CHAPTER 1

1.1 INTRODUCTION

Thyroid disorders are highly prevalent in both underdeveloped and industrialized regions of the world. In general, these disorders are more common in women than men and increase in prevalence with age. The consequences of thyroid disease are far reaching in terms of its effect on the normal physiological functioning of the body. The clinical presentation may vary from mild and asymptomatic to severe and overt disease. The presentation may depend on the patient's age, gender, physical condition, and the rate at which thyroid disease develops.

One of the earliest effects of altered thyroid hormone synthesis is the change in basal metabolic rate. A deficiency or excess in thyroid hormone has effects on growth and development, on intermediary metabolism, on central nervous system development and function, cardiovascular, skeletal, gastrointestinal, and reproductive system activity. Diagnosis of thyroid disease cannot be confirmed by clinical examination alone and thus thyroid function tests are required in order to assess thyroid status.

There exists a myriad of thyroid function tests but all of them are not indicated for confirming the diagnosis of thyroid disease. The thyroid function tests are costly and in the case of private patients belonging to a medical aid scheme, the ordering of unnecessary tests could have an impact on the funds that are available to them for the rest of the financial year.

Discovery Health noticed the unnecessary requests for thyroid function tests that were not indicated for the diagnosis of disorders of thyroid function. In order to educate the clinician with regard to the use of thyroid function tests Discovery Health published a set of evidence-based guidelines (Appendix 1) in the South African Medical Journal dated March 2003 (Guidelines, 2003). This study will focus on comparing whether there is any difference in requesting patterns of thyroid function tests prior to March 2003 (before

publication of the evidence-based guidelines) and after March 2003 (after publication of evidence-based guidelines).

TABLE 1.1 THYROID FUNCTION TESTS

Thyroid Function Tests	Medical Scheme Code Number	Price
TSH	4507	R112-30
Free T4	4482	R100-20
Free T3	4509	R100-20

1.2 THYROID PHYSIOLOGY

The production of thyroid hormone is the end result of a complex series of pathways and feedback mechanisms that involve the hypothalamic-pituitary-thyroid-axis. Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the production and release of thyrotropin from thyrotropic cells in the anterior pituitary. Thyrotropin (TSH) stimulates thyroid gland hyperplasia. This enhances synthesis of thyroglobulin, and stimulates the synthesis and release of the thyroid hormones, thyroxine (T4) and triidothyronine (T3). These thyroid hormones, in turn, inhibit the secretion of thyrotropin at the level of the thyrotropic cells and antagonize the effects of TRH by down regulating TRH receptors at the thyrotropic cells (Fig. 1). Changes in thyroid hormone levels produce inverse logarithmic changes in thyrotropin (TSH) secretion, underscoring the exquisite control and regulation of the entire system. Thus, thyrotropin (TSH) levels are sensitive to minute and sub-clinical changes in T4 levels. This delicate relationship is the basis of obtaining thyrotropin (TSH) levels as first line testing for thyroid dysfunction (Bouknight, 2003).

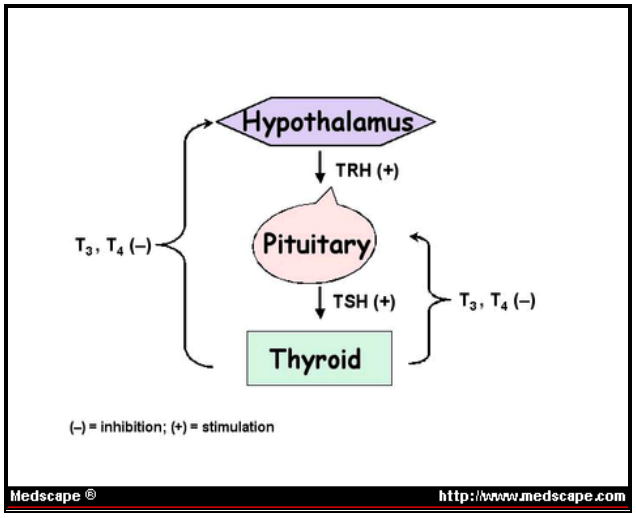

Fig. 1. Hypothalamic-pituitary-thyroid axis (Bouknight, 2003)

The normal concentrations of T4 and T3 are 60-150 nmol/L and 1.0-2.9 nmol/L, respectively. Both hormones are extensively protein bound, some 99.98% of T4 and 99.66% of T3 being bound principally to a specific thyroxine-binding globulin (TBG) and to a lesser extent prealbumin and albumin. TBG is approximately one third saturated at normal concentrations of thyroid hormones. It is generally accepted that only the free, non protein-bound, thyroid hormones are physiologically active. Although the total T4 concentration is normally 50 times that of T3, the different extents to which these hormones are bound to protein mean that the free T4 (FT4) concentration is only 2-3 times that of free T3 (FT3). In the tissues, most of the effects of T4 probably result from its conversion to T3, so that T4 itself is essentially a pro-hormone (Marshall, 2000).

1.3 HYPERTHYROIDISM

Hyperthyroidism is the consequence of excessive thyroid hormone action. The causes of hyperthyroidism include the following:

- Toxic diffuse goiter (Graves' disease)
- Toxic adenoma
- Toxic multinodular goiter
- Painful subacute thyroiditis
- Silent thyroiditis, including lymphocytic and postpartum variations

- Iodine-induced hyperthyroidism (for example, related to amiodarone therapy)
- Excessive pituitary TSH or trophoblastic disease
- Excessive ingestion of thyroid hormone

The signs and symptoms of hyperthyroidism are attributable to the effects of excess thyroid hormone in the circulation (AACE Task Force, 2002). The severity of signs and symptoms may be related to the duration of the illness, the magnitude of the hormone excess, and the age of the patient. The development of sensitive TSH assays has considerably fascilitated the diagnosis of hyperthyroidism. The sensitive TSH test refers to a TSH assay with a functional sensitivity of 0.02 or less. Hyperthyroidism of any cause (except excess TSH production) results in a lower-than-normal TSH level (AACE Task Force, 2002). The sensitive TSH assay is the single best screening test for hyperthyroidism, and in most outpatient clinical situations, the serum TSH is the most sensitive test (small changes in serum thyroid function cause logarithmic amplification in TSH secretion) for detecting mild (subclinical) thyroid hormone excess or deficiency (AACE Task Force, 2002).

In patients with unstable thyroid states, such as those recently treated for hyperthyroidism or those who have been receiving excess thyroid hormone replacement, Free T4 measurement more accurately indicates the thyroid status than does serum TSH. Patients with chronic or recent severe hyperthyroidism or hypothyroidism will benefit from having both TSH and Free T4 monitored for one year until their condition becomes stable (AACE Task Force, 2002).

1.4 PRIMARY HYPOTHYROIDISM

Primary hypothyroidism is caused by a decreased production of thyroid hormones by the thyroid gland. It is a relatively common disease in both iodine-deficient and iodine-sufficient populations. Almost all cases of adult

hypothyroidism result from primary thyroid failure. The most common cause of hypothyroidism is destruction of the thyroid gland by autoimmune disease or by ablative therapies (iodine 131 therapy or external radiation to the head and neck). Hypothyroidism may also be caused by factors that negatively affect the synthesis of thyroid hormones, such as iodine deficiency or excess, and inherited defects in thyroid hormone biosynthesis. Pharmacologic agents such as lithium and amiodarone may inhibit thyroid hormone synthesis (Lindsay et al, 1997).

TABLE 1.2 AETIOLOGY OF PRIMARY HYPOTHYROIDISM

Transient	Thyroiditis (sub acute, silent, postpartum) Non-thyroidal illness
Autoimmune	Atrophic Hashimoto's After Graves' disease treatment with antithyroid drugs
Iatrogenic / Destructive	After radioiodine After thyroidectomy Infiltrative disease (sarcoidosis, amyloidosis, lymphoma)
Environmental	Iodine deficiency
Drugs	Amiodarone Lithium Iodine: oral or topical (in patients with pre-existing autoimmune disease) Antithyroid medication (carbimazole, propylthiouracil) Cytokines (interferon alpha, interleukin-2, macrophage colony stimulating factor)

Much rarer causes of hypothyroidism are hemochromatosis (Shirota et al, 1992), sarcoidosis (Bell, 1991) and amyloidosis (Rich, 1995).

1.5 SECONDARY HYPOTHYROIDSIM

Secondary and tertiary syndromes are often classified as hypothyroidism of central origin resulting from pituitary or hypothalamic disease. They are rare

causes of hypothyroidism. In contrast to primary hypothyroidism, secondary hypothyroidism is caused by pituitary gland dysfunction that results in a diminished secretion of biologically active TSH (Lindsay et al, 1997).

1.6 TERTIARY HYPOTHYROIDISM

Tertiary hypothyroidism is caused by hypothalamic dysfunction and results in a decreased production and/or reduced delivery of TRH to the pituitary gland. Although tertiary hypothyroidism occurs in conjunction with pituitary disease, it can occur independently (Lindsay et al, 1997).

1.7 AUTOIMMUNE DISEASE

Most disease states that commonly affect the thyroid gland fall within the general classification of autoimmune diseases. The antibodies that form have either direct destructive effects on the thyroid gland or cause abnormal function of some phase of thyroid metabolism (Wilson, 2002). The most common and best understood of these autoantibodies (Wilson, 2002) are Thyroglobulin antibodies (Tg abs), TSH receptor-stimulator antibodies (TSH RS abs), TSH receptor-blocker antibodies (TSH RB abs), and thyroid peroxidase antibodies (TPO abs).

1.8 GRAVES DISEASE

Graves disease is an autoimmune thyroid disorder that is caused by the presence of TSH receptor-stimulator antibodies (TSH RS abs) that have been identified as a "G" immunoglobulin (IgG) that attaches itself to receptor sites in the follicular cell of the thyroid gland (Wilson, 2002). When this occurs, the thyroid gland functions in an autonomous manner, stimulated internally by the TSH RS abs, and the normal thyroxine-thyrotropin negative-feedback system is ineffective. The net result is excess production of T4 and T3 in the follicle, initially causing hyperthyroidism and ultimately thyrotoxicosis (Wilson, 2002).

1.9 THYROIDITIS

Thyroiditis occurs in several forms that are differentiated by cause and symptomology (Wilson, 2002). The most common forms are chronic

autoimmune thyroiditis, silent thyroiditis, postpartum thyroiditis, and subacute thyroiditis. Three of these four are autoimmune diseases whereas the fourth, subacute thyroiditis, is most likely of viral origin (Wilson, 2002).

1.10 DIAGNOSTIC MODALITIES IN THYROID DISEASE

Thyroid disease is evaluated and diagnosed using either clinical laboratory investigations, radiographic imaging studies, or tissue sampling. Clinical laboratory investigations usually form the first line of investigation and more often than not provide the information necessary to adequately assess a thyroid disorder. Radioisotope scanning and ultrasound imaging are used in order to obtain additional diagnostic or confirmatory data. In the event that a definitive diagnosis is not obtained with these modalities then tissue may be sampled either by means of fine needle aspiration or surgery (Dayan, 2001).

1.11 DIAGNOSTIC TESTING

Thyroid function tests are among the most common investigations ordered in clinical laboratories. Although these tests are relatively inexpensive individually, they account for a disproportionately large amount of health care expenditure for diagnostic testing. Appropriate laboratory investigation is critical to establish the diagnosis and cause of hypothyroidism in the most cost-effective way. The most valuable test is a sensitive measurement of TSH level (Marshall, 2000). In the past; physicians were unable to detect a thyroid disorder until a patient's symptoms were fairly advanced. With the sensitive TSH test, however, physicians are able to diagnose thyroid disorders at an earlier stage. A TSH assay should always be used as the primary test to establish the diagnosis of suspected primary hypothyroidism (Marshall, 2000). TSH testing is the preferred approach because:

1. TSH is central to the negative-feedback system.
2. Small changes in serum thyroid function cause logarithmic amplification in TSH secretion ("sensitivity").
3. The most advanced (third-generation) chemiluminescent TSH assays can now detect both elevation and significant lowering of TSH levels, and are capable of reliably measuring values <0.1mU/L, thus aiding the detection of subclinical thyrotoxicosis (Supit et al, 2002).

Measurement of FT3 is of no additional value in the diagnosis of hypothyroidism (Guidelines, 2003).

1.12 TESTS OF THYROID FUNCTION

Laboratory tests of thyroid function are required to assist in the diagnosis and monitoring of thyroid disease.

1.13 TOTAL THYROXINE (tT4) AND TRIIODOTHYRONINE (tT3)

Measurement of plasma total T4 (tT4) concentration was formerly widely used as a test of thyroid function, but has the major disadvantage in that it is dependent on binding protein concentration as well as thyroid activity. For example, a slightly elevated plasma tT4 concentration, compatible with mild hyperthyroidism, can occur with normal thyroid function if there is an increase in plasma binding protein concentrations (Marshall, 2000).

With the introduction of reliable assays for free T4 (FT4), there is now little if any justification for laboratories continuing to measure tT4 as a test of thyroid function. Plasma total T3 (tT3) concentration is almost always raised in hyperthyroidism (usually to a proportionately greater extent than tT4, hence it is the more sensitive test for this condition) but may be normal in hypothyroidism due to increased peripheral formation from T4. However, tT3 concentrations, like those of tT4, are dependent on the concentration of binding proteins in plasma and their measurement is being superseded by measurements of free T3 (Marshall, 2000).

1.14 FREE THYROXINE (FT4) AND FREE TRIIODOTHYRONINE (FT3)

The measurement of free hormone concentrations poses major technical problems since the binding of free hormones in an assay, for example by an antibody, will disturb the equilibrium between bound and free hormone and cause release of hormone from binding proteins (Lindsay et al, 1997).

Various techniques have been developed which allow the estimation of free T4 and T3 concentrations in plasma. Such measurements, in theory, circumvent the problems associated with protein binding. They have rendered obsolete

the techniques for the indirect assessment of free hormone concentrations, such as resin uptake test, calculation of the free thyroxine index of measurement of the T4/TBG (thyroglobulin) ratio. However, with gross abnormalities of binding protein concentrations, the results of measurements of free hormones may be misleading owing to technical limitations of the assays. Also, naturally occurring antibodies to thyroid hormones are sometimes present in plasma and can interfere with free hormone assays to give high results. Measurement of TSH (thyroid-stimulating hormone) may help in both these circumstances (Marshall, 2000).

Just as tT3 concentration can be normal in hypothyroidism (especially in mild cases), so, too, can FT3 concentration, and its measurement is of no value in the diagnosis of this condition (Marshall, 2000).

1.15 THYROID-STIMULATING HORMONE (TSH)

Since the release of TSH from the pituitary is controlled through negative feedback by thyroid hormones, measurements of TSH can be used as an index of thyroid function. If primary thyroid disease is suspected and the plasma TSH concentration is normal, it can be safely inferred that the patient is euthyroid (state of normal thyroid gland function). In overt primary hypothyroidism, TSH concentrations are greatly increased, often to ten or more times the upper limit of normal. Smaller increases are seen in borderline cases and TSH measurement is more sensitive than T4 under these circumstances. TSH can also increase transiently during recovery from non-thyroidal illness (Guidelines, 2003).

Plasma TSH levels are suppressed to very low values in hyperthyroidism, but low concentrations can also occur in individuals with sub-clinical disease and in euthyroid patients with non-thyroidal illness. Indeed, in hospital patients, a low plasma TSH concentration is more often due to non-thyroidal illness than to hyperthyroidism. A slightly elevated concentration is as frequently due to recovery from such illness as to mild or incipient hypothyroidism. It is in cases such as these that one may be required to measure the FT4 level in addition to the TSH level in order to avoid misdiagnosis. Another indication

for the measurement of FT4 in addition to TSH is in the diagnosis of thyroid dysfunction secondary to a pituitary disorder, although this is far less common than primary thyroid disease (Marshall, 2000).

1.16 THYROGLOBULIN

The measurement of serum thyroglobulin concentration is used to monitor the response to treatment of thyroid carcinoma in those patients with pretherapy elevations of thyroglobulin. Serum thyroglobulin is not diagnostically useful; as levels are also raised in goitres, sub acute thyroiditis and Graves' disease (Walmsley et al, 1994).

1.17 CLINICAL PRACTICE GUIDELINES

Guidelines describing cost effective and clinically appropriate care have been published. The clinical guidelines provide latitude in decision-making and take into account varying practice styles and patient presentation (AACE, 1995). However, the appropriate use of thyroid function tests, in the diagnosis of thyroid disease, has received little attention in South Africa. In an attempt to encourage a more focused application of thyroid function tests Discovery Health has issued guidelines (March 2003) sourced from evidence-based documents (Guidelines, 2003). he guidelines were directed toward the clinician.

Clinical practice guidelines are intended to promote optimal practices of medicine and endocrinology. Unfortunately, many clinical practice guidelines, including most of those relevant to thyroid disease, rely on narrative literature reviews and expert opinion rather than systemic evaluation of the published literature and explicit acknowledgement of underlying values. Incorporation of rigorous systematic reviews of literature interpreted by multidisciplinary experts strengthens recommendations, as do attempts to reflect objectives of patients and society. Increasing implementation of high quality guidelines is almost as vital as improving the science underlying them (Belin, 2002). The Institute of Medicine defines clinical guidelines as "*systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances*"

(Belin, 2002). Guidelines provide recommendations regarding optimal screening, diagnosis, and therapy and determine appropriate time frames for interventions. In so doing, they attempt to impact quality, efficiency, and cost effectiveness. Management questions related to screening and new treatments within thyroid disease can benefit from relevant clinical practice guidelines (Belin, 2002).

The guidelines are drawn up based on the evidence that exists in clinical practice as to the management of the disease in question. Guidelines pertaining to thyroid disease are currently in wide use in countries such as the USA, UK and Canada (Woolf et al, 1999). The aim of this study is to investigate whether publication of evidence-based guidelines succeeds in reducing the number of thyroid function tests ordered inappropriately for the diagnosis of thyroid disease. Limitations to the use and implementation of evidence-based guidelines have been documented specifically with regard to the clinician.

1.18 IMPLEMENTING CLINICAL PRACTICE GUIDELINES

The presence of guidelines does not guarantee changes in practice behaviour by the clinician. Extensive work based on literature review, focus groups, and prospective assessment has defined the components of guideline implementation by physicians: *awareness* of guideline recommendations, *agreement* with proposed approach, and *ability to adopt* suggested practice (Fig. 2) (Belin, 2002; Cabana et al, 2000; Feder et al, 1999; Russell, 2001; Woolf et al, 1999).

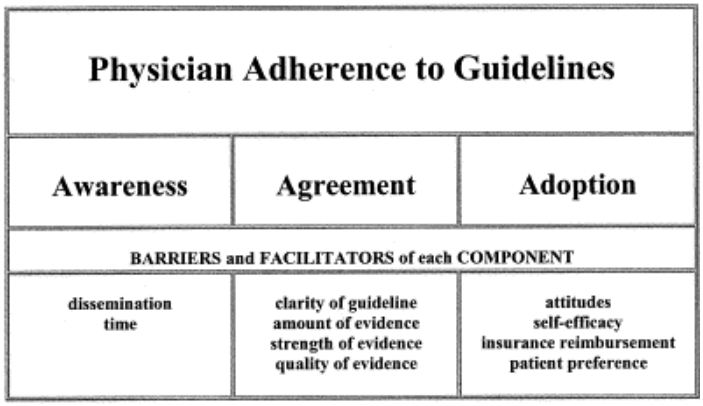

Fig. 2. Components of physician adherence to guidelines (Belin, 2002; Cabana et al, 2000; Feder et al, 1999; Russell, 2001; Woolf et al, 1999).

Due to ongoing research, guidelines should be updated on a regular basis in that way providing patients with the best care possible as well as maintaining cost-effectiveness.

1.19 COMPUTERS FOR GUIDELINE IMPLEMENTATION

Computers hold promise for helping overcome barriers to guideline adoption. Computerized protocols for standardizing clinical decisions, could improve adherence to clinical practice guidelines by increasing physician awareness and agreement (Belin, 2002).Computerized protocols can be initiated by ordering a test and can include much more information than that available on a flow diagram (Belin, 2002). For example, when a clinician orders a test, the program could present relevant evidence, possible alternatives, and patient oriented materials. Observation of clinicians' approaches to making clinical decisions through the computer could allow rigorous evaluation of the decision-support tool and of the clinical interventions themselves (Belin, 2002).

1.20 LIMITATIONS OF CLINICAL PRACTICE GUIDELINES

Deficient implementation of clinical practice guidelines restricts their potential impact. Other difficulties also may interfere with the goals of improving quality and efficiency of health care. Although some problems with clinical practice guidelines stem from weakness within a particular guideline, flaws inherent to the general process of clinical guideline development further limit their utility (Table 1.10) (Belin, 2002).

TABLE 1.3 IMPACT OF CLINICAL PRACTICE GUIDELINES (Belin, 2002)

	ADVANTAGES	LIMITATIONS
Individual patient care	Improved quality Increased efficiency Decreased variability	Decreased quality of care (if guidelines are flawed, obfuscating, or outdated). Decreased variability may impede individualized care.
Education	Enhanced awareness: Patients Physicians Policy makers	—
Health care cost and policy	Decreased costs. Improve compensation for preferred care. Stimulate funding for investigations in which evidence is lacking. Basis for evaluating quality of care.	Higher costs if utilization increased. Costly to maintain updated guidelines. Discourage funding and motivation for investigations because of complacency with current evidence.

1.21 POORLY CRAFTED GUIDELINES

Deficiencies in the development process for particular clinical practice guidelines can limit their effectiveness. Flawed, biased, outdated, or

conflicting clinical guidelines may lead to recommendations that are not optimal (Belin, 2002; Cabana et al, 2000; Feder et al, 1999; Russell, 2001; Woolf et al, 1999).

1.22 GUIDELINE MAINTENANCE

Initially useful guidelines may later have limited utility with the appearance of new studies and improved technologies. Delays exist between the promise of ongoing new research, investigation of its benefit, communication of new evidence, and incorporation of new findings into clinical practice guidelines. Studies have evaluated the sustained validity of evidence-based guidelines and their analysis supported reassessing clinical practice guidelines every three years for possible updating (Belin, 2002; Cabana et al, 2000; Feder et al, 1999; Russell, 2001; Woolf et al, 1999).

1.23 STIFLED FLEXIBILITY AND INNOVATION

Ironically, some of the attractive qualities of guidelines – standardization of care and authority of recommendations – also may prove to be limitations. Guidelines may limit access to individually tailored care if they are used to rationalize inflexible decisions about payment. They also may limit resources available for filling in gaps within the literature because of a false sense of complacency from guideline recommendations (Belin, 2002; Cabana et al, 2000; Feder et al, 1999; Russell, 2001; Woolf et al, 1999).

1.24 POTENTIAL FOR INCREASED RESOURCE UTILIZATION

Clinical guidelines often increase resource use and costs to improve the quality of care(Belin, 2002; Cabana et al, 2000; Feder et al, 1999; Russell, 2001; Woolf et al, 1999). Clinical practice guidelines that have been based upon evidence collected recently that include literature reviews as well as guidance by groups with multidisciplinary expertise aid in optimising health care. There is an ever- increasing demand for evidence-based guidelines in the field of medicine as they provide the clinician with a baseline for reaching a diagnosis in the shortest time without incurring unnecessary expenditure. This has a

direct impact on the patient who can only benefit from affordable as well as effective health care (Belin, 2002).

Due to ongoing research, guidelines need to be reviewed on a regular basis in order to provide the most cost effective care while at the same time delivering the best care available.