity may be normal, or hypoechogenic. Diffuse parenchymal hypervascularity is often visible.[17]

Thyroid scintigraphy is a useful modality in assessing the various subtypes of thyrotoxicosis. TS is performed using either Technetium-99m (^{99m}Tc) or, less frequently, radioiodine-123 (^{123}I). The findings usually include diffuse, increased, hypervascularity, and homogenous uptake of ^{123}I. [25] ^{123}I has the advantage of a shorter half-life and no beta radiation, although it is of limited availability and expensive. However, ^{99m}Tc is widely available, more affordable and the scintigraphy can occur within a shorter time interval.[26]

Access to thyroid imaging in sub-Saharan Africa is variable. There are limited studies describing this, a Cameroonian study reported poor access to TS. The availability of US may be better although the quality of the US may vary with the experience of the ultrasonographer.[27-29] However, in the PAES, thyroid scintigraphy is still utilised as a diagnostic tool for imaging the thyroid in GD. Although, ultrasound scan has replaced this modality in well-resourced centres.[30]

1.1.4. Management

Treatments that are currently available for children with GD include antithyroid drugs (ATD), radioactive iodine (RAI) therapy and surgery.[10] Drug therapy is first line treatment for GD in children and duration is usually longer than in adults.[2].

Antithyroid drugs

The ATD most often used in children are Carbimazole (CMZ) and its metabolite Methimazole (MMI). They inhibit thyroid hormone synthesis by preventing the iodination of thyroglobulin tyrosine residues by thyroid peroxidase. Propylthiouracil (PTU) is contraindicated in children, and only used in patients that have had a toxic reaction to CMZ and only briefly while awaiting definitive treatment.[31] Minor adverse reactions (e.g. arthralgia, skin rashes, urticaria, and gastrointestinal problems) are reported in about 5%-25% of cases. These reactions tend to be mild and temporary.[2, 32] The severer adverse effects, include drug-induced hepatitis and agranulocytosis, which has a frequency of 0.2 - 0.5% for both drugs [17, 33] Contrary, Ohye *et al* reported higher overall incidence of complications associated with methimazole and propylthiouracil, 21.4% and 18.8% respectively. Though no complications were fatal. Most complications (91.6%) were reported within the first three months of ATD treatment. Despite the higher ATD adverse reactions, the authors concluded that prolonged ATD treatment was still a useful treatment option for children with GD.[32]

Radio-active Iodine (RAI)

In most centres RAI is used as second line treatment for children that relapse after an appropriate course of drug treatment, a lack of compliance on the part of the patient or the parents, or the patient experiences ATD toxicity.[2, 34] The duration of ATD therapy before definitive treatment is debatable.[34] It is known that children experience a higher relapse after 2 years of ATD, the risk of remission increases by 25% for every additional 2 years of treatment.[35]

A major complication of RAI is that most patients are rendered hypothyroid and require life-long treatment with L-Thyroxine. A review by Chao reported a cure rate after RAI of 49.8% (933/1,874), an incidence of hypothyroidism 37.83% (709/1,874), and a relapse of 1.55% (29/1,874).[36] RAI is contraindicated during pregnancy and breastfeeding, and should be avoided in very young children, because it may potentially increase the risk of cancers. Thyroid malignancy and hyperparathyroidism are also a concern, but recent studies have shown that the increase in cancer risk in adult patients is related to their hyperthyroidism and rather than the RAI.[17] RAI has shown to have no significant deleterious effects on fertility or the progeny of children and adolescents, who were treated with RAI.[37, 38]

A retrospective descriptive study conducted in Thailand, assessed the dangers of RAI in children and adolescents and found that RAI was effective and safe.[39] No thyroid cancer or leukaemia was detected after 36 years of follow-up in childhood.[37] Fewer than 10% of experienced mild tenderness over the thyroid. Although, 95.6% of the subjects ended up hypothyroid, 71.7% after the first course of RAI and 23.9% were after the second.[39]

A concern is the association of iodine-131 therapy and the development or progression of ophthalmopathy.[40] Contrary to adults, children rarely develop severe thyroid eye disease (TED). Proptosis is generally mild, nonprogressive, and TED is usually reversible. Safa et al, described that from 87 children treated with iodine-131 for GD, 90% had eye sign improvement, 7.5% remained the same, and 3% worsened after treatment.[41]

Surgery

Surgery is recommended in patients with especially large goiters (>80 g) and in very young children who do not respond to ATD or experience untoward consequences related to ATD.[42] Studies conducted in 2016 that reviewed RAI and thyroidectomies for the definitive treatment of GD in children, found that those who underwent surgery were more likely experience complications, such as post-thyroidectomy hypoparathyroidism. RAI was therefore

recommended by the authors as first line treatment (after ATD) for children and adolescents with GD.[43]

Remission and relapse

Approximately 30% of children on ATD for two years will go into remission, and by 4.5 years half of children on ATD will go into remission.[2, 44] No significant predictors of remission have been proven.[32] Higher serum TRAb titres has been thought to predict patient's response to ATD. Relapse is more likely in those with positive TRAbs at remission.[45]

1.1.5 Conclusion

An increase in the incidence of Graves disease has been noted over recent years.[6] The paucity of data from the sub-Saharan region challenges the physician in identifying the best suited treatment strategies for the patient population in their setting. The Paediatric and Adolescent Endocrine Services described the patients treated for GD and their response to therapies.

1.1.6. Methodological aspects

In the manuscript the methodology is expressed clearly. However, the researcher believed further clarity was required about the inclusion criteria. This was a retrospective patient folder review of all children and adolescents diagnosed with GD, attending the PAES at RCCH and GSH in Cape Town, Western Cape, South Africa.

Inclusion criteria

The diagnosis of GD was made when the serum fT4 and/or fT3 levels were above the reference range and the serum TSH below the reference range on the initial (PAES or diagnosing health care provider) thyroid function test plus, one of the following:

i. A positive TRAb titre done at diagnosis or within 12 months.
ii. Diagnostic thyroid scintigraphy demonstrating diffuse and increased uptake suggestive of GD.
iii. Thyroid eye disease as identified by the PAES physician or an ophthalmologist.
iv. Diagnosis made by the PAES attending physician based on clinical findings (goitre, thyroid eye disease, tremulousness, tachycardia, diaphoresis, emotional lability, proximal myopathy, pretibial myxoedema, acropachy).

The patients that were included in this study, were diagnosed with GD between the ages of 1 and 20 years old. Patients were considered if the GD was diagnosed after their first birthday and before their 20th birthday.[46] The neonatal and infant period was excluded to mitigate the inclusion of congenital thyroid disease. The World Health Organization definition of adolescence has been used to determine the upper age cut-off.[46]

Exclusion criteria

i. Patients that did not have adequate patient records (either in-patient or clinic folder).
ii. Patients that were referred into the PAES more than one year after their initial GD diagnosis.

Sample size

The researchers expected relatively small numbers, anecdotally PAES physicians anticipated one to two new cases of GD entered the service per year. These small numbers, it was expected, would be further compromised by missing and incomplete patient records.

Study period

The study extended over two decades. The patient was included if their first visit to the PAES fell between 01 January 1998 and 31 December 2018. The follow up period continued until the 31 December 2019.

Data Management

The principal researcher was solely responsible for data collection, capture and collation. The in-patient and clinic folders were used as the source of information. Incomplete records were included, and any missing data were noted in the analyses. When appropriate the nominal and numerical data were categorised and coded for analyses. A study tool was developed using Microsoft® Excel® version 2009.

Variables

The study variables investigated in this study were those set to answer the three objectives (Table 1):

i. Describe the patient population with Graves disease
ii. Describe the treatment modalities utilized
iii. Determine the numbers of remission and relapse

Table 1: List of variables by objective

Objective 1:	age, sex, BMI, comorbidities, TSH, fT4, fT3, antibody titres, pubertal status, goitre, thyroid eye disease, tremulousness, tachycardia, diaphoresis, emotional lability, proximal myopathy, pretibial myxoedema, acropachy radio-imaging findings
Objective 2:	treatment modalities, adverse reactions, CMZ doses, beta-blockade (BB)
Objective 3:	Duration of treatment, numbers of remissions, numbers of relapsed cases

Statistical Analyses

Stata release 13.0 (StataCorp LP) for Microsoft Windows, was the preferred software tool for analyses. The descriptive analyses reported proportions and percentages (Table 2). The central tendency and data dispersion were described in non-normally distributed data by the median and inter-quartile range (IQR).[47]

Table 2: Univariate analyses of data and relevant variables

Analyses	**Variable**	**Distribution**	**Description**	**Variables**
Univariate	categorical	-	percentages, proportions	sex, treatment modalities, comorbidities, pubertal staging, HR, tremor
	continuous	non-normal	median (IQR)	age, BMI, TSH, fT4, fT3, TRAbs, time intervals

In subgroup analyses Fisher's Exact test was used for categorical data whilst the Wilcoxon-Mann-Whitney test was used for continuous data in two independent groups (Table 3). A p-value of < 0.05 was considered statistically significant.

Table 3: Bivariate analyses of data and relevant variables

Analyses	Variable	Distribution	Statistical test	Variables
Bivariate	categorical	-	Fisher's Exact	sex, relapse, remission,
	continuous	non-normal	Mann-Whitney	TSH, fT4, fT3, TRAbs

The steps taken to fabricate the comprehensive patient list for possible inclusion is detailed in the manuscript in Chapter 2. The authors relied on the various sources to compile a complete list of all patients seen in the service over the past 20 years. Therefore, it was not possible to verify that all patients with GD who have attended PAES were included in the study. However, anecdotally investigators believed there were approximately one to two new GD cases entering the PAES each year, predicting a sample size between 20 to 40.

1.2 Ethical considerations

This study was a retrospective record review. There were no questionnaires, interventions or placebo administered in the study.

The ethical considerations in this study were predominantly related to patient privacy and anonymity. The patients' identifiable information (name, date of birth and folder number) and relevant study numbers were kept in a reference chart. The reference chart was securely kept in the possession of the principal investigator. The study numbers were then used in data collection, data capture and analyses.

The researchers ensured that appropriate approval was obtained from all relevant research review committees, clinical departments, and health facilities. Initially, the research protocol and study concept were approved by the Department of Paediatrics and Child Health, Departmental Research Committee (DRC) Office. The study then obtained ethics approval from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC) REF: 443/2019. The Research Review Committees from both RCCH and GSH gave the researchers permission to undertake the research in their relevant hospitals. The list of departments and units that gave approval included:

i. Nuclear medicine departments at RCCH and GSH
ii. Pharmaceutical departments at RCCH and GSH.
iii. Health information management units at RCCH and GSH
iv. Paediatric and adolescent endocrinology department at RCCH and GSH

1.3 Author guidelines of the South African Medical Journal

Journal: South African Medical Journal

Link: http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines

Impact Factor: 1.500 in 2018

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content' but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

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Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
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Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods,

results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
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- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.

- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
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References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

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CHAPTER 2: PUBLICATION-READY MANUSCRIPT

A descriptive analysis of children and adolescents with Graves' disease attending the paediatric endocrinology services of the Red Cross War Memorial Children's Hospital and Groote Schuur Hospital over 20 years.

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INTRODUCTION

Hyperthyroidism occurs in about 1 per 5000 children and adolescents.[1] GD is the most common cause for thyrotoxicosis in children and adolescents. The incidence of GD in children is currently estimated to be increasing worldwide, also reported in a South African GD study conducted in adults.[2, 3] Majority of the incidence data arise from international studies. In Denmark the incidence rates range from 0.79 per 100,000 person-years.[4, 5] Léger reported incidence rates of 0.1per 100,000 person-years in young children and 3 per 100,000 person-years in adolescents in other Northern European countries.[6] In Hong Kong, a rate of up to 6.5 per 100,000 person-years has been stated.[7] Data from France reported incidence of GD to be 4.8 per 100,000 in those younger than 15 years.[2] Adult data from South Africa described an average annual incidence for females as 8,75 per 100,000 and for males 0,70 per 100,000.[3]A female predominance is well described in literature.[5-7]

The incidence rate of GD increases with age, and approximately 80 percent of paediatric cases occur after 11 years of age.[48] The vast majority of patients with GD produce thyroid stimulating hormone receptor antibodies (TRAbs); these are specific for GD.[2] Stozek et al demonstrated that 88.7% of patients with GD were positive for TRAbs.[13] Children at risk of autoimmune diseases, for example those with Down syndrome (DS), Type 1 Diabetes (T1DM) and Coeliac disease etc, have a higher incidence of GD.[14] A South African study conducted in Type 1 Diabetics in Durban found a high prevalence of coexistent autoimmune thyroid disease, the prevalence of GD being 1.5%.[15] Children with GD may present with non-specific

symptoms often delaying the diagnosis.[2] The laboratory findings in patients with GD demonstrate a suppressed serum thyroid stimulating hormone (TSH) concentration (<0.3 mU/l) with elevated serum free thyroxine (fT4) and free triiodothyronine (fT3) levels.

Treatments that are currently available for children with GD include antithyroid drugs (ATD), radioactive iodine (RAI) therapy and surgery.[10] Drug therapy is first line treatment for GD in children and duration is usually longer than in adults.[2]. Occasionally a block and replace (BR) strategy is utilised in PAES setting. An antithyroid drug is given in conjunction with L-Thyroxine to alleviate symptoms while controlling GD. GD treatment policies can differ slightly within and between countries and is largely dependent on local practices and resources, patient age and preferences, disease severity and goitre size.[2] The ATD most often used in children are Carbimazole (CMZ) and its metabolite Methimazole (MMI). Ohye *et al* reported that the overall incidence of complications associated with methimazole was 21.4%. Adverse reactions listed included liver dysfunction, cutaneous reactions and neutropaenia. There were no fatal adverse reactions reported. The majority of complications (91.6%) occurred within the first three months of ATD treatment, and the authors concluded that prolonged ATD treatment was a useful treatment option for children with GD.[32]

RAI is generally used for children who do not achieve a permanent remission after a period of treatment with an ATD or experience serious adverse reactions. A major complication of RAI is that most patients are rendered hypothyroid and require life-long treatment with L-Thyroxine. In Thailand, a retrospective descriptive study to assess the dangers of RAI in children and adolescents found that RAI was an effective and safe treatment for children and adolescents with GD,[39] and may be preferable over thyroidectomy in children and adolescents with GD.[43] However, surgery is recommended in patients with especially large goiters (>80 g) and in very young children that fail ATD, as RAI is not yet considered suitable.[42]

The incidence of thyroid disease, in particular GD has been reported to be on the increase in recent years.[6] Data for GD in children and adolescents are limited from sub-Saharan Africa with most epidemiological data quoted in the literature relating to adult patients with thyroid

disease.[11] The paucity of data from the sub-Saharan region challenges the physician in identifying the best suited treatment strategies for the patient population in their setting.

METHODOLOGY

This was a retrospective patient folder review of all children and adolescents diagnosed with GD, attending the Paediatric and Adolescent Endocrinology Services (PAES) at Red Cross War Memorial Children's Hospital (RCCH) and Groote Schuur Hospital (GSH) in Cape Town, Western Cape, South Africa. The patients that were included in this study, were diagnosed with GD between the ages of 1 and 20 years old.[46]

The diagnosis of GD was made when the serum fT4 and/or fT3 levels were above the reference range and the serum TSH below the reference range on the initial (PAES or diagnosing health care provider) thyroid function test plus, one of the following:

i. A positive TRAb titre done at diagnosis or within 12 months of diagnosis.
ii. Diagnostic radioactive iodine uptake scan demonstrating diffuse and increased uptake suggestive of GD.
iii. Thyroid eye disease as identified by the PAES physician or an ophthalmologist.
iv. Diagnosis made by the PAES attending physician based on clinical findings.

The patient was included if their first visit to the PAES fell between 01 January 1998 and 31 December 2018. The study follow-up continued to 31 December 2019. The aim was to describe the population group attending the services; their demographic profile, reason for presentation, clinical and laboratory findings, the treatment modalities utilised and the disease progression.

Various sources were employed to compile a complete list of all patients seen in the service over the past 20 years:

i. Nuclear medicine departments at RCCH and GSH - a list of all children and adolescents that had undergone a diagnostic nuclear medicine thyroid uptake scan suggestive of GD was formulated.
ii. Pharmaceutical departments at RCCH and GSH - the list of all children and adolescents prescribed anti-thyroid drugs during the study period.
iii. Health information management units at RCCH and GSH - the hospitals' Clinicom Hospital Information System programme was used to identify all patients attending

the in-patient and out-patient services of the hospitals. The International Statistical Classification of Diseases and Related Health Problems 9th Revision (ICD9) and ICD10 codes that represent thyrotoxicosis (hyperthyroidism), thyroiditis and all their derivatives were used to compile a list of patients.

iv. Paediatric and adolescent endocrinology department at RCCH and GSH – all current and archived in-patient & clinic endocrine folders with a diagnosis of GD were reviewed.

The relevant patient folders were evaluated and only patients that met the criteria (an accurate diagnosis of GD, appropriate timing of diagnosis and relevant age) were included. Finally, a list of 32 patients was compiled (Diagram 1). One patient was excluded as the in-patient and clinic folder were not found. The remaining patients were anonymised and given study numbers before relevant data were captured into Epi Info™ for Microsoft Windows.

All the laboratory data referred to in this study were obtained at the first PAES clinical visit, unless otherwise stated. The TRAb tires values were included in the analyses if taken at the first PAES clinical visit or within 12 months from the time of the GD diagnosis. For the sake of this study, the term remission refers to a patient that achieves clinical and laboratory findings that allows for ATD to be stopped. The term relapse, refers to a patient that has a recurrence of GD, diagnosed clinically and biochemically, after being in remission.

Stata release 13.0 (StataCorp LP), for Microsoft Windows, was utilised for analyses. The data were described as proportions and percentages. For non-normally distributed data the central tendencies were reported as median, and inter-quartile range (IQR).[47] In subgroup analyses Fisher's Exact test was used for categorical data whilst the Wilcoxon-Mann-Whitney test was used for continuous data in two independent groups. A p-value of < 0.05 was considered statistically significant.

Ethics approval was obtained from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee HREC REF: 443/2019. Approvals were obtained from the relevant hospitals and departments.

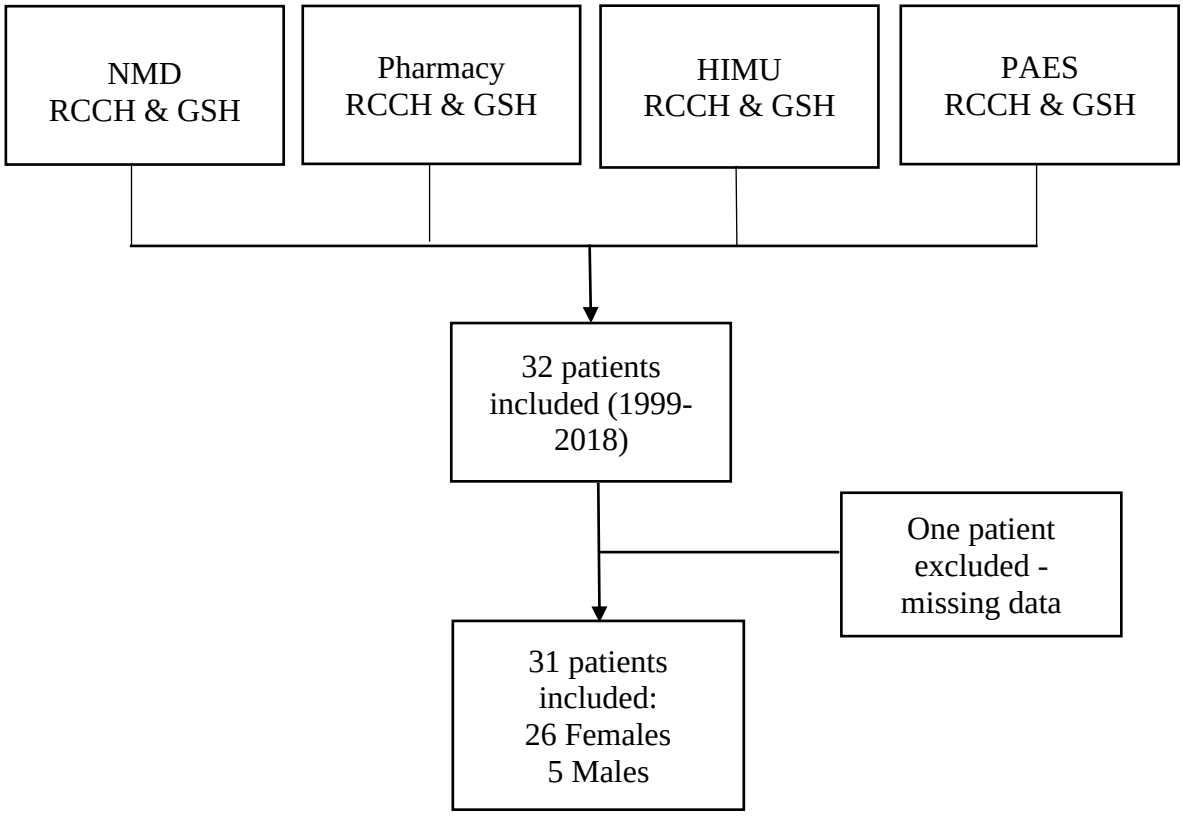

Diagram 1: Study flow utilised to identify all patients with Graves disease attending RCCH & GSH in the past two decades (1999-2018)

NMD Nuclear medicine department, HIMU Health information management unit, PAES Paediatric and adolescent endocrine service

RESULTS

Demographics

Denominators have been reported where the total number of responses were less than the total study number. Thirty-one patients were included in this study (n=31). The median duration in the study was 2.6 years (IQR: 1.4; 4.9). Twenty-six patients were female (83.9%). The female to male ratio in this group was 5.2:1. The median age at presentation to PAES was 10.1 years (IQR: 8.9; 11.7). The age at presentation for female and male patients were similar, 10.0 years (IQR: 8.9; 11.4) and 10.2 years (IQR: 9.9; 12.6) respectively (Mann-Whitney; p=0.61). Fifteen patients had their pubertal staging documented, seven (46.7%) staged at Tanner I, seven (46.7%) as Tanner II, and one (6.7%) staged as Tanner III. There was an equal distribution of referrals from the public and private health sector.

Reason for presentation

Twenty-two patients' presenting complaints were documented. Twelve (54.5%) complaints referred to weight loss; 10 (45.5%) complaints about emotionally lability. Five (22.7%) about abnormal eye changes, and four (18.2%) reports were made about heart palpitations. An additional four patients with Down syndrome were referred to PAES due to abnormal thyroid functions (TF) identified by screening.

Clinical presentation

Thyroid eye disease (TED) was identified in 19 (63.3%) patients. Of the patients with TED, 15 (79%) had proptotic eyes, three (15.8%) had lid lag and one (5%) reported diplopia, none had corneal involvement or vision loss. Twenty-seven folders had a clinical note made about the patient's thyroid appearance. Twenty-six (96%) were noted to have presented with a goitre. Five (16%) were reported to have had an audible bruit. Tremor was documented in 10 (33%) of the patients, nine (30%) demonstrated proximal myopathy and only 8 (27%) were tachycardic. There were no patients reported to have thyroid dermopathy or acropachy. Twenty-four (80%) of patients had a normal body mass index (BMI), two (6.7%) had a BMI categorised as overweight, two (6.7%) were categorised as thin and two (6.7%) as severely thin.

Co-morbidities

At the first consultation, the comorbidities that were self-reported by the patient or the caregiver included:

- Down syndrome (n=8; 25.8%)
- Atopy (allergic rhinitis/asthma/eczema) (n=6; 19.4%)
- Type 1 diabetes mellitus (n=2; 6.5%)
- Attention deficit & hyperactivity disorder (n=1; 3.2%)
- Anxiety requiring anxiolytics (n= 1; 3.2%)
- Slipped capital femoral epiphysis (n=1; 3.2%)

Laboratory results

Ninety-four percent (n=29) had a TSH level lower than the reference range. Two patients had had normal TSH as they had been on treatment before PAES visit, however initial TSH had been lower than the reference range. Free T4 was elevated in 26 (83.9%) patients. Fifteen patients had a fT3 tested, all of which were elevated; two (13%) of these patients with elevated fT3 had a normal fT4 at the time of testing.

Twenty-five patients had antithyroid antibodies tested. Nineteen patients had TRAbs tested, 18 (94.7%) patients had an elevated TRAb titre; the median titre was 26.7 IU/L (IQR: 7.95; 36.9). Seventeen patients were tested for anti-TPO antibodies, and 12 (70.6%) had an elevated titre. Eleven patients were tested for both TRAbs and anti-TPO and six (54.5%) had both elevated.

Radio imaging

Nineteen (61.3%) underwent diagnostic thyroid scintigraphy (TS). Seventeen (89.5%) had TS report that suggested of GD. One report was not available, and one report was reported as thyroiditis. Four (12.9%) patients underwent a thyroid ultrasound during the study period.

Treatment

Carbimazole & Beta blockade

Half of the patients had been started on CMZ by their attending physician before their first PAES visit, and two patients had been started on beta blockade. Fifteen patients were started on CMZ and ten on beta blockers at their first visit. The median CMZ dose that patients were commenced on was 15mg per day (IQR: 10;20) or 0.44mg/kg per day (IQR: 0.4; 0.6). Throughout the study period, the maximum median CMZ dose prescribed was 20mg per day (IQR: 15; 30) or 0.6mg/kg per day (IQR: 0.5; 0.9). In five patients (16%) a block and replace (BR) strategy was employed.

Adverse reactions

In two instances, patients reported experiencing complications attributed to CMZ. Both these adverse reactions were reported within the first 12 months of GD diagnosis. Mild arthralgia and vivid dreams were the two complaints attributed to the CMZ by the caregivers, these symptoms resolved spontaneously and without dose adjustments. There were no cases of agranulocytosis or liver dysfunction identified during the study period.

Time intervals

All patients were initially treated medically with CMZ. Diagram 2 delineates the patient group into those that were able to have a decrement in CMZ and those that did not. Twenty-three (74.2%) achieved TF profiles that resulted in a decremental dosage adjustment of CMZ. The median time taken to achieve the first decrement was 7.7 months (IQR: 4.7; 14) from first PAES consultation. The median time patients required beta blockade was 2.9 months (IQR: 1.5; 7.8).

In twelve of the 31 (39%) patients the CMZ was stopped after a median of 16.3 months (IQR: 8.6; 35.1) from first PAES consultation. Four (n=4/12; 33%) patients relapsed after a median of 4 months (IQR: 2.1; 6.1) off CMZ therapy. One relapsed patient underwent RAI thyroid ablation. Three patients were retreated with CMZ for another median of 15.1 months (IQR:

14.2; 46.7) before their laboratory and/or clinical profiles allowed CMZ to be stopped. One of these patients experienced a relapse for the second time and was therefore reinitiated on CMZ.

Ten patients required RAI for definitive management after CMZ failed to control GD or due to relapse. One patient relapsed after remission was achieved by CMZ therapy and underwent RAI after 82 months (6.8 years) from first PAES consultation. The remaining nine patients who did not attain remission underwent RAI after a median of 24.4 months (IQR: 18.6; 49.7) from first PAES visit.

At the study's conclusion nine (29%) patients had achieved and continued in remission after first course of CMZ, nine (29%) remained on CMZ therapy, ten (32%) underwent RAI thyroid ablation and three (10%) relapsed once or twice before GD remission.

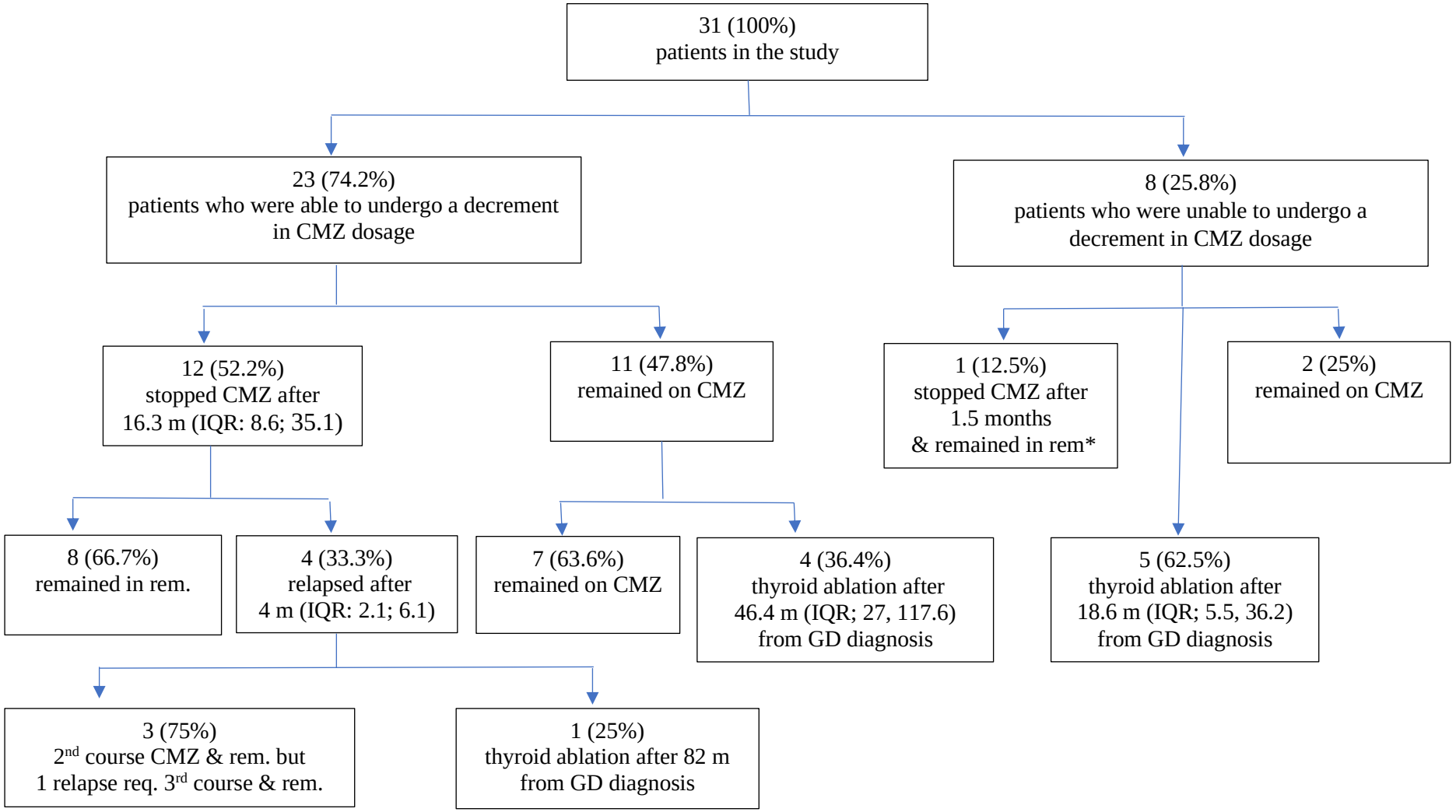

Diagram 2: Flow diagram of treatment requirements and outcomes over study period (n=31)
*CMZ=Carbimazole; m=months; IQR=interquartile range; rem=remission at study end; req=required; *patient folder records incomplete appears patient stopped treatment (prescribed/compliance unsure) and remained in remission*

Subgroup analyses

Remission

There were no statistically significant differences demonstrated between the group that achieved and remained in GD remission after a first/single course of CMZ (patients went into remission after their first/single course CMZ therapy) and their counterparts (still on CMZ therapy, required RAI or ever relapsed) (Table 1). Although not statistically significant (Mann-Whitney; p=0.23), the remission group was treated for almost one year longer before weaning off CMZ than the counterparts.

Table 1: Comparison between patients in remission after single course of Carbimazole and all other study patients

Variable	Remission: single CMZ course (n=9)	Other (n=22)	Test	p-value
Female n (%)	7 (87.5)	19 (82.6)	Fishers Exact	0.61
Age (years) (Median/IQR)	9.9 (9.3; 10.6)	10.2 (8.9; 11.9)	Mann-Whitney	0.58
TRAb titre (mIU/L) (Median/IQR)	19.6 (2.31; 26.9)	32.8 (17.7; 39.4)	Mann-Whitney	0.15
Months to 1st decremental dosage adjustment CMZ (Median/IQR)	9.3 (3.3; 1.6)	7.1 (5.6; 12.7)	Mann-Whitney	0.82
Months until CMZ stopped (Median/IQR)	25.8 (8.6; 44.8)	14.4 (7.2; 16.3)	Mann-Whitney	0.23

Down Syndrome

One-quarter of the patients (n=8) were patients known with Down syndrome. All the patients were female. These patients presented at a significantly younger age (Mann-Whitney; $p<0.05$) than those without DS (Table 2). Patients with Down syndrome presented with similar TRAb titres and similar relapse rates.

Table 2: Characteristics between patients with Down syndrome compared to those without Down syndrome

Variable	DS (n=8)	Without DS (n=23)	Test	p-value
Female n (%)	8 (100)	18 (78.3)	Fishers Exact	0.20
Age (years) (Median/IQR)	8.9 (8.3; 9.9)	10.7 (9.3; 12.2)	Mann-Whitney	0.02
TRAb titre (mIU/L) (Median/IQR)	29.7 (12.8; 38.2)	23.2 (7.7; 33.4)	Mann-Whitney	0.64
Months to 1st decremental dosage adjustment CMZ (Median/IQR)	10.9 (5.6; 14.5)	6.5 (3.3; 11.0)	Mann-Whitney	0.56
Months until CMZ stopped (Median/IQR)	19.6 (8.9; 27.5)	15.9 (8.4; 38.7)	Mann-Whitney	0.81
Relapse events n (%)	1/8 (12.5)	3/23 (13.0)	Fishers Exact	0.73

DISCUSSION

The sample size in this study was small, as well as follow up periods between patients were variable, therefore, the ability to make statistically significant conclusions were limited. This study demonstrated that patients presented younger than international studies, there was a female predominance. Most patients presented with a normal BMI. All patients were treated medically, and no severe adverse effects were reported. Those that remained on CMZ longer remained in remission (not statistically significant). RAI was utilised in circumstances where treatment failed. There were no thyroidectomies conducted as definitive treatment.

One to two new GD cases were referred to the PAES each year on average. Three-quarter of the patients had presented by 11.7 years of age, similar to another African study.[8] However studies beyond the continent report the majority of children presenting older than 11 years of age.[48] The female predominance in those with GD is well described across various settings and similarly seen in this study.[4, 6, 48]

Most of the patients presented with a normal or higher BMI, despite loss of weight being the most common complaint from caregivers. Veenendaal recently described that patients with GD in their setting had similar BMI to the general population.[49] Only one-third of patients presented because of emotional lability and poor school performance, but this was almost always accompanied with a physical complaint, for example weight loss, heart palpitations or eye changes. Symptoms like tremor and goitre were mentioned less often than reported the United Kingdom and Ireland.[6]

Free triiodothyronine was elevated in all patients tested. A fT3 result can be valuable in T3 toxicosis or if ATD has been started.[17, 21] Antibodies against thyroperoxidase and thyroglobulin may be positive and simply assist the confirmation of autoimmune thyroid disease.[22] In this study half of the patients had elevated anti-TPO antibodies with positive TRAbs, a well described occurrence that could lead to a misdiagnosis of Hashitoxicosis.

Notably, thyroid scintigraphy in the bulk of patients merely reaffirmed the diagnosis in patients that had positive clinical and laboratory findings of GD. This concurs with consensus statements and other studies that diagnostic thyroid scintigraphy is not necessary in making the diagnosis of GD, and thyroid ultrasound can be utilised instead[2, 17, 23]

All the patients in the study were initially treated medically, no life-threatening complications were reported and two experienced mild adverse reactions that resolved spontaneously. This study concurs with the suggestions that long term ATD is a safe and viable option in treating children with GD.[32]

One-third of the patients were started on beta blockade at their first PAES consultation. Half of the patients required beta blockade for at least three months. An important consideration for attending physicians commencing ATD in children and adolescents for the diagnosis of GD, is whether the patient's symptomology could be further ameliorated by beta blockade. The BR strategy was well tolerated in the five patients on BR. In our setting it remains a beneficial strategy when GD symptomology is difficult to manage with CMZ alone.[50] No serious side effects were observed during the BR strategy. It may offer a therapeutic option in cases when definitive treatment needs to be postponed or cannot be managed by CMZ alone.[50, 51] Although, Léger et al have recommended against its use in their 2018 consensus article because of side effects.[2]

Historically, RAI for definitive management was preferable earlier on, and this was demonstrated in this study. Half of the patients that had undergone RAI did so after 2 years of on CMZ. Evidence is now suggesting that long term CMZ is safe and beneficial in children and adolescents and increases the chances of remission.[32, 35] This raises the question of whether prolonging the duration of ATD would result in an increase in remission rates and a decrease in RAI in this setting? In the subset analyses, patients that went into remission and remained in remission were on CMZ for almost two times longer than their counterparts. Literature has suggested that higher TRAb titres were associated with relapse, however in our subgroup analyses this was not identified, possibly as a result of the small sample size.[21] During the two decades, no thyroidectomies were performed for GD.

A quarter of the patients in this study were children known with Down syndrome and all were female. Recent studies however report that in patients with Down syndrome GD affects both sexes equally.[52, 53] Similar to other contexts, the DS patients presented younger than the patients that did not have DS.[52, 53] Most of the patients with DS were identified by routine screening of thyroid functions. Hypothyroidism is a well-known sequalae in those with DS. This study emphasises the importance of considering GD when screening or undertaking the work up for vague symptomology in DS patient.[54-56] Patients with DS took longer to achieve the first decrement in CMZ dose compared to those without DS, even though the time taken to stop CMZ therapy was similar across both groups. These results are contrary to De Luca's findings that patients with DS stopped ATD treatment earlier than those without DS. [52] There was no difference in relapse between the groups.

LIMITATIONS

This was a retrospective record review, hence the quality of data used were dependent on clinical notes and findings identified by the attending physician. In certain circumstances data were missing from the older folders. The follow up period is variable depending on when the patient was first diagnosed with GD and this may influence the findings of this study. The small sample size limited the comparative analyses, and no statistically significant results were obtained other the younger age at presentation in children with DS. Although sample number was small, it included most of the patients with GD treated in the PAES over the past 20 years.

However, this cursory overview may be one of the larger studies describing children and adolescents with GD in the sub-Saharan region. It may highlight important aspects of managing GD in this population group in a resource constrained setting. In addition, the multipronged method used to identify the list of patients with GD over the past two decades could be helpful for other health practitioners wanting to conduct similar research.

CONCLUSION

This folder review of the last two decades has demonstrated that children diagnosed with GD managed in the PAES are similar in sex distribution, slightly younger in age and tolerate CMZ better than those sited in other similar studies. This study has given the unit the confidence to continue and enhance the close collaboration between health practitioners in the public and private health sector. It has also assisted in the rationalisation of our clinical practice, by minimizing the unit's reliance on diagnostic thyroid scintigraphy in the workup of GD, especially when the diagnosis can be confirmed by other parameters. The unit now also considers prolongation of CMZ therapy and retreatment with CMZ after relapse, as a safe and viable alternative to RAI in certain circumstances. Additional studies are needed to identify if these changes in practice lead to any improved clinical outcomes in the short and long term.

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