PREVALENCE OF THYROID DYSFUNCTION IN AMBULANT PATIENTS WITH TYPE 2 DIABETES ATTENDING DIABETES CLINICS AT KENYATTA NATIONAL HOSPITAL

DISSERTATION SUBMITTED IN PART FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE IN INTERNAL MEDICINE OF THE UNIVERSITY OF NAIROBI

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This Research proposal is my original work and has not been presented for a degree at any other university.

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LIST OF ABBREVIATIONS

BMI  Body Mass Index.
CVD  Cardiovascular disease.
ELISA  Enzyme Linked Immunosorbent Assay.
FFA  Free Fatty acids.
FT3  Free Triiodothyronine.
FT4  Free Thyroxine.
GAD  Glutamic Acid Decarboxylase.
GLUT-2  Glucose Transporter type 2.
GLUT-4  Glucose Transporter type 4.
HTN  Hypertension.
IR  Insulin Resistance.
KNH  Kenyatta National Hospital.
NHANES  National Health and Nutritional Examination Survey.
PI  Principal Investigator.
rT3  Reverse Triiodothyronine.
TSH  Thyroid Stimulating Hormone.
TRH  Thyroid Releasing Hormone.
T2DM  Type 2 Diabetes Mellitus
UON  University of Nairobi
US  United States.
WHO  World Health Organisation.
ABSTRACT

Background
Thyroid disease and Diabetes are two common endocrinopathies found in the general population. Thyroid disease is a pathological state which can adversely affect Diabetes control and contribute to negative patient outcomes. Hyperthyroidism contributes to hyperglycemia while hypothyroidism contributes to episodes of hypoglycemia. This not only impedes management of Type 2 Diabetes but also worsens metabolic control. However, uncontrolled diabetes on the other hand has been shown to impair TSH response to TRH which normalizes with improvement in glycemic control

Objectives
To determine the prevalence and patterns of thyroid dysfunction in patients with Type 2 Diabetes Mellitus.

Methodology
This was a cross-sectional descriptive survey of participants who were over the age of 30 years selected from patients with type 2 Diabetes attending outpatient diabetes clinics. Systematic random sampling was done on patients meeting the inclusion criteria. A sample size of 180 was obtained. Consenting participants’ had their demographic data and medical history collected by use of structured pre-tested questionnaires and a physical examination was done thereafter. This was followed by drawing of venous blood samples for assessment of, i.e. TSH & fT4. Assays for thyroid hormones were done using specific antibodies and enzyme markers for specific thyroid hormones using Enzyme Linked Immuno Sorbent Assay technology. (ELISA)

Results
In this study, majority of the patients were female (62.4%), with a mean age of 59 years and had a mean duration of 9.5 years with diabetes mellitus. Those with a previous diagnosis of thyroid dysfunction were about 10.6% and 22.7% had a positive family history of thyroid dysfunction. The prevalence of thyroid dysfunction in patients with type 2 Diabetes was found to be 61%, of which subclinical hypothyroidism was the most predominant type at 58%. No patient was found to have evidence of overt hyperthyroidism.
Conclusion
The prevalence of thyroid dysfunction among patients with type 2 Diabetes is high, particularly sub clinical hypothyroidism. The clinical significance of this thyroid status on metabolic control and outcomes need further evaluation.
1.0 INTRODUCTION

Thyroid disorders and Diabetes have a propensity to appear together in patients and this is as a result of interaction between thyroid hormones and Insulin\(^1\). Thyroid diseases and Diabetes mellitus are the two most common endocrine disorders encountered in clinical practice. They have been shown to mutually influence each other and associations between both conditions have been reported previously\(^2,3\). Thyroid disease is common in the general population, and the prevalence increases with age\(^4\). However, there is reported higher prevalence of thyroid dysfunction in type 2 Diabetics than in the general population\(^5\).

Insulin and thyroid hormones are both involved in cellular metabolism hence excess or deficit of either of these hormones could result in the functional derangement of the other i.e. Hyperthyroidism can result in hyperglycemia or Hypothyroidism results in hypoglycemia\(^6,7,8\).

Unrecognized thyroid dysfunction may impair metabolic control i.e. glycemic control and lipid profile, by causing hypoglycemia or hyperglycemia and it can cause an additional cardiovascular disease risk in patients with Diabetes\(^12\). Continuing deterioration of endocrine control exacerbates the metabolic disturbances and leads primarily to hyperglycemia as is the case if one has hyperthyroidism. It has been noted that sustained reduction of hyperglycemia will decrease the risk of developing micro vascular complications and most likely reduce the risk of macro vascular complications in patients with type 2 Diabetes\(^12\).

Screening for thyroid dysfunction is indicated in certain high-risk groups, such as neonates\(^9\), due to the serious consequences of congenital hypothyroidism like mental retardation with delayed milestones. The elderly however, tend to be asymptomatic and thyroid dysfunction in this particular group is associated with dyslipidemias if hypothyroid or arrhythmias if hyperthyroid\(^10\). While screening in patients with type 1 Diabetes is the norm at diagnosis due to association of autoimmunity, it has been noted that there is a higher prevalence of thyroid dysfunction in patients with type 2 Diabetes than the general population, hence justification in testing for it.
1.1 LITERATURE REVIEW

1.2 EPIDEMIOLOGY

1.2.1 BURDEN OF DIABETES MELLITUS

WHO estimates in August 2011 reveals that 346 million people around the globe have Diabetes mellitus, of whom 90% have type 2 Diabetes mellitus (T2DM), largely the result of physical inactivity and excess body weight\textsuperscript{13}. WHO projects that diabetes deaths will double between 2005 and 2030. In 2010, 12.1 million people were estimated to be living with DM in Africa, projected to increase to 23.9 million by 2030\textsuperscript{14}. T2DM accounts for well over 90% of DM in Sub-Saharan Africa, and population prevalence proportions ranged from 1% in rural Uganda to 12% in urban Kenya\textsuperscript{15}.

1.2.2 PREVALENCE OF THYROID DYSFUNCTION

The prevalence of thyroid disease as per Colorado Thyroid Disease prevalence conducted in 1995 was estimated to be 6.6% in the general population, with hypothyroidism being the commonest presentation\textsuperscript{16}. Of these participants, 9.5% were found to have elevated TSH and 6% were diagnosed with thyroid disease before screening. About 9.9% were found to have unrecognised thyroid abnormality, predominantly elevated TSH. Higher prevalence of thyroid disease has been noted in women ranging from 4-21%, while rate in men is 2.8-16\textsuperscript{16}. However, Wickham Survey which was conducted in the north of England in 1996 found a prevalence of overt thyrotoxicosis of 2% in females & 0.2% in males\textsuperscript{17}.

Thyroid disease prevalence increases with age as noted by Colorado study where prevalence in 18 year olds was 3.5% as compared to 18.5% for those above 65 years of age. NHANES III Study revealed that 4.6% and 1.3% of the U.S population had Hypothyroidism & Hyperthyroidism respectively\textsuperscript{18}. The incidence of progression from sub clinical hypothyroidism to overt hypothyroidism was 5-15% per year, with women with positive thyroid auto antibodies being more at risk\textsuperscript{16}. The incidence of progression of subclinical hyperthyroidism to overt hyperthyroidism was 5% per year, especially in patients with autonomous thyroid adenoma and nodular goiter\textsuperscript{19}. 
1.2.3 PREVALENCE OF THYROID DYSFUNCTION IN TYPE 2 DIABETICS

The prevalence of thyroid disease in type 2 diabetes is higher than in the general population \(^{21}\). The prevalence of thyroid disease in Diabetes has been estimated at 10.8\% with most of cases being hypothyroidism at 30\% and subclinical hypothyroidism at 50\%. Hyperthyroidism on the other hand accounts for 12\% and postpartum thyroiditis for 11\%\(^{20}\).

The Fremantle Diabetes study found a prevalence of subclinical hypothyroidism of 8.6\% in women with Type 2 Diabetes in Australia\(^{22}\), as opposed to study in Jordan, which studied prevalence of autoimmune thyroid disease in type 2 Diabetes and found it to be 12.5\% ,with subclinical hypothyroidism at 5\%\(^{23}\).

There is a notable increased risk of thyroid autoimmunity in adult type 2 diabetics with GAD 65 auto antibodies, which have been confirmed in pediatric populations as well \(^{24,25}\). Prevalence of subclinical hypothyroidism is higher in patients with metabolic syndrome than in non-metabolic syndrome subjects due to concomitant presence of obesity, Hypertension, Insulin resistance and deranged lipid concentrations found in both conditions \(^{26}\).

Table 1: Summary of prevalence studies of thyroid dysfunction in type 2 diabetes:

<table>
<thead>
<tr>
<th>TYPE OF STUDY</th>
<th>N-SAMPLE SIZE</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>El Nobre et al (Portugal) 2002(^{27})</td>
<td>Retrospective 499</td>
<td>12.7%</td>
</tr>
<tr>
<td>Radaideh et al (Jordan) 2004(^{23})</td>
<td>Cross-sectional 908</td>
<td>12.5%</td>
</tr>
<tr>
<td>Cardoso C et al (Nigeria) 1995(^{28})</td>
<td>Cross-sectional 60</td>
<td>8.3%</td>
</tr>
<tr>
<td>Papazafiropoulou et al (Greece) 2010(^{29})</td>
<td>Cross-sectional 1092</td>
<td>12.3%</td>
</tr>
<tr>
<td>Akbar et al (Saudi) 2006(^{30})</td>
<td>Cross-sectional 100</td>
<td>16%</td>
</tr>
<tr>
<td>Perros et al (Scotland) 1995(^{31})</td>
<td>Cross-sectional 1310</td>
<td>13.4%</td>
</tr>
<tr>
<td>Pasupathi et al (India) 2008(^{32})</td>
<td>Cross-sectional 200</td>
<td>45%</td>
</tr>
<tr>
<td>Udiong et al (Nigeria) 2007(^{33})</td>
<td>Cross-sectional 266</td>
<td>46.5%</td>
</tr>
<tr>
<td>Al-Wazzan et al (Kuwait) 2009(^{34})</td>
<td>Cross-sectional 1580</td>
<td>12.9%</td>
</tr>
<tr>
<td>Bazrafashan et al 2000(^{35})</td>
<td>Cross-sectional 210</td>
<td>17.5%</td>
</tr>
</tbody>
</table>
1.3 EFFECT OF DIABETES ON THYROID FUNCTION

In euthyroid individuals with diabetes mellitus, glycemic status influences serum T3 levels, basal TSH levels and TSH response to thyrotropin releasing hormone (TRH) \(^{36}\). Poorly controlled diabetes, both Type 1 and Type 2, may induce a low serum total and free T3 levels, increase in reverse T3 (rT3) but near normal serum T4 and TSH concentrations by reduction in peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3) via 5’monodeiodination reaction\(^{37}\).

Studies have shown that long term diabetic control can determine the plasma T3 levels. Diabetes that is poorly controlled may result in impaired TSH response to TRH or loss of normal nocturnal TSH peak\(^1\). TSH responses and “low T3 state” may normalize with improvement in glycemic status, however even with good diabetes control, the normal nocturnal TSH peak may not be restored in patients with totally absent pancreatic beta cell function\(^{38}\).

1.4 EFFECT OF HYPERTHYROIDISM ON GLYCEMIC STATUS

Graves Disease is the commonest cause of hyperthyroidism. Variable glucose intolerance has been noted in up to 50% of patients with Grave’s disease and in 2-3% of patients with frank diabetes, when hyperthyroidism develops in previously euglycemic individuals. In known diabetic patients, the development of hyperthyroidism results in deterioration of diabetic control. Varied metabolic changes tend to occur as a result of hyperthyroidism which contributes to the deterioration of glycemic control\(^{37}\).

Changes include accelerated gastric emptying, enhanced intestinal glucose absorption and increase in portal venous blood flow in the gastrointestinal system\(^{37}\). With regards to insulin secretion; hyperthyroidism may cause decreased insulin secretion\(^{39,40}\) or normal or increased levels of insulin in the peripheral and portal circulation\(^{41}\). There could be a masking of increase in insulin secretion due to increased degradation of insulin. In hyperthyroidism, the insulin clearance rate is reported to be increased by about 40%\(^{42}\). Long term thyrotoxicosis has been shown to cause beta cell dysfunction resulting in reduced pancreatic insulin content, poor insulin response to glucose and decreased rate of insulin secretion \(^{43}\).
Recent studies have shown that thyroid hormones cause beta cell apoptosis which contribute to deterioration in glucose control in patients with thyrotoxicosis \(^{44}\).

**Figure 1: Thyrotoxicosis effect on glucose homeostasis** \(^{66}\)

1.5 EFFECT OF HYPOTHYROIDISM ON GLYCEMIC STATUS

Hypothyroidism results in impaired or decreased liver glucose output thereby compensating for insulin resistance present in peripheral tissues and accounting for the diminished insulin requirement for glycemic control in hypothyroid diabetic patients \(^{44}\).

As regards to beta-cell function, normal or reduced basal plasma insulin levels have been described in hypothyroidism hence the attenuated endogenous glucose production in the hypothyroid state.

On the other hand, increased glucose-stimulated insulin secretion has been recently described as a response to elevated whole-body insulin resistance increasing demand on beta cells \(^{45}\).

The rate of hepatic glucose output is decreased probably due to reduced gluconeogenesis. A post receptor defect has been proposed to explain the decrease in insulin stimulated glucose utilization in peripheral tissues. The net effect is an increased risk of recurrent hypoglycemia in a diabetic individual \(^{46}\)(figure 3).
Although most of these observations apply to overt hypothyroidism, insulin resistance has been also reported in subclinical hypothyroidism ⁴⁷.

**Figure 2: Hypothyroidism effect on glucose homeostasis** ⁶⁶
Furthermore, it has been shown, both in euthyroid non-diabetic and diabetic adults, that small variations in TSH at different levels of insulin sensitivity might exert a marked effect on lipid levels \(^{48,49}\). The interaction between insulin resistance and lower thyroid function might be a key determinant for a more atherogenic lipid profile in these populations (figure 4)\(^{67}\)

**Table 2: Interaction between Diabetes mellitus and thyroid disease \(^{67}\)**

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Effect on Glycemia</th>
<th>Effect on Thyroid function/ Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus (DM)- In euthyroid individuals</td>
<td>—</td>
<td>↓ Serum T3 ↑ rT₃ ↓ TSH response to TRH Impaired nocturnal TSH peak</td>
</tr>
<tr>
<td>Diabetes Mellitus – In hyperthyroidism individuals</td>
<td>Poor glycemic control ↑ Incidence of dysthyroid optic neuropathy</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism – In euglycemic individuals</td>
<td>Glucose intolerance in 50% cases —</td>
<td>Overt diabetes in 2-3%</td>
</tr>
<tr>
<td>Hyperthyroidism- In diabetic individuals</td>
<td>Deterioration of diabetes control —</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism- In diabetic individuals</td>
<td>Predisposition to recurrent hypoglycemia —</td>
<td></td>
</tr>
<tr>
<td>In Autoimmune Type 1 individuals</td>
<td>—</td>
<td>↑ Prevalence of thyroid disease</td>
</tr>
</tbody>
</table>

**1.6 EFFECT OF THYROID DYSFUNCTION ON OTHER ORGAN SYSTEMS**

Hyperthyroidism results in deterioration of diabetic control while hypothyroidism increases the susceptibility to hypoglycemia in diabetic patients thereby complicating the diabetes management in these individuals.
1.6.1 EFFECT OF HYPOTHYROIDISM

The Rotterdam data showed that subclinical hypothyroidism was associated with a greater prevalence of aortic atherosclerosis (odds ratio 1.7) and myocardial infarction (odds ratio 2.3) unaffected by cholesterol level, blood pressure, or smoking status. The attributable risk percentage for CVD from subclinical hypothyroidism was found to be equivalent to risk factors such as dyslipidemia, hypertension, smoking status, and diabetes. Overt hypothyroidism is associated with significant increases in circulating concentrations of total and low density lipoprotein cholesterol (LDL-C). Treatment of the thyroid disorder potentially improves dyslipidemia and reduces risk for CVD.

Patients with subclinical hypothyroidism had a higher prevalence of retinopathy, especially the sight-threatening form, when compared with their type 2 diabetic euthyroid counterparts. On the other hand a retrospective analysis of a diabetes database of 6,540 patients showed a lower mortality rate in patients with elevated TSH levels at baseline (mean age of patients was 73 years) versus an age-matched euthyroid group. These results support the previous notion that the higher mortality risk in a subclinical hypothyroid patient is mainly observed in patients below 65 years of age.

In 2005, Den Hollander et al reported that treating hypothyroidism improved renal function in diabetic patients. A higher frequency of retinopathy and nephropathy was observed in diabetic patients with subclinical hypothyroidism, and more severe retinopathy was noted as well, hence management of thyroid dysfunction is important in the maintenance of good glyceamic control. Furthermore, an increased risk of nephropathy was shown in type 2 diabetic patients with subclinical hypothyroidism which could be explained by the decrease in cardiac output and increase in peripheral vascular resistance seen with hypothyroidism and the resulting decrease in renal flow and glomerular filtration rate.
1.6.2 EFFECT OF HYPERTHYROIDISM

When hyperthyroidism occurs in the setting of euglycemia, 2-3% of these individuals may become diabetic. Excess thyroid hormone resembles increased sympathetic nervous system activity by increased beta-adrenergic stimulation, leading to increased heart rate, tremors, and excessive sweating. This stimulation could interfere with diabetic patients’ ability to recognize hypoglycemia. In a patient with preexisting Graves Orbitopathy, the risk of visual loss is increased and chances of visual recovery is less if co-existing diabetes is present.

On the other hand, thyrotoxicosis can induce many cardiovascular effects such as sinus tachycardia, systolic hypertension, changes in ventricular systolic and diastolic function, and predisposition to dysrhythmias, especially atrial fibrillation.

1.7 EFFECT OF DRUGS ON THYROID FUNCTION

Several classes of drugs have been shown to contribute to thyroid hormone dysfunction especially in this particular cohort of patients. Use of oral hypoglycemic agents contributes to preexisting thyroid dysfunction. 1st generation sulfonylureas like carbutamide, chlorpropamide inhibit binding of (Triiodothyronine) T3 and (Thyroxine) T4 to TBG competitively hence affect peripheral thyroid function and they also inhibit thyroid hormone synthesis. Similar note has been made of effect of second generation sulfonylureas.

In addition most of patients on Metformin were found to have reduced TSH levels, while those on Thiazolidinediones had associated Orbitopathy. Due to fact that patients with type 2 diabetes are prone to other co-morbidities; patients with Arrhythmias on Amiodarone are prone to developing either hypothyroidism or hyperthyroidism as it inhibits peripheral conversion of T4 to T3, clearance of T4 and T3, direct cytotoxic effect on thyroid follicular cells and its metabolite desethylamiodarone acts a competitive antagonist of T3 at cardiac cellular level.
1.8 OUTCOME OF TREATMENT OF THYROID DYSFUNCTION

Velija et al.\textsuperscript{62} and Beciragic et al.\textsuperscript{63} selected a cohort of patients with type 2 Diabetes with subclinical hypothyroidism and subjected them to low dose of thyroxine at 25ug. After 1 month and 6 months of treatment, end points achieved were a sustained reduction in levels of HbA1C, fasting and post prandial glucose levels, fasting Insulin levels, levels of C reactive Proteins and levels of total cholesterol and triglycerides.

On the other hand, Fica et al.\textsuperscript{64} and Al Shoumer et al.\textsuperscript{65} selected cohort of patients with concomitant Diabetes and hyperthyroidism and treated them with Carbimazole. They noted that with stabilization of thyroid function; levels of HbA1c, fasting insulin and pro insulin levels were markedly reduced, as well as amount of Insulin needed to control Diabetes reduced after patient became euthyroid.
2.0 STUDY JUSTIFICATION

Diabetes mellitus is an important health problem affecting major populations worldwide.

Despite strides made in management of Diabetes, numerous patients still present with complications due to impaired glycemic control. Underlying thyroid disorders may go undiagnosed because the common signs and symptoms of thyroid disorders are similar to those for diabetes and can be overlooked or attributed to other medical disorders.

Thyroid dysfunction has been shown to contribute to significant cardiovascular morbidity in the general population and is particularly increased in type 2 Diabetics.

The benefit of early identification of both diseases has a significant impact on improving cardiovascular function, blood pressure, and lipid profile, thereby reducing long-term cardiovascular risk and improving quality of life for persons with diabetes.

There is paucity of data on thyroid dysfunction in type 2 diabetics in our population, implying the burden of the same may be over/under estimated.

This study may form a foundation for future studies which can influence screening and management of thyroid dysfunction in attempting to achieve glycemic control in type 2 diabetics.

3.0 RESEARCH QUESTION

What was the burden of thyroid hormone dysfunction among patients with type 2 Diabetes at KNH.
4.0 OBJECTIVES

4.1 BROAD OBJECTIVE
To determine the prevalence and patterns of thyroid hormone dysfunction in ambulant patients with type 2 Diabetes.

4.2 SPECIFIC OBJECTIVES
1. To determine Prevalence of thyroid dysfunction in patients with type 2 Diabetes.
2. To describe the Patterns of thyroid dysfunction in patients with type 2 Diabetes.

5.0 METHODOLOGY

5.1 STUDY SITE
Kenyatta National Hospital Diabetes outpatient clinics. The clinics are run on a daily basis from Monday to Thursday and Main clinic that is run on Friday. Type 2 Diabetics form the bulk of the patients about 80%.

5.2 STUDY POPULATION
Patients with Type 2 Diabetes seeking ambulatory care from Diabetes outpatient clinics at Kenyatta National Hospital.

5.3 STUDY DESIGN
Cross-sectional descriptive survey.

5.4 SAMPLE SIZE
The sample size was calculated using the following formula:
\[ n = \frac{z^2 \times p(1-p)}{d^2} \]

\[ n = \text{minimum sample size required} \]
\[ z = \text{confidence interval at 95% (standard value of 1.96)} \]
\[ p = \text{estimated prevalence of thyroid dysfunction from Al Wazzan et al, 2009 study} = 12.9^{34} \]
\[ d = \text{margin of error (0.05)} \]
\[ N = (1.96)^2 \times 0.129(1-0.129) \]
\[ (0.05)^2 \]
The minimum sample size for this study was 172 patients with Type 2 Diabetes. To cater for hemolysed or lipemic samples. Data was collected from a minimum of 181 patients.

5.5 SAMPLING METHOD

Patient inclusion was done by perusing through the files to select the patients with type 2 Diabetes.
Systematic random sampling was used in selecting the cases, whereby patients were allocated numbers such that every third patient was included in the study after obtaining written informed consent.

5.6 CASE DEFINITION

5.6.1 TYPE 2 DIABETES—

Patients previously diagnosed to have type 2 Diabetes and are currently on management and follow up at Diabetic outpatient clinic.

5.6.2 THYROID HORMONE REFERENCE RANGES

Table 3: Assay of thyroid hormones

<table>
<thead>
<tr>
<th>Assay</th>
<th>Adult</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4</td>
<td>0.8-2.0 ng/dl</td>
<td>0.8-2.2 ng/dl</td>
</tr>
<tr>
<td>TSH</td>
<td>0.3-6.2 mIU/l</td>
<td>0.3-6.2 mIU/l</td>
</tr>
</tbody>
</table>

The reference ranges used in this particular study were based on manufacturers test kit as there are no population reference ranges available for African population.
Table 4: Interpretation of thyroid hormones

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>TSH</th>
<th>fT3</th>
<th>fT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt Hypothyroidism</td>
<td>Increased</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Subclinical Hypothyroidism</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Overt Hyperthyroidism</td>
<td>Reduced</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Subclinical Hyperthyroidism</td>
<td>Reduced</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Secondary Hyperthyroidism</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Secondary Hypothyroidism</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Sick Euthyroid Syndrome</td>
<td>Normal</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
</tbody>
</table>

5.7 INCLUSION AND EXCLUSION CRITERIA

5.7.1 INCLUSION CRITERIA
1. Patients diagnosed to have type 2 Diabetes.
2. Age above 30 years.
3. Written informed consent.

5.7.2 EXCLUSION CRITERIA
1. Patients diagnosed to have type 1 Diabetes.
2. Patients who fail to give consent.
3. Patients below the age of 30 years.
5.8 SCREENING AND RECRUITMENT AND CONSENTING

The principal investigator (PI) with the help of research assistants reviewed files of patients attending the Diabetes outpatient clinics. The files of patients who met the criteria were selected. The patients were then given all the relevant information about the study and those who gave written informed consent (appendix I) were recruited.

5.9 PROCEDURES

5.9.1 CLINICAL EXAMINATION

A Brief history and physical examination were done. The duration of Type 2 Diabetes, associated co-morbidity i.e Hypertension and medication were sought from patient records. This information was then entered into the study proforma (appendix II) for analysis.

5.9.2 LABORATORY METHODS

5.9.2.1 Specimen Collection, Transportation and Storage

Four mls of blood was collected from each patient and immediately put in a plain vaccutainer (red top) and subsequently delivered to the Immunology laboratory at the end of the day’s collection for storage and batch assaying once the study sample size is achieved. Cooler boxes with ice packs at approximately 4º C (2-8 ºC) were used for temporary storage to facilitate transport to the laboratory. Serum was separated, which was frozen & stored in the laboratory. Batch assaying was done once required numbers of samples were achieved. Specimens were only thawed once. Thawed specimen were homogenized. Particulate matter was eliminated by centrifugation or filtration.

5.9.2.2 Specimen analysis

TSH: Principle of assay for Thyroid Stimulating Hormone is based on the classic sandwich ELISA technique. It makes use of the extremely high affinity of the system Biotin-Streptavidine. Streptavidine is coated on the surface of microtitre wells and along with specimens, controls and enzyme conjugate (peroxidase labelled anti-TSH) and a second biotinylated monoclonal anti-TSH are mixed to form the sandwich complex bound to the surface
of the wells by interaction of biotin with immobilized streptavidine. The kit method was followed for analysis of TSH.

**FT4:** Principle of assay for free Thyroxine is competitive binding between fT4 in a test specimen and T4 peroxidase conjugate for a limited number of binding sites on the anti-T4 (monospecific, sheep) coated well. The kit method was followed for analysis of fT4.

### 5.10 QUALITY ASSURANCE

Standard operating procedures for specimen collection, preparation and storage were followed to minimize pre-analytical errors. To ensure quality was maintained, the laboratory tests were carried out in Immunology laboratory, University of Nairobi. Calibration of machines was ensured and standard Internal quality control was run with each batch of tests. Random number of samples i.e. about ten samples, with each sample selected after every twenty samples taken, were used for verification at a private laboratory for purpose of external quality control. Highly lipemic or hemolysed specimens were not used but replaced with others. Internal quality control was used for each assay and only results which passed Internal Quality control were reported.
5.11 STUDY VARIABLES AND DEFINITIONS

5.11.1 INDEPENDENT VARIABLES

This included the following socio demographic and clinical variables;

Age: It was determined to be nearest number of years as the period from the reported or documented date of birth.

Gender: It was determined by the observed phenotypical sex, which is, observed secondary sexual characteristics of male or female sex.

Duration of disease: This was determined as the period in the nearest number of years from the reported or documented date of disease onset. The date of disease onset was the date when the patient learnt about the diagnosis for the first time or documentation of the date when the diagnosis was made for the first time.

Treatment modality: This was defined as the current pharmacotherapeutic modalities being employed by the patient to achieve glycemic control. 3 categories of treatment modalities were used; Oral antidiabetic agents, Insulin, Insulin and oral anti diabetic agents.

5.11.2 DEPENDENT VARIABLES

Serum thyroid hormone levels i.e. T4, TSH.

5.12 DATA MANAGEMENT AND ANALYSIS

Data was entered into a password protected Microsoft Access database managed by the statistician. Once data entry was complete, data from the Microsoft Access Database was compared with data on the hard copy forms to ensure accuracy. Inconsistencies were detected by running simple frequencies and correlations and those identified were addressed before data analysis began.

Data was summarized using tables, pie charts, histograms, bar charts and line graphs where necessary. Continuous data e.g. age, duration of Diabetes mellitus, blood pressure, weight, height, BMI, TSH and fT4 were summarized using measures of central tendency (Means, Medians, mode, minimum, maximum and standard deviations). Nominal variables e.g. gender, marital status, education level, types of medication used, history of thyroid disease or management of
thyroid disease, clinical evaluation of thyroid disease and patterns of thyroid dysfunction were summarized using counts, frequencies and proportions. Analysis was done using SPSS version 17.0.

5.13 STUDY ADMINISTRATION
It was the responsibility of the PI to brief the study patients about the study. The PI would then subsequently recruit those willing to participate in the study and obtain their informed consent. The research assistants would work with the PI to ensure that data was collected efficiently, on time and that it was recorded accurately. All recorded data was verified by the PI, who would also ensure that all relevant forms were completed. The supervisors offered guidance to the PI throughout the process. The statistician did offer guidance during proposal development, data entry, analysis and presentation of the final statistical analysis.

5.14 ETHICAL CONSIDERATIONS
The study was undertaken after approval by the Department of Clinical Medicine & Therapeutics and the KNH/UON Ethics and Research Committee. The objectives and purposes of the study were clearly explained to eligible participants in a language suitable to them prior to inclusion into the study. Only patients who gave informed consent were enrolled. Patients were free to withdraw during the study period without discrimination. Information gathered from the study participants was kept confidential. Only blood samples intended for study were drawn and thereafter discarded after analysis. The study results were disseminated to health care providers to aid in patient care.
6.0 RESULTS

Figure 4: Results

A total of 190 patients were evaluated from diabetes outpatient clinics that were eligible for inclusion in the clinical evaluation and laboratory testing. Three patients declined consent because they had previously been involved in other research studies earlier in the year. The number of patients evaluated was 187. However during sample collection, 6 samples were noted...
to be haemolysed hence not suitable to be run for thyroid function tests, hence discarded. A total of 181 active patients were analysed for the clinical and laboratory outcomes of thyroid dysfunction.

The social demographic characteristics of the 181 patients studied are summarised in table 5 below:

**Table 5: Socio demographic characteristics of patients with type 2 diabetes**

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68</td>
<td>37.6</td>
</tr>
<tr>
<td>Female</td>
<td>113</td>
<td>62.4</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>11</td>
<td>6.1</td>
</tr>
<tr>
<td>Married</td>
<td>149</td>
<td>82.3</td>
</tr>
<tr>
<td>Divorced</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>Separated</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Widowed</td>
<td>16</td>
<td>8.8</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>36</td>
<td>19.9</td>
</tr>
<tr>
<td>Secondary</td>
<td>52</td>
<td>28.7</td>
</tr>
<tr>
<td>Tertiary</td>
<td>60</td>
<td>33.1</td>
</tr>
<tr>
<td>None</td>
<td>33</td>
<td>18.2</td>
</tr>
</tbody>
</table>

The population comprised mainly of females at 62.4% compared to males at 37.6%. About 82.3% were married, with over 81.7% having attained some form of education (table 5).
Table 6: Clinical and other demographic parameters of patients with type 2 Diabetes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.37(12.32)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>30-97 years</td>
</tr>
<tr>
<td>Duration of Diabetes</td>
<td>9.56(7.16)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-43 years</td>
</tr>
<tr>
<td>BMI</td>
<td>29.88(6.11)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Min-Max</td>
<td>18.39-60.20</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>143(23) mmhg</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>Min-Max</td>
<td>100-200 mmhg</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>76(15) mmhg</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Min-Max</td>
<td>40-110mmhg</td>
</tr>
</tbody>
</table>

The average age of the patients with Type 2 Diabetes was 59 years ± 12.32 ranging from 30-97 years. The average duration was about 9.56 years ± 7.16, ranging from 1 year to 43 years. The mean BMI as per WHO standards was 29.88, predominantly overweight population. The average systolic BP was 143 ± 23mmhg while Diastolic BP was 76+15 mmhg.(table 6).
On further elaboration, it was noted majority of patients were mainly in the group of between 40 and 70 years, with a peak between 60 years and 70 years. This indicated population in this study was predominantly an elderly population (figure 5).
In this study population, over 60% of patients had a duration of 1 to 10 years since diagnosis of type 2 diabetes, and of note is as the number of years exponentially increased of having type 2 diabetes, the fewer the number of patients, more of an indication of natural progression of the disease (figure 6).
Table 7: Medication used by the study patients with type 2 Diabetes:

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Metformin</td>
<td>131</td>
</tr>
<tr>
<td>1st Gen Sulfonylureas</td>
<td>28</td>
</tr>
<tr>
<td>2nd Gen Sulfonylureas</td>
<td>4</td>
</tr>
<tr>
<td>Insulin</td>
<td>104</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>9</td>
</tr>
</tbody>
</table>

All the patients who were studied were on combination drugs rather than single drug medications for Type 2 diabetes. Most of patients were either on Metformin (72.4%) or Insulin (57.5%) as basic medication with other drugs. (table 7).

Table 8: History of thyroid disease or management in patients with type 2 Diabetes

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Family history of Thyroid disease</td>
<td>41</td>
</tr>
<tr>
<td>History of Thyroid surgery</td>
<td>10</td>
</tr>
<tr>
<td>History of radioiodine ablation</td>
<td>1</td>
</tr>
<tr>
<td>History of Diagnosis of Thyroid disease</td>
<td>7</td>
</tr>
<tr>
<td>Patient on medication for Thyroid dysfunction</td>
<td>1</td>
</tr>
</tbody>
</table>
It was noted that 22.7% of patients had family history of thyroid disease in a first degree relative. In this population about 10.6% were previously diagnosed to have some form of thyroid dysfunction, i.e. 5.5% had surgery in form of partial or total thyroidectomy, 1 patient had radiiodine ablation and only one patient was currently on medication for thyroid dysfunction. This indicated that this population already had a significant number of patients with preexisting thyroid dysfunction (table 8).

**Figure 7: BMI of type 2 Diabetes mellitus patients**

![BMI Chart]

It was noted in this population, over 72% of these participants were overweight or Obese, with only 18.4% having normal weight as per WHO standards (figure 7).
Table 9: Clinical evaluation for Thyroid dysfunction in study participants:

<table>
<thead>
<tr>
<th>No. of patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Evidence of Thyroid enlargement</td>
<td>4</td>
</tr>
<tr>
<td>Evidence of protruding eyes</td>
<td>10</td>
</tr>
<tr>
<td>Evidence of puffy face</td>
<td>20</td>
</tr>
<tr>
<td>Evidence of hand tremors</td>
<td>8</td>
</tr>
</tbody>
</table>

This population did not have examination findings in keeping with thyroid disease and some of findings could also have been attributed to Type 2 diabetes or its complications (table 9).

Table 10: Thyroid Function tests results of patients with type 2 Diabetes:

<table>
<thead>
<tr>
<th>Mean/</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Percentile 25</th>
<th>Percentile 75</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH 0.3-4.0 mIU/ml</td>
<td>8.98</td>
<td>7.50</td>
<td>.20</td>
<td>39.40</td>
<td>4.30</td>
<td>12.80</td>
</tr>
<tr>
<td>FT4 0.8-2.2 ng/dl</td>
<td>1.04</td>
<td>1.03</td>
<td>.30</td>
<td>1.60</td>
<td>.90</td>
<td>1.20</td>
</tr>
</tbody>
</table>

The average TSH was elevated in majority of these patients with an elevated median of 7.50 ± 5.93. Whereas, fT4 was normal i.e. within reference range i.e. 1.03 ± 0.20 (table 10).
It was noted that only 39\% of the patients were euthyroid, with majority of the study participants having subclinical hypothyroidism at 58\% and only 2\% had overt hypothyroidism. The prevalence of thyroid dysfunction in this population was approximately 61\% (figure 8).
7.0 DISCUSSION

Diabetes mellitus is a major problem in populations worldwide and despite advances in treatment a large number of patients present with complications due to poor glycaemic control. One of the possible factors that contribute to poor glycaemic control is thyroid dysfunction, which tends to occur concomitantly with diabetes mellitus. This study sought to find out the prevalence of thyroid dysfunction in patients with type 2 diabetes mellitus.

The study population consisted mainly of females at 62.4%, who were predominantly elderly as per WHO standards with a mean age of 59 years and had been diagnosed to have type 2 Diabetes for an average of 9.5 years. Most of the patients were either on Metformin at 72.4% or Insulin at 57.5%. It was important to note that up to 22.7% of patients had a positive family history of thyroid disease and 10.6% of patients had preexisting thyroid dysfunction. Enquiries into symptoms suggestive of hypothyroidism or hyperthyroidism were not fruitful, with very few patients experiencing overt symptomatology. Overall prevalence of thyroid dysfunction was 61%, with majority having subclinical hypothyroidism at 58% and only 2% had overt hypothyroidism.

The study population was predominantly female at 62.6% and males at 37.4% giving a ratio of female: male at 1.6:1. This is comparable to studies done locally, Saira et al72 found female predominance at 58%, as well as Omari et al71, who found female predominance of 60%. This could be partly explained by the fact that autoimmune diseases tend to occur predominantly in females.

Most of the study participants were mainly on combination medication i.e. either Metformin as backbone of medication at 72.4% or Insulin at 57.5%. Very few patients were on 1st or 2nd generation sulfonylureas at only 17.7%. This is comparable to what was found locally by Saira et al72 whereby, 51.6% were on Insulin and other oral hypoglycemic agents, Omari et al71 found 61% to be on Insulin with oral hypoglycemic agents. It has been noted in other studies eg. Bassyouni et al69, found use of Insulin at 82% in population of patients with type 2 Diabetes attending medical clinics at National Institute of Diabetes and Endocrinology (NIDE). This high prevalence of insulin use could be due to longer duration of disease hence higher likelihood of
complications. It was important to know the type of medication used by these study participants as the medication used may alter thyroid function tests.

Insulin is an anabolic hormone which enhances levels of fT4 while suppressing T3 levels by inhibiting conversion of T4 to T3, while phenylthioureas suppress levels of fT4 and T4. Metformin on the other hand, inhibit binding of T4 and T3 to Thyroxine binding globulin, thereby inhibiting thyroid hormone synthesis but it also reduces TSH. This then indicates that medication used by patients with type 2 Diabetes may alter thyroid function; hence care should be taken when interpreting thyroid function tests in this cohort of patients.

The mean age of our study participants was 59 years, a predominantly elderly population. This is comparable to Celani et al who found a mean age of 60 years in study participants in a study conducted in a hospital in Italy, and Papazafiroupoulou et al in their study conducted in a Greek hospital in patients with type 2 diabetes, mean age was noted to be slightly higher than ours at 65 years. This is similar to other studies that have shown population of patients with type 2 diabetes is predominantly of older age group.

It was also noted in these study participants, a wide age range of 30-97 years, and this has also been noted in other studies like Diez et al in Spain, Bal et al in India. Of note, however is that majority of patients were above age of 60 years, hence higher likelihood of developing thyroid dysfunction. Population surveys done by Canaris et al in the Colorado thyroid disease prevalence revealed that prevalence of thyroid dysfunction is about 6.6%, with prevalence at 18 years being 3.5% and increasing to about 18.5% as one reaches 65 years and above. It is postulated that aging leads to development of organ specific and non organ specific antibodies, hence higher prevalence of autoimmune thyroid dysfunction.

The mean duration of diabetes in this subset of population was 9.5 years; however this could have been an underestimation since it was based on documentation from time of diagnosis, although most patients had reported symptoms earlier. There was a wide duration between 1 and 43 years and as duration extended beyond 10 years, number of patients significantly reduced possible relating it to natural history of the disease. This is comparable to Al-Wazzan et al in
Kuwait\textsuperscript{34}, who found a median duration of 10 years, while Radaideh et al in Jordan\textsuperscript{23} found a median duration of 8.3 years. However, previous studies like Al-Wazzan et al\textsuperscript{34} have not been able to demonstrate a correlation between duration of diabetes mellitus and subsequent development of thyroid dysfunction. It is more likely that one develops thyroid dysfunction as a result of aging.

A large proportion of patients had a positive family history of thyroid dysfunction at 22.7\% and this could probably have contributed to high prevalence of thyroid dysfunction in this subset of the population. This was also noted by Al-Wazzan et al\textsuperscript{34} who found family history of 17.6\% in a cross section of the population in Saudi Arabia, further sub analysis of these patients when done thyroid auto antibodies were significantly elevated, hence there could be genetic component in this cohort of patients with type 2 Diabetes.

The prevalence of patients previously diagnosed to have thyroid dysfunction was 10.6\%, with 5.5\% having previously had thyroidectomy done and the rest (4.5\%), had either received radioactive iodine ablation, were on medication or were diagnosed but not yet on medication. This could have also contributed to high overall prevalence of thyroid dysfunction. Other similar studies have shown prevalence of 22.7\% as noted by Diezet et al\textsuperscript{67} in Spain and 6.7\% by Perros et al in Scotland\textsuperscript{31}. However, the difference in prevalence could be due to effectiveness of screening programmes for thyroid dysfunction available in different countries.

The study participants had very few symptoms suggestive of overt thyroid dysfunction in form of hyperthyroidism or hypothyroidism. This could be attributed to the fact that majority of the patients had subclinical form of hypothyroidism and it is often difficult to diagnose thyroid dysfunction based solely on symptomatology as there is considerable overlap between the two endocrinopathies.

The study participants had associated co morbidities like hypertension, whose prevalence was 100\% and at the time of study were found to have poorly controlled hypertension in spite of being on medication. This is comparable to Ghazali et al\textsuperscript{68} in Nigeria who found in a cross section of Nigerian patients with type 2 diabetes, prevalence of hypertension was 87.5\% and
Papazafiropoulou et al in Greece was 85%. Due to the fact that population was elderly, likelihood of having other co morbidities like hypertension was high; hence results were as expected in this particular cohort of patients. However, it is not known to what degree the effect of thyroid dysfunction has with regards to development of hypertension due to other variables like age and hyperlipidemia.

The prevalence of Obesity in this subset of population was remarkably high at 72%, with a mean BMI of 29.8, which is similar to local studies eg. Saira et al found average BMI of 28.7%. Similar to Bassyouni et al in Egypt, who found patients with type 2 Diabetes to have BMI of 31 and so did Papazafiropoulou et al in Greece, found BMI of 31. This high prevalence however could be due to underlying Diabetes mellitus or presence of hypothyroidism, mainly subclinical or a combination of both disease processes or as a result of intervention in form of Insulin use in these patients.

The thyroid function tests were carried out using ELISA to assess for TSH and fT4, similar to method used by Pasupathi et al and Radaideh et al. The prevalence of thyroid dysfunction in the study participants was 60%, with majority having subclinical hypothyroidism at 58%, 2% had overt hypothyroidism and only 1 subject had subclinical hyperthyroidism.

The overall prevalence is almost similar to what was found by Pimenta et al and Bazrafasham et al who found 51.6% and 47.5% respectively. Our study included patients already diagnosed to have thyroid dysfunction hence possible reason as to why it was higher than the other studies. However this is in contrast to Radaidehet al and Perros et al who found prevalence of 12.5% and 13.5% respectively. Possible reason could be the age group in our population was mainly elderly and had a higher prevalence of women compared to this other studies.

In this study, we found similar results to what has been found in earlier studies done in other populations and due to fact that we found a high prevalence, it would be important to screen general population who are found to be elderly with diabetes.
8.0 CONCLUSION

• Prevalence of thyroid dysfunction is high at 61% in this population of patients with type 2 Diabetes.
• High prevalence of subclinical hypothyroidism at 58% in this population.

9.0 LIMITATIONS

Due to financial constraints:

• Unable to assess glycaemic control and lipid profile and correlate it with regards to thyroid dysfunction.
• Unable to do T3 assay.
• Unable to do thyroid autoantibody assays in this population.

10.0 RECOMMENDATIONS

• In view of the high prevalence of subclinical hypothyroidism that was found in this population with type 2 Diabetes, it would be advisable to screen such patients at diagnosis and follow them up periodically.
• Further research needs to be done with regards to thyroid antibodies bearing in mind strong family history and high prevalence of thyroid dysfunction in this population.
11.0 REFERENCES


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17. VanderpumpMP ,Tunbridge WM ,French JM et al. The Incidence of thyroid disorders in the community;a twenty year follow up of the Whickham Survey.


55. Sathyapalan T, Manuchehri AM, Rigby AS et al. Subclinical hypothyroidism is associated with reduced 11-cause mortality in patients with type 2 diabetes. *Diabetes Care* 2010; 33:e37


72. Saira S et al. Prevalence of poor sleep quality and high risk of obstructive sleep apnoea in ambulant individuals with type 2 diabetes mellitus attending outpatient clinics at the Kenyatta National Hospital. *(Mmed Thesis) University of Nairobi* 2013.


12.0 APPENDICES

APPENDIX 1: DATA ABSTRACTION TOOL

Study number ___________________________ Date: ___________________________

1. Age: ___________________________

2. Gender: Male----- Female -------

3. Marital status (Tick one):
   Single ---- Married ---- Divorced ---- Separated ---- Widowed ----

4. Level of education (tick one):
   Primary----- Secondary----- Tertiary----- None -----

5. Duration of Diabetes ________________

6. Type of medication used for Diabetes________
   ___________________________
   ___________________________
   ___________________________

7. Other medication other than Oral hypoglycemic agents or Insulin______________

8. Hypertension Present------ Absent -------------

9. Family history of thyroid disease Yes------ No-------

10. History of Thyroid surgery Yes------ No-------

11. History of radioiodine ablation Yes------ No-------

12. History of Diagnosis of Thyroid disease Yes ------ No -------
   If yes, which type of thyroid dysfunction _________
   Is the patient on medication for thyroid dysfunction Yes------ No-------

13. Do you have any of the symptoms below :( Tick where appropriate)
   Symptoms of Hypothyroidism like:  Symptoms of Hyperthyroidism like:
   Sensitivity to cold-----  Insomnia--------
   Puffy face-------------  Irritability----------
   Poor memory--------  Unexplained weight loss-------
   Constipation---------  Palpitations------------
   Depression----------  Brittle hair-------------
Dry skin---------------- Hand tremors----------------
Hoarse voice--------- Warm, flushed skin---------
Weight gain---------- Protruding eyes-----------

Physical Examination
Temp...........°C PR....................../min RR.............../min BP .................mm/Hg
Weight.........Kg Height.......... m BMI...............Kg/m²

Local exam: Evidence of Thyroid enlargement. Yes---- No-----
Evidence of protruding eyes Yes---- No-----
Evidence of puffy face Yes---- No-----
Evidence of hand tremors Yes---- No-----
## APPENDIX 2: BUDGET

<table>
<thead>
<tr>
<th>ITEM</th>
<th>COST (K/SH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STATIONERY AND PRINTING</td>
<td>20,000</td>
</tr>
<tr>
<td>LABORATORY</td>
<td>120,000</td>
</tr>
<tr>
<td>STATISTICIAN</td>
<td>25,000</td>
</tr>
<tr>
<td>2 RESEARCH ASSISTANTS</td>
<td>30,000</td>
</tr>
<tr>
<td>CONTINGENCY / MISCL</td>
<td>20,000</td>
</tr>
<tr>
<td>ETHICS FEES</td>
<td>2,000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>217,000</strong></td>
</tr>
</tbody>
</table>