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Factors associated with hypothyroidism among patients attending primary health care clinics in Hebron governorate: A case-control study

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Factors associated with hypothyroidism among patients attending primary health care clinics in Hebron governorate: A retrospective case-control study

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Thesis Approval

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Jerusalem – Palestine

1435 - 2014

DEDICATION

To my dear parents

To my dear brothers and sisters

DECLERATION

I certify that this thesis submitted for the degree of Master is the result of my own research, except where otherwise acknowledged and that this thesis (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Mustafa Mahmoud Barham

Jerulsalem

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ABSTRACT

Background: Several risk factors are associated with hypothyroidism, which are divided into socio- demographic factors, lifestyle factors, family history of autoimmune disease, and medical condition such as having diabetes type 1. Obesity was also shown to be a risk factor for having hypothyroidism and vice versa. However, no study focused on hypothyroidism in Palestine which makes it a rich area for investigation due to its importance in preventing its occurrence and/or any of its complications.

Aim: The aim of the study was to determine the risk factors associated with hypothyroidism among patients attending the primary health care clinics in Hebron District. The main objective was to examine the associations between socio- demographic factors; lifestyle factors; family history of autoimmune disease; history of diagnosis; medical condition; and medication with the incidence of hypothyroidism.

Study methodology: The study was carried out in two main endocrinology clinics; the Karantina and Dora clinics. The study was done in two stages: descriptive analysis (stage 1) and a case-control study (stage 2). In stage 1, All files present in the two selected clinics were included in the study. In the second stage, 206 participants; including 103 cases and 103 controls participated in the study. The control group comprised of patients attending other sub specialist clinics. Data were collected through face-to-face interview using a structured questionnaire. TSH test was done to all control participants in order to exclude the probability of having undiagnosed hypothyroidism.

All data were analyzed using IBM-SPSS software. For stage 1, frequencies of all variables were calculated and data were presented in figures and tables. For stage 2, univariate analysis were presented showing the association between hypothyroidism and the studied determinants. T-test was used to examine the difference of TSH levels between cases and controls. Also, multiple logistic regression was done to all statistically significant variables in the univariate analysis to obtain the odds ratio (OR) and 95% confidence interval. For all analysis significance was set with p-values ($P<0.05$).

Results: Stage 1 results showed that hypothyroidism was the most diagnosed endocrine disorder with the prevalence of 17.1% among patients attending the clinics. In addition, hypothyroidism subtypes rates were 87.0% for primary hypothyroidism, 5.2% for secondary hypothyroidism and 7.8% for congenital hypothyroidism. These types of hypothyroidism were shown to be associated with turner syndrome, thyroid cancer, goiter, thyroidectomy, postpartum thyroiditis, diabetes type 1, hypopituitarism and beta thalassemia.

In stage 2, the multiple regression model showed that living area, working status and household monthly income were associated with hypothyroidism (P <0.05). furthermore, daily physical activity and smoking by others in closed places were significantly associated with hypothyroidism (P<0.05). Moreover, consumption of carrots, banana, and red meat were associated with hypothyroidism (P <0.05). While, iron intake was the only food supplement intake that was significantly associated with hypothyroidism (P <0.05).

Conclusion and Recommendation: Although this study is a clinical based study, its results emphasized on the role of positive effect (i.e. monthly income, passive smoking, consumption of carrots and red meat intake) and negative effect (i.e. working status, living area, physical activity rate, consumption of bananas and iron supplement intake) in acquiring hypothyroidism. These factors are important in setting preventive measures for hypothyroidism.

The study results are important for future planning of policies including setting a national screening program for hypothyroidism & risk factors that will help to prevent and/or delay of its complications or any of its related disabilities. Further population based epidemiological studies are needed to establish the accurate prevalence and predominant etiological factors of thyroid disorders.

العوامل المرتبطة بقصور الغدة الدرقية بين المرضى الذين يراجعون عيادات الرعاية الصحية الأولية في محافظة الخليل: دراسة الحالات والشواهد.

إعداد: مصطفى برهم

اسم المشرف: د. نهى الشريف

ملخص الدراسة

خلفية الدراسة: يرتبط مرض قصور الغدة الدرقية بالعديد من عوامل الخطر، والتي تنقسم إلى: العوامل الاجتماعية والديموغرافية، وعوامل نمط الحياة، والتاريخ العائلي لأمراض المناعة الذاتية، والحالة الصحية للمريض مثل كونه مريض بداء السكري من النوع الأول. أيضا،أظهرت العديد من الابحاث بأن السمنة هي أحدي العوامل المرتبطة بقصور الغدة الدرقية، والعكس صحيح. ومع ذلك، لم تعنى أي من الدراسات الصحية في فلسطين بـأمراض قصور الغدة الدرقية، مما يجعل من هذه الدراسة ذات اهمية كبيرة للوقاية من حدوث قصور الغدة الدرقية أو أي من مضاعافاتها.

أهداف الدراسة: ان الهدف الرئيس لهذه الدراسة هو تحديد عوامل الخطر المرتبطة بقصور الغدة الدرقية بين المرضى الذين يراجعون عيادات الرعاية الصحية الأولية الحكومية في محافظة الخليل. اما الاهداف الفرعية فتتلخص باختبار العلاقة بين العوامل الإجتماعية الديموغرافية، وعوامل نمط الحياة، والتاريخ العائلي لأمراض المناعة الذاتية، وتاريخ التشخيص، والحالة الصحية للمريض، والأدوية التي يتناولها، ومدى حدوث قصور الغدة الدرقية.

منهجية الدراسة: أجريت هذه الدراسة في عيادتي الغدد الرئيسة في محافظة الخليل: وهي عيادة الكرنتينا، وعيادة دورا وقد أجريت الدراسة على مرحلتين: الأولى التحليل الوصفي، والثانية دراسة الحالات- والشواهد.

تضمنت المرحلة الأولى جميع سجلات المرضى في العيادتين، أما المرحلة الثانية فقد تكونت عينة الدراسة من 206 مشاركا، 103 مرضى مصابين بقصور الغدة الدرقية (الحالات)، فيما تم اختيار 103 أشخاص كعينة ضابطة من المرضى الذين يراجعون العيادات المتخصصة الفرعية الأخرى. وقد تم جمع البيانات من خلال المقابلة وجها لوجه باستخدام استبيان، فيما تم إجراء فحص مستوى هرمون الغدة الدرقية (TSH) لجميع المشاركين في العينة الضابطة من أجل استبعاد احتمال وجود قصور الغدة الدرقية لديهم.

تم إدخال جميع ادخال البيانات وتحليلها باستخدام برنامج SPSS-IBM. ففي المرحلة الأولى، تم حساب التكرارات لجميع المتغيرات، وقد عرضت البيانات في جداول وأشكال بيانية، أما في المرحلة الثانية تم المتغيرات لفحص العلاقة بين قصور الغدة الدرقية مع عوامل الإختطار عند مستوى الدلالة الاحصائية ($P < 0.05$)، كما تم حساب فحص العامل المستقل (t-test) لرصد اختلاف مستويات TSH بين حالات الدراسة والمجموعة الضابطة، كذلك تم حساب نموذج الانحدار اللوجيستي المتعدد لجميع المتغيرات عند الدلالة الاحصائية ($P < 0.05$) في تحليل وحيد المتغير للحصول على نسبة الترجيح ودرجة الثقة (95%).

النتائج الرئيسية: أظهرت نتائج تحليل البيانات في المرحلة الأولى من الدراسة في ملفات المرضى أن مرض قصور الغدة الدرقية الأكثر تشخيصا بين أمراض الغدد التي تم تشخيصها بين المرضى الذين يراجعون عيادات الرعاية الصحية الأولية في محافظة الخليل، وكان معدل انتشار قصور الغدة الدرقية بين المراجعين 17.1% (16.9% في الكرنتينا، 17.5% في دورا). كما أظهرت النتائج أن أنواع قصور الغدة الدرقية هي على النحو الأتي: قصور الدرقية الأولي87.0%، وقصور الدرقية الثانوي 5.2%، وقصور الغدة الدرقية الخلقي 7.8%، وكانت هذه الأنواع مرتبطة مع متلازمة تيرنر، وسرطان الغدة الدرقية، والدراق، والتهاب الغدة الدرقية ما بعد الولادة، ومرض السكري النوع 1، ومرض قصور الغدة النخامية، ومرض الثلاسيميا.

وفي المرحلة الثانية من الدراسة أظهرت نتائج نموذج الانحدار اللوجيستي المتعدد أن منطقة المعيشة والعمل والدخل الشهري للأسرة يرتبط مع قصور الغدة الدرقية، حيث جاءت قيمة مستوى الدلالة الإحصائية أقل من 5%، بالإضافة إلى أن معدل النشاط البدني اليومي والتدخين من قبل الآخرين في أماكن مغلقة يرتبط مع قصور الغدة الدرقية، حيث جاءت قيمة مستوى الدلالة الإحصائية أقل من 5%، وعلاوة على ذلك ارتبط استهلاك الجزر واستهلاك الموز واستهلاك اللحوم الحمراء مع قصور الغدة الدرقية، حيث جاءت قيمة مستوى الدلالة الإحصائية أقل من 5%، وإضافة إلى ذلك كان تناول مكملات الحديد هو الوحيد بين مكملات الفيتامينات مرتبطا مع قصور الغدة الدرقية، حيث جاءت قيمة مستوى الدلالة الإحصائية أقل من 5%.

الاستنتاج والتوصيات: على الرغم من أن هذه الدراسة هي دراسة تطبيقية سريرية، إلا أن نتائجها أكدت على الدور الايجابي لكل من الدخل الشهري والتدخين السلبي واستهلاك الجزر واستهلاك اللحوم الحمراء، والدور السلبي لكل من منطقة المعيشة والعمل ومعدل النشاط البدني واستهلاك الموز وتناول مكملات الحديد في تحديد قصور الغدة الدرقية، هذه العوامل مهمة في وضع تدابير وقائية لقصور الغدة الدرقية.

فإن نتائج هذه الدراسة ذات أهمية كبيرة للتخطيط المستقبلي للسياسات المتعلقة بامراض الغدد الصماء، مثل وضع برنامج الفحص الوطني الذي من شأنه أن يمنع حدوث قصور الغدة الدرقية أو يحد من مضاعفاتها، كما أن هناك حاجة إلى المزيد من الدراسات الوبائية السكانية من أجل تحديد معدلات الانتشار الدقيق والعوامل المسببة لأمراض الغدة الدرقية.

LIST OF ABBREVIATIONS

MOH	Ministry of Health
UNRWA	United Nation Refugees Work Agency
NGOs	Non-governmental organizations
PMMS	Palestinian Military Medical Services
PCBS	Palestinian Central Bureau Statistics
ATA	American Thyroid Association
AACT	American Association of Clinical Endocrinologist
BTF	British Thyroid foundation
ATID	Autoimmune thyroid disease
SCH	Subclinical Hypothyroidism
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
PA	Pernicious Anemia
TS	Turner Syndrome
SLE	Systemic Lupus Erythematosus
RA	Rheumatoid Arthritis
PSS	Primary Sjogren's Syndrome
CD	Celiac Disease
MS	Multiple Sclerosis
PPTD	Postpartum thyroiditis
GO	Graves' Ophthalmopathy
HT	Hashimoto's Thyroiditis
GD	Graves' Diseases
AT	Atrophic Thyroiditis
RAI	Radioactive iodine
CBZ	Carbimazole
MMI	Methimazole
PTU	Propylthiouracil
I	Iodine
Se	Selenium
TSH	Thyroid Stimulating Hormone
T4	Thyroxine
T3	Triiodothyronine
TPOAb	Thyroid peroxidase antibody
TG	Thyroglobulin
ATA	Anti-thyroglobulin
L-T4	levothyroxine
SPSS	Statistic Package for Social Science
SD	Standard deviation
OR	Odds ratio
CI	Confidence Interval
HR	Hazard Ratio

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Chapter 1: Introduction

1.1 Background

Hypothyroidism is defined according to the American Thyroid Association as" an underactive thyroid gland, means that the thyroid gland cannot make enough thyroid hormone to keep the body running normally ". The common causes are autoimmune disease, surgical removal of the thyroid, and radiation treatment (ATA, 2012a).

Hypothyroidism is classified into two types: primary and secondary hypothyroidism. Primary hypothyroidism is the most common type and it is caused by disorder of thyroid gland itself. Central or secondary hypothyroidism results from hypothalamic or pituitary disease (Jayakumar, 2011). Also, hypothyroidism can be classified on the basis of severity into subclinical hypothyroidism and overt or frank hypothyroidism. Subclinical hypothyroidism is referred to as mild hypothyroidism, as an abnormal serum thyroid-stimulating hormone level and free thyroxin and triiodothyronine levels within their reference ranges (Wilson and Curry, Jr., 2005b). The overt or frank hypothyroidism, is defined as an elevated TSH and a low serum free T4 (Aminorroaya et al., 2009).

The prevalence of hypothyroidism varies around the world. In the general population of the USA, UK and Scotland it ranges from 3.8%–4.6% (Chakera et al., 2012); the subclinical ranges from 1% to higher than 20 % and 1-2% for overt hypothyroidism (Aminorroaya et al., 2009). In developed countries like USA, Japan, United Kingdom, and Northern Europe, the prevalence ranges from 0.6 -12 per 1000 women and between 1.3 - 4.0 per 1000 men (Vanderpump, 2011). In developing countries like Iran, the overall prevalence of hypothyroidism is 4.8% in men and 12.8% in women (Aminorroaya et al., 2009). In Libya the prevalence of subclinical hypothyroidism is 6.18% (Nouh et al., 2008).

Several risk factors are associated with hypothyroidism, that are divided into: socio-demographic factors (e.g. age, gender) (Mao et al., 2010b,Aoki et al., 2007b), lifestyle factors (e.g. iodine intake in food and smoking), family history of autoimmune disease (Strieder et al., 2003,Dittmar et al., 2011), medical condition (e.g. diabetes type1) (Ardestani et al., 2011,Denzer et al., 2013) and medication (e.g. radioactive iodine) (Lankarani et al., 2008).

In Palestine, there is no national screening program for hypothyroidism or any other thyroid diseases. Moreover no study was concerned with hypothyroidism, which makes it a rich area for research due to its importance in preventing its occurrence and/or the expression of its complications.

1.2 Study justification

Hypothyroidism is diagnosed by physical examination, a medical and family history. Diagnosis is confirmed by measuring blood levels of thyroid hormones, are TSH (thyroid stimulating hormone) and T4. TSH is the most sensitive test for the diagnosis of hypothyroidism (AACE, 2006).

Hypothyroidism might lead to several complications such as cardiovascular disease (Mayer, Jr. et al., 2006) which put patients at risk of developing atherosclerosis and myocardial infarction (Hak et al., 2000), hypertension (Stabouli et al., 2010), diabetes (Kakleas et al., 2009), anemia (Mehmet et al., 2008), infertility in both men and women (Krassas et al., 2010), and it might lead to depression (Haggerty, Jr. et al., 2008). Therefore, determining the risk factors of hypothyroidism puts the represent a cornerstone towards the prevention of hypothyroidism or at least decrease related disability consequences.

The American Thyroid Association (ATA) recommends that adults should be screened for thyroid dysfunction by measuring serum thyrotropin concentration, beginning at age 35 years and every 5 years thereafter (Ladenson et al., 2000b). The screening of thyroid dysfunction is more favorable recommended among high risk population who might have goiter, iodine deficiency disorder, any autoimmune disorder,…etc (Staub et al., 1992). In Palestine, the MOH still screen all newborn children at the fourth day of the birth for congenital hypothyroidism. However, there is no screening program specialized for individuals at higher risk for developing thyroid dysfunction at other ages.

The epidemiology of thyroid dysfunction is neglected in Palestine. Moreover, the annual reports of the MOH lack data about the prevalence, incidence rate, and type of thyroid disorders. In addition, no study was concerned with hypothyroidism. Therefore, this study represents a pilot study at major MOH primary health care center "Karantina" endocrinology clinic in Hebron city. In this study, we screened all patients' files to estimate the prevalence of hypothyroidism among patients attending that clinic. Our study revealed that

hypothyroidism is the most thyroid disorder diagnosed and followed in that clinic. Its prevalence was 16.9% among patients attending Karantina endocrinology clinic from year 2008 until the April 2012 (see figure 1).

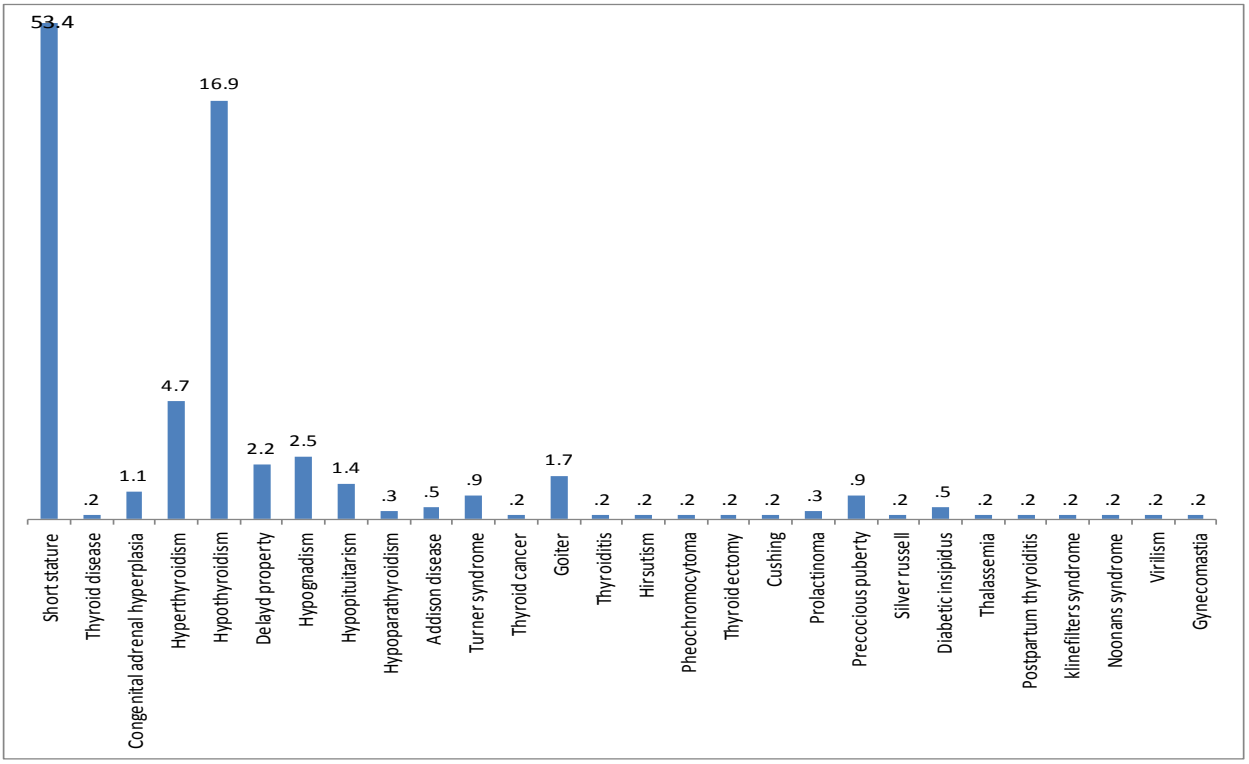

Figure 1: distribution of patients attending the endocrine clinic at the karantina

In Palestine, the risk factors associated with hypothyroidism are unknown, and there are no previous studies about risk factors for hypothyroidism. Therefore, this study was carried out to determine the risk factors associated with hypothyroidism among patients attending a primary health care clinics in Hebron district. The results of this study provide a preliminary baseline for policy makers for setting national policy for controlling hypothyroidism and its complication.

1.3 Study problem:

Hypothyroidism can be associated with several adverse health effects. These adverse effects can create a huge human and economic burden that can be prevented by early screening for the high risk population and the adoption of appropriate preventive or therapeutic measures.

Having hypothyroidism might lead to several complications; therefore, having a screening program for hypothyroidism will help in preventing any of the above complications, if this disorder is detected in its early stages. However, in Palestine the prevalence of hypothyroidism and the risk factors associated with this disorder are unknown. This study can be used as a baseline study for future planning of policies such as setting a national screening program that will or might prevent and/or delay of its complication or any of its other related disabilities.

1.4 Study aim

The overall aim of this study is to determine the risk factors associated with hypothyroidism among patients attending the primary health care clinics in Hebron district.

1.5 Study objectives:

1. To identify the type of endocrine diseases among patients attending the two study clinics (Dura and karantina)
2. To determine the association between socio-demographic factors (e.g. age and sex) and hypothyroidism.
3. To investigate the association between family history of autoimmune diseases and hypothyroidism.
4. To examine the relationship between patients' health status (e.g. diabetes mellitus, vitiligo, pernicious anemia, turner syndrome and down syndrome) and hypothyroidism.
5. To identify the association between lifestyle factors (e.g. iodine intake in food, smoking and alcohol consumption) and hypothyroidism.
6. To examine association between patients' diagnosis history at primary health care and hypothyroidism.

1.6 Study limitation:

1. Recall bias might be a major bias in this study. A lot of questions answered by patients about their health status, medication, family history, life style as well as types of food that consumed. This type of design has its limitations and possible not to give the correct information
2. The present study is a case control- clinical based study; therefore, it may not represent the whole population.
3. The present study is based only on TSH, therefore, it could have been strengthened if free T_3, free $T_{4,}$ Total T_4, Total T_3, anti-thyroperoxidase (anti-TPO) were also measured.
4. Medical files did not contain all information about patients.

1.7 Expected outcome:

We expect that the study will provide evidence and recommendations to decision makers for setting national policy for controlling hypothyroidism and its complication by identifying high risk individuals.

1.8 Thesis chapters' description:

This thesis is presented in 6 chapters, listed as follows:

Chapter one: Introduction

This chapter contains the background, study justification, study problem, objectives, and expected outcome and study limitations.

Chapter two: Literature review

This chapter includes the literature review of previous studies that are related to research topic.

Chapter three: Conceptual frame work

This chapter presents definitions of hypothyroidism, causes, diagnosis, treatment, and factors associated with hypothyroidism. These factors include: socio-demographic factors, life style factors, genetic factors and family history, medical, medication and history of diagnosis of hypothyroidism.

Chapter four: Methodology

In this chapter, the research methodology is presented. The study area, study population, study type, design, tools, the sampling method, statistical analysis, ethical consideration, and variables operational definitions are presented.

Chapter five: Results

In the chapter, results are presented in 3 parts. The first part presents a descriptive analysis of patients' files and study cases. The second part presents a descriptive analysis of the study population. And in the third part the univariate and multivariate analysis model are shown.

Chapter six: Discussion, Conclusion and Recommendations

In this chapter, the main study findings are interpreted and discussed. In the last part of this chapter, the study's conclusion and recommendations are presented.

Chapter two: Literature Review

2.1 Introduction

Literature showed that several factors are associated with hypothyroidism. These factors are divided into: socio- demographic factors such as age, gender (Mao et al., 2010a) (Aoki et al., 2007a), lifestyle factors such as iodine intake in food and smoking (Carle et al., 2006,Knudsen et al., 2002), family history of autoimmune thyroid diseases (Parle et al., 1991a), and person medical condition such as having diabetes (Kakleas et al., 2009); and anemia (Mehmet et al., 2011). Also, obesity was shown to be associated with having hypothyroidism and vice versa (El Mansoury et al., 2005b). In this chapter we are presenting the literature review concerning those risk factors.

2.2 Socio-demographic factors

Several epidemiological studies showed that age and sex as risk factors for increased risk of hypothyroidism. These studies are summarized in table 2.1.

According to Vanderpump M, the prevalence rate of hypothyroidism is higher in elderly people, especially in older women compared to men (MC, 2012,Vanderpump, 2011). According to Myo clinic, women are more likely to have hypothyroidism especially those older than 60 years of age compared to men (MC, 2012). In the USA, the National Health and Nutrition Examination Survey (NHANSE) reported that the prevalence of hypothyroidism (TSH > 4.5 mIU/L) in the general population was 3.7%. Among women of reproductive age (12-49 years) hypothyroidism was 3.1%. Individuals aged 80 years and older had five times greater odds for having hypothyroidism compared to younger aged individuals (12- 49 years) (Aoki et al., 2007b). The prospective population-based study in Denmark showed that hypothyroidism was three times predominant in women and there was a steep increase in the incidence of hypothyroidism in females aged 40–50 years, while among males, the increase seemed to occur two or three decades later in life (Carle et al., 2006). The population-based study in China showed that the prevalence of diagnosed with hypothyroidism was 1.7% in females and 0.3% in males. Subclinical hypothyroidism was more common in females (males 2.4% versus females 5.8%, $P < 0.001$) and with increasing age ($P < 0.001$) (Mao et al., 2010b).

Similar finding was seen among Arabs populations In Saudi Arabia, a hospital based study showed that of 391 patients 196 (54 male and 142 female) had hypothyroidism (Lamfon, 2008).

2.3 Lifestyle factors

Table 2.2 summarizes epidemiological studies that investigated lifestyle factors that are associated with hypothyroidism. Iodine intake, selenium, tobacco smoking, alcohol consumption and physical activity factors are reviewed in the coming sections.

2.3.1 Iodine intake

According to the American thyroid association, approximately 40% of the world's population remains at risk for iodine deficiency. Thus, iodine deficiency can lead to enlargement of the thyroid (goiter), hypothyroidism, and mental retardation in infants and children whose mothers were iodine deficient during pregnancy. Even excess iodine can also lead to hypothyroidism (ATA, 2012b).

In china, a comparative population-based cross-sectional study showed that the population with iodine intake (MUI 261 μg/l) in Rongxing had higher prevalence of subclinical hypothyroidism than a population with (MUI 145 μg/l) in Chengshan (5.03 vs. 1.99%, P<0.001) (Teng et al., 2011). In Denmark, a comparative study demonstrated that thyroid abnormalities in populations with low iodine intake in Jutland (approximately 40 to 70 μ g/d) and those with high iodine intake develop in Iceland (approximately 400–450 μ g/d) were in opposite directions: higher goiter and hyperthyroidism when iodine intake is relatively low, and higher hypothyroidism when iodine intake is relatively high (Laurberg et al., 1998).

2.3.2 Selenium

A comparative study in Zaire reported severe selenium deficiency associated with endemic myxedematous cretinism in the core of endemic- area with iodine deficiency (Vanderpas et al., 1990). A prospective, randomized, placebo-controlled study in Italy has shown that 200 microg/d selenium supplementation during pregnancy and in the postpartum period reduced thyroid inflammatory activity and the incidence of hypothyroidism (Negro et al., 2007). These findings have been supported by a prospective, placebo-controlled clinical study in Germany. The study demonstrated, that a substitution of 200 microg sodium selenite for

three months in patients with autoimmune thyroiditis reduced thyroid peroxidase antibody (TPO-Ab) concentrations significantly (Gartner and Gasnier, 2003).

2.3.3 Tobacco smoking

Studies evaluating Tobacco smoking and thyroid disorders have yielded conflicting results**.** Studies report either negative association, or a positive association between smoking and hypothyroidism. In Iran, a cross-sectional community based survey suggested that smoking was associated with lower risk of hypothyroidism and possibly with a lower frequency of thyroid autoimmunity (Mehran et al., 2012b). These findings also have been supported by the cross-sectional population-based study in Norway which showed that smoking was negatively associated with hypothyroidism but positively associated with hyperthyroidism.(Asvold et al., 2007). In contrast, a case-control study in Denmark found that smoking was a powerful risk factor for thyroid disease, especially in populations with a high smoking frequency (Vestergaard et al., 2002). In Japan, a retrospective study suggested that smoking may increase the risk of hypothyroidism in patients with Hashimoto's thyroiditis (Fukata et al., 1996).

2.3.4 Alcohol consumption

A few studies have demonstrated the direct effect of alcohol consumption on the prevalence and incidence of hypothyroidism, but on the other hand there are other studies that have addressed other effect of alcohol on the thyroid gland.

A nested case-control studies in the prospective Amsterdam AITD cohort study revealed that moderate alcohol consumption was to be protective for the development of overt hypothyroidism in subjects susceptible for developing autoimmune thyroid disease (AITD) (Effraimidis et al., 2012). These findings also have been supported by the population-based case-control study in Denmark. The study found that alcohol, in doses up to 3 units/day, may have a protective role in the development of overt autoimmune hypothyroidism in both men and women aged 60 years or below (Carle et al., 2012).

2.3.5 Physical activity

A few scientific studies have addressed the impact of physical activity on thyroid function. In Brazil, a double-blind, randomized study revealed that that sub-maximal cardiopulmonary exercise performance improved after six months of TSH normalization

could help enhance the ability to carry out daily life activities in patients with subclinical hypothyroidism (Mainenti et al., 2009). In Italy, a double-blind, randomized, placebo-controlled trial found that exercise altered both the tolerance and pattern of blood glucose, lactate, pyruvate, free fatty acid and glycerol concentrations in subclinical hypothyroidism patients compared to healthy subjects (Caraccio et al., 2005b).

2.4 Genetics, Family history of autoimmune thyroid disease (AITD)

Table 2.3 summarizes epidemiological studies that investigated genetic factors and family history that are associated with hypothyroidism

Several epidemiological studies revealed that Hashimoto's thyroiditis is one of the most prevalent causes of hypothyroidism, its influenced by both genetic and environmental factors (Erkan Sar et al., 2011). In Germany, a familial study showed that increased familial risk of developing autoimmune thyroid disease (AITD), especially for the first-degree relatives with (AITD), compared with the general population. Also, the study found that in particular, children and siblings of patients with Hashimoto's thyroiditis had a 32-fold and 21-fold increased risk, respectively, for developing immunethyroiditis (Dittmar et al., 2011). A prospective cohort study in Netherlands found that the prevalence rate of autoimmune thyroid disease (AITD) was 27% among first- and second-degree relatives of AITD patients (Strieder et al., 2003). In USA, observational study shown that the sibling risk ratios (λ_s) were 16.9 % in siblings of autoimmune thyroid disease (AITD) patients for developing AITD compared to the general population (Villanueva et al., 2003). A population-based twin study in Denmark showed that significantly higher concordance rates of autoimmune hypothyroidism in monozygotic compared to dizygotic pairs, indicating that genetic factors play a role in the etiology of Hashimoto's thyroiditis (HT), and atrophic thyroiditis (AT) (Brix et al., 2000).

2.5 Medical conditions and hypothyroidism

Many epidemiological studies showed that many NCDs are associated with the occurrence of hypothyroidism. Persons having diabetes mellitus type 1; pernicious anemia; turner syndrome; down Syndrome; vitiligo; rheumatoid arthritis; systemic lupus erythematosus; celiac disease; multiple sclerosis; Sjögren's syndrome and adrenal insufficiency were at greater risk to develop hypothyroidism, and vice versa, compared to others without having

these diseases. Also, goiter, obesity and pregnancy were shown to be associated with having hypothyroidism. These studies are summarized in table 2.4

2.5.1 Diabetes and hypothyroidism

Studies demonstrated that diabetes and thyroid disorders tend to coexist in patients. A cross-sectional study in Germany showed that the prevalence rate of subclinical hypothyroidism was 7.2% in children, adolescents, and young adults (age <25 years) with type 1 diabetes (Denzer et al., 2013). In the USA, a longitudinal study found that hypothyroidism was more common in female (41%) than in male (19%) subjects with type 1 diabetes, especially those patients with positive TPO (Umpierrez et al., 2003). Similar finding were shown in studies in less economically developed countries. In Iran a cross-sectional study showed that children and adolescents with T1DM had higher prevalence of subclinical hypothyroidism than nondiabetic (Ardestani et al., 2011). A retrospective study in Saudi Arabia reported that 15.83% of children and adolescents with T1DM had hypothyroidism (Al-Agha et al., 2011).

In Mexico, a retrospective cross-sectional study showed that the rate of hypothyroidism three times higher in patients with T2DM than nondiabetic (Tamez-Perez et al., 2012). In India a study revealed that the prevalence rate of hypothyroidism was 23.75% among type 2 diabetes (T2D) (Singh et al., 2011). In Greece, a cross sectional study showed that prevalence rate of subclinical hypothyroidism was 5.2% in males and 8.4% in females with T2D (Papazafiropoulou et al., 2010).

2.5.2 Pernicious anemia and hypothyroidism

In China, a prospective longitudinal study revealed that primary hypothyroidism was the main thyroid dysfunction encountered in pernicious anemia (PA) patients (Chan et al., 2009). In USA, a study showed that the prevalence of hypothyroidism was 11.7% among patients with pernicious anemia (Carmel and Spencer, 1982). See table 2.5 for more details.

2.5.3 Turner syndrome and hypothyroidism

A cohort study in Denmark revealed that the overall risk of autoimmune disease among women with Turner's syndrome was twice than women in the general population (Jorgensen et al., 2010). A large Cohort study in Sweden showed that hypothyroidism was common in adult women with Turner syndrome (TS) and significantly more common than in the random

population sample, with an annual incidence 3.2% after 5-year follow-up (El Mansoury et al., 2005a). See table 2.6 for more details.

2.5.4 Down syndrome and hypothyroidism

The prospective study in Nepal reported that the prevalence of hypothyroidism in Downs' children was 15%, of which 12.5% had a compensated hypothyroidism while the other had a 3.1% uncompensated hypothyroidism (Shaw et al., 2006). The longitudinal study in Sweden found that hypothyroidism developed in one third of patients with Down's syndrome before the age of 25 years (Karlsson et al., 1998). See table 2.7 for more details.

2.5.5 Vitiligo and hypothyroidism

In Brazil, a cross-sectional study found that the prevalence of autoimmune thyroid diseases was 22.4% in patients with vitiligo. (Nunes and Esser, 2011). A case-control study in India found that the incidence rate of hypothyroidism among patients with vitiligo was 12% compared with healthy subjects (Gopal et al., 2007). See table 2.8 for more details.

2.5.6 Rheumatoid arthritis and hypothyroidism

The case-control study in Egypt revealed that thyroid dysfunction, especially hypothyroidism were more frequently in systemic lupus erythematosus and rheumatoid arthritis patients compared with the general population (Mousa et al., 2012). The study-population in Netherlands showed that clinical hypothyroidism was threefold in female rheumatoid arthritis (RA) patients than females in the general population. (Raterman et al., 2008). For details, see table 2.9 (Annex a).

2.5.7 Systemic lupus erythematosus and hypothyroidism

In India a prospective study showed that thyroid dysfunction was more frequent in systemic lupus erythematosus (13.1%) than in rheumatoid arthritis (5.1%). In Systemic lupus erythematosus (SLE) patients. Subclinical hypothyroidism occurred in 17.1%, while clinical hypothyroid was present in 73.2%. In Rheumatoid arthritis (RA) patients subclinical hypothyroid was seen in 20% , while clinical hypothyroid was 60% (Porkodi, 2004). A retrospective study in the UK showed that the prevalence of hypothyroidism in systemic lupus erythematosus (SLE) patients was (5.7%) higher than the normal population (1%) (Pyne and Isenberg, 2002). For details, see table 2.9 (Annex a).

2.5.8 Sjögren's syndrome and hypothyroidism

A case-control study in Kuwait showed that the frequency of subclinical hypothyroidism, especially among female patients with primary Sjogren's syndrome (PSS) were significantly higher than in the healthy controls (Al Awadhi et al., 2008). In Italy, a case control study reported that the prevalence rate of hypothyroidism was (13.4%) among primary Sjögren's syndrome patients (Punzi et al., 1996). For details, see table 2.10 (Annex a).

2.5.9 Celiac disease and hypothyroidism

A cross-sectional study in Pakistan reported a high prevalence of subclinical hypothyroidism in Celiac pediatric patients (Butt et al., 2011). In Italy, a multi-center study showed that the prevalence of hypothyroidism in celiac patients was (8.1%) higher than control subjects (3.5%) (Ansaldi et al., 2003b). For details, see table 2.10 (Annex a).

2.5.10 Multiple sclerosis and hypothyroidism

A prospective study in Spain found that a significant higher prevalence of subclinical hypothyroidism in multiple sclerosis (MS) patient group compared with the control group (6.45% vs. 2.24%, P 0.03) (Munteis et al., 2007). A follow-up study in Italy reported that at baseline the prevalence of subclinical was 2.8% among patients with Multiple sclerosis (Caraccio et al., 2005a).

2.5.11 Adrenal insufficiency and hypothyroidism

Several epidemiological studies have been recognized both primary and secondary adrenal insufficiency as risk factors for developing hypothyroidism. A cohort study in South Africa found that primary hypothyroidism were the most common autoimmune thyroid diseases associated with primary adrenal insufficiency (Addison's disease) (Ross et al., 2010). Similar results also have been seen in a national registry-based cohort study in Norway. The result showed that a higher prevalence rate of hypothyroidism among patients with primary adrenal insufficiency (Addison's disease) (Erichsen et al., 2009).

In Poland, a study report of 111 cases with secondary adrenal insufficiency. They found that primary hypothyroidism were the most frequent autoimmune diseases associated with secondary adrenal insufficiency (Kasperlik-Zaluska et al., 2003). Pregnancy and hypothyroidism.

According to the publication of an American thyroid association postpartum thyroiditis occurs in approximately 5-10% of women, also approximately 20% of those women with postpartum thyroiditis that go into hypothyroidism phase will remain hypothyroid (ATA, 2012d). Furthermore, literature showed that 20–40% of women with postpartum thyroiditis develop permanent hypothyroidism over the ensuing 3–12 years (Stagnaro-Green, 2012). In Australia, a study found that hypothyroidism was present in 38% (71 women) who had postpartum thyroiditis (PPTD) at baseline with a significant adjusted odds ratio 9.7 for postpartum hypothyroidism (Stuckey et al., 2010). In Finland, prospective population-based cohort study in revealed that overt and subclinical hypothyroidism and thyroid antibodies detected in early pregnancy seem to predict later thyroid disease morbidity of the mother (Mannisto et al., 2010).

2.5.12 Obesity and hypothyroidism

Epidemiological studies have found that obesity is a risk factor for hypothyroidism and vice versa. In Italy, a cross-sectional study was performed in a tertiary care center revealed that obesity can increase the risk of thyroid autoimmunity, this being associated with leptin level (Marzullo et al., 2010). A cross sectional community based survey in Iran suggested that a significant positive association exists between TSH and BMI in euthyroid nonsmokers (Mehran et al., 2012a). A retrospective, observational study in India found that primary hypothyroidism was more prevalent in individuals with extreme obesity as compared to moderate obesity patients (56% versus 41%) (Verma et al., 2008).

2.5.13 Goiter and hypothyroidism

A case-control study in India found that hypothyroidism (subclinical and clinical) was in 3.2 per cent in children with goiter and 2.4 per cent without goiter (Das et al., 2011). A cross-sectional study in Iran showed the hypothyroidism was three times higher among goitrous adult compared to non-goitrous adult (Aminorroaya et al., 2010).

2.6 Medication and hypothyroidism

Epidemiological studies have demonstrated that some medications such as: interferon, amiodarone, lithium, radioactive iodine, thyroid surgery and thionamides (methimazole, propylthiouracil, carbimazole) were associated with increased risk of developing hypothyroidism. These studies are summarized in table 2.6.

2.6.1 Interferon and hypothyroidism

A cohort study in Pakistan found that patients of chronic hepatitis C undergoing treatment with interferon and ribavirin were eleven times more likely to develop thyroid dysfunction as compared to patients with chronic hepatitis C without treatment (Nadeem and Aslam, 2012). A prospective study in Brazil showed that patients with chronic hepatitis C (HCV) had a relative risk of 3.5 for developing hypothyroidism during the first treatment with α-interferon course (Pavan et al., 2011).

2.6.2 Amiodarone and hypothyroidism

A retrospective population-based cohort study in Canada reported that the rate of hypothyroidism was 15.8% among patients using the brand-name of amiodarone and 16.6% among patients using generic formulations of amiodarone (Tsadok et al., 2011). The retrospective study in China found that the prevalence of hypothyroidism was 22% among patients who had been prescribed amiodarone for at least 6 months. Also, they found TSH hormone of 4 mIU/L or above appeared to be predictive of amiodarone-induced hypothyroidism, in which associated with a 4.7-fold increase in the risk of developing hypothyroidism among patients using amiodarone (Lee et al., 2010).

2.6.3 Lithium and hypothyroidism

In France, a cross sectional study reported that the prevalence of hypothyroidism was 37% in men, and 9% in women patients with bipolar disorder who had been treated with lithium (Henry, 2002). In Scotland, a retrospective study found that the prevalence of clinical hypothyroidism during lithium treatment was 10.4%(Johnston and Eagles, 1999).

2.6.4 Radioactive iodine and hypothyroidism

A retrospective cohort study in USA found that the prevalence of hypothyroidism was 40% among patients were treated with RAI therapy at 6-8 weeks (Stan et al., 2013). In Qatar, a retrospective study found that the incidence rate of hypothyroidism among patients were treated with RAI therapy was 55.8% at 6 months and 67.9% at one year (Ghadban et al., 2003).

2.6.5 Thyroid Surgery and hypothyroidism

A retrospective study in Korea found that the incidence of hypothyroidism following thyroid lobectomy was 21.1% within 35.7 months of follow-up (Cho et al., 2011d). In Iran, a cross section hospital based study reported that 35.2% of cases of thyroidectomy developed hypothyroidism on average 5 ± 3.2 months after surgery (Lankarani et al., 2008).

2.6.6 Thionamides (Methimazole, Propylthiouracil, Carbimazole) and hypothyroidism

A prospective randomized study in Thailand found that the incidence rate of hypothyroidism among hyperthyroidism patients were treated with a fixed-15 mg daily dosage of Methimazole (MMI) for 12 weeks was 31.4%, while hypothyroidism not seen in patients were treated with Propylthiouracil (PTU) (Homsanit et al., 2001). A prospective open multicentre trial in the United Kingdom showed that Carbimazole (CBZ) -related hypothyroidism developed in approximately in 25% of patients who received 40 mg CBZ/day for 4 weeks compared to the patients who received 20 mg CBZ/day (Page et al., 1996).

2.7 History of diagnosis

A descriptive case study in Pakistan included 100 consecutive cases of hypothyroidism from birth to twelve years. The study found that delayed diagnosis was among 42% (n=100) of cases and were between 1-5 years of age, also 66% of these cases had developmental delay. The authors concluded that early diagnosis of hypothyroidism is recommended to prevent the effects of delayed diagnosis. (Malik and Butt, 2008c). Another longitudinal study of 20 children in Turkey, revealed that height prognosis in late diagnosed congenital hypothyroidism (Kandemir and Yordam, 2001).

2.8 Studies in Arab countries

The studies in Arab countries investigated the risk factors that are associated with hypothyroidism including: excessive iodine intake (Alsayed et al., 2008), genetic factors (Bougacha-Elleuch et al., 2011), family history of thyroid disease (Abdel-Rasoul et al., 2011), diabetes type 1 (Al-Agha et al., 2011), diabetes type 2 (Al wazan et al., 2010), down syndrome (Rabah M Shawky, 2005), vitiligo (Mousa et al., 2012), rheumatoid arthritis (Mousa et al., 2012,Al Awadhi et al., 2008) systemic lupus erythematosus (Mousa et al.,

2012,Al Awadhi et al., 2008), sjögren's syndrome (Al Awadhi et al., 2008), goiter (Qari, 2005) , obesity (Nouh et al., 2008) and pregnancy (Alkafajei et al., 2012).

Table 2.1: Summary of studies on socio-demographic variables association with hypothyroidism.

Author, Country of study	Type of study	Sample	Objectives	Main finding	Conclusion
(Aoki et al., 2007b), USA	National Health and Nutrition Examination Survey (NHANES)	4392 participants aged ≥12 years	To describe thyrotropin (TSH) and thyroxine (T4) levels in the U.S. population and their association with selected participant characteristics.	- Individuals aged 80 years and older had five times greater odds for hypothyroidism compared to 12- to 49-year-old (adjusted odds ratio [OR] = 5.0, p = 0.0002). ORs were adjusted for sex, race, and annual income.	Hypothyroidism was more common in females, and with increasing age.
(Carle et al., 2006), Denmark	A prospective population-based study	Aalborg (moderate iodine deficiency, n = 311,102) and Copenhagen (mild iodine deficiency, n = 227,632)	To study the incidences of sub types of primary, overt hypothyroidism in a Danish population cohort and compared incidences in two sub-cohorts with different levels of iodine intake.	-Hypothyroidism was more common among females with a female/male incidence rate ratio of 3.5. -A steep increase in the incidence of hypothyroidism in females aged 40–50 years , while among males, the increase seemed to occur two or three decades later in life.	Hypothyroidism was more common in females, and the incidence of hypothyroidism increase with age.
(Mao et al., 2010b), China	A population-based study	10405 >20 years	To determine the prevalence of major thyroid dysfunctions including overt and subclinical hyper- and hypothyroidism in a stable cohort.	-Subclinical hypothyroidism was more common in females (male 2.4% vs. female 5.8%, P < 0.001) and with increasing age (P < 0.001).	Subclinical hypothyroidism was more common in females, and with increasing age.
(Lamfon, 2008), Saudi Arabia	A cross-sectional study	391patients	To study the prevalence of thyroid diseases among patients.	196 patients have hypothyroidism (54 male and 142 female).	Hypothyroidism was more common in female patients than male patients.

Table 2.2: Summary of studies that investigated lifestyle factors association with hypothyroidism

Author\years Place of study	Kind of study	Sample size	Objectives	Main finding	Conclusion
(Teng et al., 2011), China	A population-based cross-sectional study	3813 individuals	Explore the associations between more than adequate iodine intake levels and the development of thyroid diseases in two Chinese populations.	The prevalence of subclinical hypothyroidism was significantly higher in Rongxing than Chengshan (5.03 vs. 1.99%, P<0.001).	High iodine intake associated with thyroid function and thyroid autoimmunity.
(Laurberg et al., 1998), Denmark	A comparative study	423subjects from Jutland, And 100subjects from Iceland	Evaluate the effect of differences in the population iodine intake on the prevalence rate of various thyroid disorders in the elderly.	-The prevalence of subclinical hypothyroidism in Iceland was 4 times than Jutland.	Low and high iodine intake levels correlated with thyroid abnormalities.
(Vanderpas et al., 1990), Zire	A comparative study	52 school children (Aged 9-18 y) and 28 cretins (aged 3-25 y)	To determine the selenium status in a population living in the core of the endemic-goiter belt of northern and in a Zairian area without endemic goiter.	-Serum selenium in subjects living in the core of the endemic goiter belt was seven times lower in 52 schoolchildren and similarly low in 23 cretins.	Selenium deficiency associated with of endemic myxedematous cretinism.
(Negro et al., 2007), Italy	A prospective, placebo-controlled clinical study	2143 euthyroid pregnant women (7.9% were TPOAb)	To examine whether Selenium (Se) supplementation, during and after pregnancy, influences the thyroidal autoimmune pattern and function.	-Permanent hypothyroidism was significantly lower in group women received selenomethionine 200 microg/d (group S1) compared with women received placebo (11.7 *vs.* 20.3%, *P* 0.01).	Selenium(Se) supplementation during pregnancy and in the postpartum period reduced the incidence of hypothyroidism.
(Gartner and Gasnier, 2003), Germany	A prospective, placebo-controlled clinical study	70 patients with autoimmune thyroiditis	To demonstrate that a substitution of 200 microg sodium selenite for three months in patients with autoimmune thyroiditis.	-TPOAb concentration decreased significantly to 63.6% (***P*** = 0.013) in the selenium group ***vs.*** 88% (***P*** = 0.95) in the placebo group.	Selenium substitution may improve the inflammatory activity in patients with autoimmune thyroiditis.

Table 2.2 continues

Author\years Place of study	Kind of study	Sample size	Objectives/hypothesis	Main finding	Conclusion
(Mehran et al., 2012c), Iran	A cross sectional community based survey	1,581randomly selected subjects with no history of thyroid disorders.	Association between smoking and serum TSH concentration and the presence of thyroperoxidase antibody (TPO Ab) in adults.	- Hypothyroidism was lower in the ever smoker group compared to the never smoker (odds ratio 0.4, 95% CI=0.2-0.8).	Smoking negatively associated hypothyroidism.
(Asvold et al., 2007), Norway	A cross-sectional, population-based study	479 20women and 10 355 men without previously known thyroid disease	Association between tobacco smoking and thyroid function.	-The prevalence of overt hypothyroidism was lower in current smokers compared with never smokers (odds ratio, 0.60; 95% CI, 0.38-0.95).	Smoking inversely associated with hypothyroidism.
(Vestergaard et al., 2002), Denmark	A case-control study	617 (542 females) hyperthyroidism and 408 (364 females) with hypothyroidism	Association between smoking and thyroid disease.	-In women, autoimmune hypothyroidism was higher in ever smoking compared to never smoking (OR = 1.5, 95% CI: 1.1-2.1) not in men	Smoking is a powerful risk factor for thyroid disease
(Fukata et al., 1996), Japan	A retrospective study	238 randomly chosen women patients with nodular goiters and 166 control women	Relationship between smoking history and thyroid function in 387 women patients with Hashimoto's thyroiditis.	-The prevalence of hypothyroid was 76.4% among smoker, 34.8% among nonsmokers, and 61.9% among the excess-smokers.	Smoking may increase the risk of hypothyroidism.
(Effraimidis et al., 2012), Netherlands	Two nested case-control study	Study A (521 euthyroid participants Study B (38 cases with hypothyroidism)	Alcohol consumption reduce the risk of developing autoimmune thyroid disease.	- Light alcohol drinkers: (1–10 units/week), OR for hypothyroidism = 0.58 - High alcohol consumers (> 11 units/week) was 0.40 - Non drinker, OR do not change - Multivariate sowed that smoking habits (OR=0.59) and family history was inversely associated hypothyroidism (OR= 0.41)	Alcohol consumption may protect against overt autoimmune hypothyroidism

Table 2.2 continues

Author\years Place of study	Kind of study	Sample size	Objectives/hypothesis	Main finding	Conclusion
(Carle et al., 2012), Denemark	A population-based case-control study	140 patients diagnosed with overt Autoimmune hypothyroidism and 560 controls	To study the association between alcohol consumption and autoimmune hypothyroidism.	-In patients who do not consume alcohol the OR for the development of hypothyroidism was twice (2.12; 95% CI, 1.31 to 3.4) that in patients who consumed 1 to 10 units of ethanol per week (n = 85).	Alcohol consumption may protect against development of overt autoimmune hypothyroidism.
(Mainenti et al., 2009), Brazil	Trial study	23 patients with subclinical hypothyroidism were randomized into treated with levothyroxine (L-T4) replacement (no=11) and untreated (no=12)	To verify possible cardiopulmonary changes during exercise in patients with subclinical hypothyroidism on L-T (4) replacement with a normal serum TSH for six months.	-Oxygen uptake, carbon dioxide production, minute ventilation, and heart rate at sub maximal exercise intensity had significant improvements in treating patients, while in untreated no changes	Submaximal cardiopulmonary exercise after L-T (4) replacement had a positive effect in subclinical patients
(Caraccio et al., 2005b), Italy	A double-blind, randomized, Placebo-controlled fashion	23 subclinical hypothyroidism patients and 10 matched euthyroid controls	To evaluate the energy and substrate response to exercise in subclinical hypothyroidism patients using a standardized protocol and to test the effect of L-T (4) replacement.	-Exercise was significantly impaired in subclinical hypothyroidism. In terms maximal power output (P = 0.02) and VO (2) max (P = 0.04) were reduced in subclinical hypothyroidism patients.	Exercise affected to subclinical hypothyroidism.

Table 2.3: Summary of studies that investigated genetic factors and family history association with hypothyroidism

Author\years Place of study	Kind of study	Sample size	Objectives	Main finding	Conclusion
(Dittmar et al., 2011), Germany	Familial study	86 AITD index cases with their 139 children and 106 AITD index cases with their 157 siblings were included.	To determine familial prevalence and recurrence risk ratio of autoimmune thyroid diseases (AITD) in Germany.	- The prevalence AITD were in 14% of children and 15% of siblings of patients with AITD. - children and siblings of index cases with Hashimoto's thyroiditis had a 32-fold and 21-fold increased risk, respectively, for developing immunthyroiditis	Screening of off spring and siblings of AITD patients for the presence of immunethyroidits.
(Strieder et al., 2003), Netherlands	Started with Prospective cohort study,' then cross sectional study	803 subjects, 440 came from families with More than one patient with documented AITD.	To determine risk Factors for developing autoimmune thyroid disease (AITD).	- At baseline AITD was 89% on subjects had at least one first degree with AITD and 11% on subjects with at least one second-degree relative with AITD. - The prevalence rate of hypothyroidism was 3.6%.	Genetic factors play a role on co-occurrence of Hashimoto's thyroiditis and Graves' disease within one family.
(Villanueva et al., 2003), USA	Observational study	131 patients with Graves' (GD) and 24 patients with Hashimoto's thyroiditis (HT)	To measure of the magnitude of genetic contribution to the development of AITD through using results of Nutrition Examination Survey III	- 9 probands had siblings with GD and 13 probands had siblings with HT. - The sibling risk ratios (λ_s) for developing AITD was 16.9 for AITD, 11.6 for GD, and 28.0 for HT.	Significant contribution of genetic factors to the development of AITD.
(Brix et al., 2000), Denmark	Population-based twin study	5890 twin pairs	To elucidate whether there is a genetic influence in the etiology of Hashimoto's thyroiditis (HT), and atrophic thyroiditis (AT).	The prevalence of autoimmune hypothyroidism between monozygotic and dizygotic twins (0.42% and 0.40%, respectively).	Genetic factors play a role in the etiology of HT/AT.

Table 2.4: Summary of studies that investigated diabetes and hypothyroidism

Author\years Place of study	Kind of study	Sample size	Objectives	Main finding	Conclusion
(Denzer et al., 2013), Germany	A cross-sectional analysis	22,747children, adolescents, and young adults (age <25 years) with type 1 diabetes	To investigate the prevalence of subclinical hypothyroidism (SCH) and associated lipid levels in young diabetic patients.	- The prevalence rate of SCH was 7.2% in children, adolescents, and young adults with type 1 diabetes.	Subclinical hypothyroidism was common in children, adolescents, and young adults with type 1 diabetes.
(Umpierrez et al., 2003), USA	Longitudinal study	58 patients (26 men and 32 women)	To determine the natural history of thyroid dysfunction in patients with type 1 diabetes	- Hypothyroidism was more common in female (41%) than in male (19%) subjects with type 1 diabetes.	Confirms the association between autoimmune thyroid dysfunction and type 1 diabetes.
(Ardestani et al., 2011), Iran	A cross sectional study	100 patients with T1DM and 184 healthy school children	To study the prevalence of thyroid disorders such as autoimmunity of thyroid (AIT), thyroid dysfunction, and goiter in children and adolescents with T1DM, compared with age- and sex-matched healthy controls in Isfahan.	-The prevalence of subclinical hypothyroidism in T1DM patients and non-diabetic subjects was 1% and 0.7%, respectively.	Children and adolescents with T1DM had higher levels of subclinical hypothyroidism than non-diabetic ones.
(Al-Agha et al., 2011), Saudi Arabia	A retrospective cross-sectional study	398 children and adolescents with T1DM aged from 1 to 18 years	To review the prevalence of T1DM among children and adolescents with T1DM and determine the factors affecting its prevalence in our population.	- The prevalence of hypothyroidism was 15.83% among children and adolescents with T1DM (92% subclinical hypothyroidism, 7.94% clinical hypothyroidism).	Screening programs for hypothyroidism among children and adolescents with T1DM.

Table 2.4 continues…..

Author\years Place of study	Type of study	Sample size	Objectives	Main finding	Conclusion
(Tamez-Perez et al., 2012), Mexican	A retrospective cross-sectional study	1848 adult patients with T2DM were compared with 3313 non-diabetic patients	To identify the rate of diabetic patients treated for hypothyroidism and compare them with a group without type 2 diabetes mellitus (T2DM)	-The rate of hypothyroidism three times higher in patients with T2DM than nondiabetic.	A strong association between T2DM and hypothyroidism.
(Singh et al., 2011), India	A cross sectional study	80 type 2 diabetic subjects and 80 healthy non diabetic subjects	To evaluate the prevalence of thyroid dysfunction in subjects with type 2 diabetes and the effect of type 2 diabetes mellitus on other bio-chemical variables.	-Hypothyroidism was present in 23.75% (15% subclinical hypothyroidism and 8.75% Primary hypothyroidism) of diabetic subjects.	High incidence of abnormal thyroid hormone level among type 2 diabetic subjects.
(Papazafiropoulou et al., 2010), Greek	A cross sectional study	1,092 patients with T2D	To determine the Prevalence of thyroid dysfunction in patients with type 2 diabetes (T2D) attending an outpatient clinic.	-Subclinical hypothyroidism was 5.2% in males and 8.4% in females with T2D.	A higher prevalence Subclinical hypothyroidism among diabetic females

Table 2.5: Summary of studies that investigated pernicious anemia and hypothyroidism

Author\years Place of study	**Kind of study**	**Sample size**	**Objectives**	**Main finding**	**Conclusion**
(Chan et al., 2009), China	Hospital-based longitudinal study of	126 patients with pernicious anemia	To determine thyroid autoimmunity in Chinese patients with pernicious anemia (PA).	- The overall rate of Autoimmune thyroid disease (AITD before and after (PA) were occurred in 23% and in 5.7% of PA patients with and without antibodies (P = 004). -9 patients PA developed primary hypothyroidism during follow-up and was associated with high TPO/Tg antibody titer.	Screen thyroid antibodies and monitor thyroid function in PA patients during follow up.
(Carmel and Spencer, 1982), USA	Observational study	62 patients with pernicious anemia	To observe on abnormal thyroid-stimulating hormone levels and on a possible association of blood group O with hyperthyroidism.	- The prevalence of hypothyroidism was 11.7% among patients with pernicious anemia.	TSH screening in patients with pernicious anemia.

Table 2.6: Summary of studies that investigated turner syndrome and hypothyroidism

Author\years Place of study	**Kind of study**	**Sample size**	**Objectives**	**Main finding**	**Conclusion**
(Jorgensen et al., 2010), Denmark	Cohort study	798 Danish women with Turner's syndrome	To investigate whether the autoimmune disease profile in women with Turner's syndrome	- The overall risk of autoimmune disease among women with Turner's syndrome was twice that among Danish women in general (Standardized incidence ratios (SIR) 2.1 [95% CI 1.6–2.7]).	Women with Turner's syndrome were at excess risk of autoimmune diseases.
(El Mansoury et al., 2005a), Sweden	A large cohort study	91 women with TS were compared with an age-matched 228 female random population	To study the prevalence and incidence of thyroid disease in adults with Turner syndrome	-The prevalence of hypothyroidism among TS women was 37% after the 5-yr follow-up.	Autoimmune hypothyroidism was common in Turner syndrome.

Table 2.7: Summary of studies that investigated Down's syndrome and hypothyroidism

Author\years Place of study	Kind of study	Sample size	Objectives	Main finding	Conclusion
(Shaw et al., 2006), Nepal	A prospective study	32 children with Down syndrome	To know the prevalence of thyroid dysfunction in Down Syndrome children below the age of 14 years and to correlate the features of Down Syndrome with those of thyroid dysfunction	-The prevalence of hypothyroidism in Downs' children was 15%, of which 12.5% had a compensated hypothyroidism while the other 3.1% had uncompensated hypothyroidism.	Screen Down syndrome children for thyroid dysfunction.
(Karlsson et al., 1998), Sweden	Longitudinal study	85 children with Down's syndrome	To study longitudinally thyroid function in patients with Down's syndrome up to the age of 25 years.	-Hypothyroidism was developed in one third of patients with Down's syndrome before the age of 25 years.	Hypothyroidism was common in Down's syndrome patients.

Table 2.8: Summary of studies that investigated vitiligo and hypothyroidism

Author\years Place of study	**Kind of study**	**Sample size**	**Objectives**	**Main finding**	**Conclusion**
(Nunes and Esser, 2011), Brazil.	A cross-sectional study	85 patients with vitiligo	To describe the epidemiological profile of vitiligo patients and to estimate the prevalence of the association of vitiligo with autoimmune thyroid diseases.	-The rate of thyroid autoimmune diseases was founded in 22.4% of patients with vitiligo (80% corresponded to hypothyroidism and 6.7% to subclinical hypothyroidism).	Autoimmune thyroid diseases common in patients with Vitiligo.
(Gopal et al., 2007), India	Case control study	150 cases of various types of vitiligo were compared with 100 nonvitiligo cases	A study of the genetic factors, systemic associations as well as ocular and auditory abnormalities of vitiligo.	-Hypothyroidism was present in 12 % of vitiligo patients but in none of the controls	Vitiligo was a part of the systemic autoimmune process.

Table 2. 9: Summary of studies that investigate rheumatoid arthritis, systemic lupus erythematosus and hypothyroidism

Author\years Place of study	Kind of study	Sample size	Objectives	Main finding	Conclusion
(Mousa et al., 2012), Egypt	Case-control study	132 SLE patients (128 females, 4 males) and 217 RA patients (174 females, 43 males) were compared with 120 controls (90 females, 30 males)	To investigate the frequency of thyroid dysfunction in Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) and whether these dysfunctions could be an additional risk factor for the development of cardiovascular diseases.	-The prevalence rate of clinical hypothyroidism was (8.3% SLE, 4.1% RA patients).	Hypothyroidism was common SLE and RA patients.
(Raterman et al., 2008), Netherlands	A cross-sectional study	358 RA patients	To determine the prevalence of hypothyroid disorders in rheumatoid Arthritis (RA) patients.	Clinical hypothyroidism was significantly 3 times higher in female RA patients than in the general population.	Clinical hypothyroidism was common in RA.
(Porkodi, 2004), India	Prospective study	153 SLE patient and 798 RA patients	To study the prevalence of thyroid dysfunction in Systemic lupus erythematosus (SLE) and Rheumatoid Arthritis (RA).	- In SLE patients subclinical hypothyroid occurred in 17.1%, while clinical hypothyroid was present in 73.2%. -In RA patients subclinical hypothyroid was seen in 20%, while clinical hypothyroid was 60%.	Thyroid dysfunction occurred more frequently and in a younger age group in patients with SLE as compared to RA.
(Pyne and Isenberg, 2002), UK	Retrospective study	300 patients with SLE	To report the prevalence of autoimmune thyroid disease and thyroid antibodies in 300 patients with SLE.	-The prevalence of hypothyroidism in SLE patients (5.7%) was higher than the normal population (1%).	Systemic lupus erythematosus had a prevalence of hypothyroidism, greater than in the normal population.

Table 2.10 Summary of studies that investigated sjögren's syndrome, celiac and hypothyroidism

Author\years Place of study	**Type of study**	**Sample size**	**Objectives**	**Main finding**	**Conclusion**
(Al Awadhi et al., 2008), Kuwait	Case-control study	177patients with rheumatoid arthritis (RA), 60 with systemic lupus erythematosus (SLE) , 25 with primary Sjogren's syndrome (pSS), and 577 healthy controls	To examine the frequencies of abnormal thyroid function tests and serum thyroid autoantibodies in healthy Kuwaitis and those with autoimmune diseases.	- Subclinical hypothyroidism was seen in 16% of pSS patients and in 1.7% of healthy controls. - Overt hypothyroidism was seen in 1.4% of controls, and in 4% of pSS patients.	Thyroid function tests for primary Sjogren's syndrome patients.
(Punzi et al., 1996), Italy	Case-control study	121with primary Sjogren's syndrome and 74 with rheumatoid arthritis and 404 controls	To evaluate the frequency of thyroid disorders in primary Sjogren's syndrome.	- Hypothyroidism was more common among Sjogren's syndrome patients (13.4%) than rheumatoid arthritis patients (3.1%) ($P < 0.05$).	Thyroid disorders common in primary Sjogren's syndrome.
(Butt et al., 2011), Pakistan	Analytical cross sectional study	50 patients with Celiac Disease and 25 healthy non class children	To assess the thyroid functions in Celiac Disease patients.	-The prevalence of subclinical hypothyroidism was 10% in patients with celiac disease	Assessment of thyroid function in patients with Celiac Disease
(Ansaldi et al., 2003a), Italy	multi-center study	343 pediatric patients with CD and 230 healthy subjects as control	To establish the prevalence of autoimmune thyroid involvement in a large series of pediatric patients with Celiac Disease (CD).	-The prevalence of hypothyroidism in celiac patients was (8.1%) higher than control subjects (3.5%). -	Thyroid status assessment at diagnosis and at follow-up evaluation of children with CD.

Table 2.11 Summary of studies that investigated multiple sclerosis and hypothyroidism

Author\years Place of study	**Type of study**	**Sample size**	**Objectives**	**Main finding**	**Conclusion**
(Munteis et al., 2007), Spain	Prospective study	93 untreated MS patients and 401 healthy subjects	To determine the prevalence of thyroid autoimmune disorders in a cohort of untreated multiple sclerosis (MS) patients and compare it with a stratified sample of an adult population.	- The prevalence of subclinical hypothyroidism in Multiple sclerosis (MS) patient was significantly higher than healthy subjects (6.45% vs. 2.24%, P 0.03).	Subclinical hypothyroidism were common in Multiple sclerosis (MS) syndrome.
(Caraccio et al., 2005a), Italy	Follow-up study	106 multiple sclerosis patients	To assess the actual occurrence of thyroid dysfunction and autoimmunity during long-term IFN-beta therapy	-At baseline the prevalence of hypothyroidism was 2.8% in 106 multiple sclerosis patients.	Both incident thyroid autoimmunity and dysfunction frequently occur in multiple sclerosis (MS) patients during IFN- therapy.
(Ross et al., 2010), South Africa	Cohort study	74 patients with Addison's disease	To determine whether autoimmunity is the predominant cause of Addison's disease in South Africa and whether human leukocyte antigen (HLA) DQ association exists.	-The prevalence rate of primary hypothyroidism was 47% among patients with Addison's disease.	Hypothyroidism frequently coexists in Addison's disease
(Erichsen et al., 2009), Norway	Registry-based cohort study	426 patients with Addison's disease	To determine the clinical, immunological, and genetic features of Primary adrenal insufficiency [Addison's disease].	- The prevalence rate of primary hypothyroidism was 41% among patients with Addison's disease.	Hypothyroidism associated with Addison's disease
(Kasperlik-Zaluska et al., 2003), Poland	Reported 111 cases	111 patients' with adrenal insufficiency	To determine on whether of adrenal insufficiency	-57% of patients with secondary adrenal insufficiency had thyroid diseases , especially primary hypothyroidism	Primary hypothyroidism was common on secondary adrenal insufficiency

Table 2.12: Summary of studies that investigated pregnancy and hypothyroidism

Author\years Place of study	**Type of study**	**Sample size**	**Objectives**	**Main finding**	**Conclusion**
(Stuckey et al., 2010), Australia	A 12-year longitudinal study	409 women (including 71 with PPTD)	To ascertain the long-term risk of hypothyroidism in women following postpartum thyroiditis (PPTD).	-Hypothyroidism was present in 38% (71 women) who had postpartum thyroiditis (PPTD) at baseline with a significant adjusted odds ratio 9.7 for postpartum hypothyroidism.	A strong predictor of hypothyroidism in the long-term. women who present with postpartum hypothyroidism
(Mannisto et al., 2010), Finland	A prospective population-based cohort	5805 Mothers	To evaluate the association between maternal thyroid dysfunction/antibodies during pregnancy and pregnancy complications or later maternal hypertension, diabetes, and thyroid disease.	-Overt hypothyroidism was associated with subsequent maternal thyroid disease [hazard ratio (HR) (95% confidence interval), 17.7 (7.8-40.6).	Thyroid dysfunction and antibodies during pregnancy seem to predict later thyroid disease.

Table 2.13: Summary of studies that investigated obesity and hypothyroidism

Author\years Place of study	Kind of study	Sample size	Objectives	Main finding	Conclusion
(Marzullo et al., 2010), Italy	A cross-sectional study	165 obese and 118 lean subjects	To clarify whether a leptin excess of obesity could increase the susceptibility to develop autoimmune thyroid disease (AITD).	- Obese had greater prevalence of hypothyroidism compared to control (P<0.05).	Obesity increases the risk AITD with an emerging role for leptin.
(Mehran et al., 2012a), Iran	Cross-sectional community-based survey	1581 randomly subjects who had no histories of thyroid disorders	To evaluate the association between normal levels of serum TSH and BMI, taking into consideration the effect of smoking tobacco.	- TSH concentrations within the reference range were positively associated with BMI (P < 0.002.)	Positive association exists between TSH and BMI in euthyroid nonsmokers.
(Verma et al., 2008), India	Retrospective Observational study	(Group I) 625 consecutive primary hypothyroidism patients, and (Group II) 450 patients Obese	To establish relationship between obesity and hypothyroidism and to analyze the frequency the frequency of primary hypothyroidism in obese patients and frequency of obesity in primary hypothyroidism patients.	- Primary hypothyroidism was more prevalent in individuals with extreme obesity as compared to moderate obesity patients (56% versus 41%).	Thyroid dysfunction was more common in obese.

Table 2.14: Summary of studies that investigated goiter and hypothyroidism

Author\years Place of study	Type of study	Sample size	Objectives	Main finding	Conclusion
(Das et al., 2011), India	Case-control study	191children with goiter and 165 children without goiter	To examine the prevalence of goiter in the post-iodization phase and the relationship of goiter with micronutrient status and thyroid autoimmunity in school children.	- 3.2per cent children with goiter and 2.4 per cent without goiter had hypothyroidism (subclinical and clinical).	Goiter associated with hypothyroidism
(Aminorroaya et al., 2010), Iran	Cross-sectional study	2,523 adults aged > 20 years	To investigate the prevalence of goiter in Isfahan, 15 years after the initiation of universal salt iodization.	- The prevalence of hypothyroidism was 6.4% and 18.6% in non-goitrous and goitrous participants, respectively.	Goiter associated with hypothyroidism

Chapter 3: Conceptual Frame Work

3.1 Introduction

This chapter presents definitions of hypothyroidism, causes, diagnosis, treatment, and factors associated with hypothyroidism (i.e. the components of the conceptual framework). These factors including: socio-demographic factors (e.g. age and sex), life style factors (e.g. iodine intake in food, selenium, smoking, alcohol consumption, physical activity and weight), genetic factors and family history, medical conditions (e.g. type 1 diabetes, autoimmune thyroid disease, systemic lupus erythematosus, pernicious anemia, rheumatoid arthritis, Sjögren's, vitiligo syndrome & autoimmune adrenal insufficiency), medication (e.g. radioactive iodine or anti-thyroid medication), and history of diagnosis.

3.2 Hypothyroidism definition and classification

Hypothyroidism is a condition where the thyroid gland produces too little thyroxine for the body's needs. It is also known as an under-active thyroid (ATA, 2012a). Hypothyroidism is classified into two types: Primary and secondary hypothyroidism. Primary hypothyroidism is the most common type and it is caused by disorder of the thyroid gland itself. Central or secondary hypothyroidism results from hypothalamic or pituitary disease (Jayakumar, 2011). Also, hypothyroidism can be classified on the basis of severity into subclinical hypothyroidism and Overt or frank hypothyroidism. Subclinical hypothyroidism is referred to mild hypothyroidism as an abnormal serum thyroid-stimulating hormone level, free thyroxin and triiodothyronine levels within their reference ranges (Wilson and Curry, Jr., 2005a). Overt or frank hypothyroidism is defined as an elevated TSH and low serum free T4 (Aminorroaya et al., 2009). Moreover, hypothyroidism can also be classified based on its time of onset congenital or acquired hypothyroidism (Brown et al., 2005).

3.3 The etiological classification of hypothyroidism

Hypothyroidism is caused by diverse causes and conditions, in which thyroid fail to secrete an adequate amount of thyroid hormone. The most etiological classification of hypothyroidism suggested by Devdhar, M, et, al, is summarized in the table (3.1).

Table (3.1): The etiological classification of hypothyroidism

Type	Causes
Primary hypothyroidism	Chronic autoimmune thyroiditis Sub-acute, silent, postpartum thyroiditis Iodine deficiency, iodine excess Thyroid surgery, I-131 treatment, external irradiation Infiltrative disorders Drugs Agencies and diagnosis of the thyroid
Central or secondary hypothyroidism	Pituitary tumors, metastasis, hemorrhage, necrosis, aneurysms Surgery, trauma Infiltrative disorders Infectious diseases Chronic lymphocytic hypophysitis Other brain tumors Congenital abnormalities, defects in thyrotropin releasing hormone, TSH, or both

Source: (Devdhar et al., 2007)

3.4 Hypothyroidism diagnosis

American Thyroid Association, British Thyroid Association, and American Association of clinical Endocrinologists set criteria for the diagnosis of hypothyroidism include physical examination, medical and family history. Diagnosis of hypothyroidism is confirmed by laboratory tests to measure the blood levels of thyroid hormones. Two tests are mainly used: TSH (thyroid stimulating hormone) test, and fT4 tests. TSH is a sensitive test for the diagnosis of primary hypothyroidism, while not reliable for the diagnosis of secondary hypothyroidism. Thus, FT4 test plus TSH test should be used for the diagnosis of secondary hypothyroidism (AACE, 2006,ATA, 2012a,BTA, 2010,Garber et al., 2012). Other tests may also help in the diagnosis of hypothyroidism including:

1) Thyroid autoantibodies, for example: anti-thyroglobulin antibodies (TgAb), and

anti-thyroid peroxidase antibodies (TPOAb).

2) Radioactive iodine uptake (RAIU) and thyroid scanning.

3) Ultrasonography of the neck and thyroid.

4) fine-needle aspiration (FNA) biopsy (Philip R Orlander, 2013).

3.5 Hypothyroidism treatment

Conventional treatment of hypothyroidism typically by replacing the missed thyroid hormone using prescription thyroid hormone replacement drugs. Levothyroxine (T4) is a synthetic thyroid hormone which is the primary drug of choice for treating of hypothyroidism (Chakera et al., 2012). The daily dosage of Levothyroxine depend particularly on body weight, moreover on age, sex, and body size (Garber et al., 2012). However, a randomized controlled trial has recommended for the starting dose of levothyroxine varies considerably: from 50 μg to a full replacement dose of 1.6 or 1.7 μg/kg in healthy adult patients younger than 65 years, and from 25 to 50 μg/d in older patients and those with known ischemic heart disease (Roos et al., 2005). Treatment of primary hypothyroidism with using combinations of T4 and T3 is still needed for more evidence to recommend (Gaitonde et al., 2012).

3.6 Hypothyroidism follow-up

American Thyroid Association (ATA) recommends that healthy adults can be screened for thyroid dysfunction by measuring of serum thyrotropin concentration, beginning at age 35 years and every 5 years thereafter (Ladenson et al., 2000a). While for patients with hypothyroidism, American Thyroid Association (ATA) recommends that they need to check TSH levels every 6 to 10 weeks after a thyroxine dose change, but babies with hypothyroidism must check TSH levels as they grow. And for pregnancy they need more often check for TSH levels (ATA, 2012a).

3.7 Theoretical and Conceptual framework

According to a literature review and after reviewing all models suggested for risk factors for hypothyroidism, the theoretical models worldwide summary; i.e. American Thyroid Association (ATA, 2012a), American Association of Clinical Endocrinologist (Garber et al., 2012), British Thyroid Association (BTA, 2010).

The risk factors are summarized as follows:

- Socio-demographic factors (e.g. age, sex, and race\ethnicity).
- Life style factors (e.g. iodine intake in food, smoking and alcohol consumption).
- Family history (e.g. having a close relative with an autoimmune disease).
- Genetic factors.

- Medical conditions (e.g. diabetes mellitus, vitiligo, pernicious anemia, turner syndrome and down syndrome).
- Medication (e.g. radioactive iodine or anti-thyroid medication).
- History of diagnosis.

Conceptual framework for this study including:

- Socio-demographic factors: (e.g. age and sex).
- Life style factors (e.g. iodine intake in food, smoking and alcohol consumption).
- Family history (have a close relative with an autoimmune disease)
- Medical conditions (e.g. diabetes mellitus, vitiligo, pernicious anemia, turner syndrome and down syndrome)
- Medication (e.g. radioactive iodine or anti-thyroid medication).
- History of diagnosis

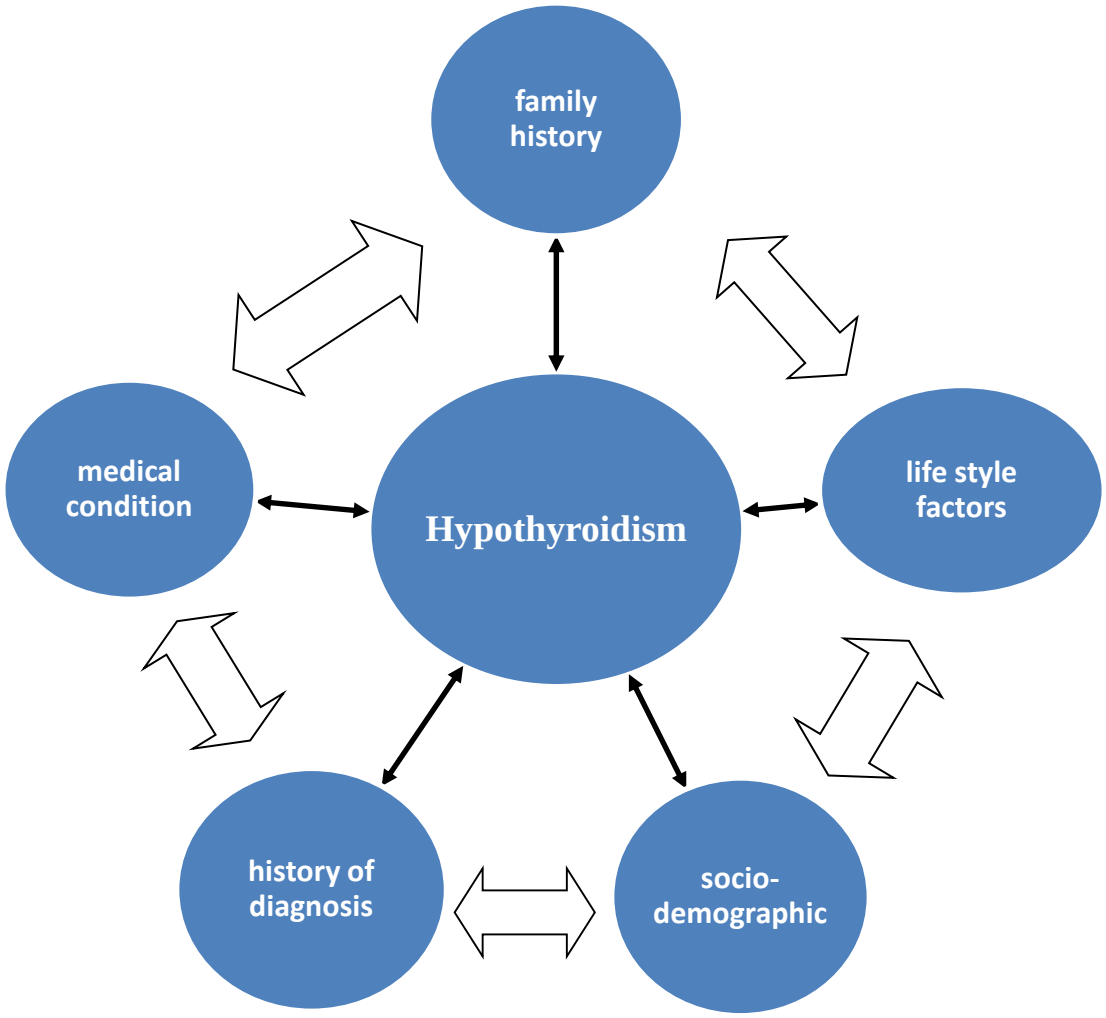

Figure 2: The study conceptual framework

The theoretical and conceptual framework will include all risk factors for hypothyroidism except race\ethnicity because hypothyroidism occurs more often in white Asians than in African Americans.

3.8 Hypothyroidism and socio-demographic risk factors

3.8.1 Age

Age is considered as a risk factor for developing hypothyroidism. The risk of hypothyroidism increasing with advancing age, especially in women older than age 60 (Mayo Clinic, 2012). Increasing the risk of hypothyroidism in elderly, principally due to the rising incidence and prevalence of autoimmune thyroiditis (Faggiano et al., 2011). As people age & aging process leads to impact of the thyroid hormone synthesis. Most studies found a

clear age-dependent decline in stimulating hormone (TSH) and (free) T3. While, other studies found in contrast an increase in TSH levels in elderly (Peeters, 2008). Moreover, many studies found increasing antithyroid with aging. This is resulting in an increase prevalence of hypothyroidism in elderly (Surks and Hollowell, 2007).

3.8.2 Gender

Gender is the strongest risk factor for hypothyroidism. A bundant epidemiological studies found that hypothyroidism is much more common in women than in men, with reports 10 times more common in women than in men (Vanderpump, 2011). The causes of higher risk in women are still unclear, but there are etiological factors that may poses increased risk of developing hypothyroidism in women which include: pregnancy, genetic factors (e.g. skewed X chromosome inactivation patterns and defects in the sex chromosomes), medical condition, and sex hormones (Jorgensen et al., 2010). Pregnancy is a major factor that increases the risk of developing of hypothyroidism in women. It affects the thyroid gland through physiological and hormonal changes that alter thyroid function. Two main hormonal changes during pregnancy affect thyroid function, which are human chorionic gonadotropin (HCG) and Estrogen. In addition, some women develop antibodies to their own thyroid during pregnancy, which causes postpartum sub-acute thyroiditis and can increase the risk of developing permanent hypothyroidism (ATA, 2012d). Genetic factor contributing to develop hypothyroidism only in women through the influence of X –chromosome inactivation, that's seen in Hashimoto's thyroiditis was very prevalent among girls with Turner's syndrome (XO karyotype) (Prummel et al., 2004). Towards that, a possible role of influence of X –chromosome inactivation may in part explain the female preponderance of Hashimoto's thyroiditis (Brix et al., 2009). Some medical conditions affect only women could be increase the risk for developing hypothyroidism such as polycystic ovary syndrome (PCOS). In Germany a prospective study demonstrated that women with polycystic ovary syndrome (PCOS) had a threefold prevalence of autoimmune thyroiditis (AIT) (Janssen et al., 2004).

3.9 Hypothyroidism and lifestyle factors:

3.9.1 Iodine intake

Iodine deficiency is the most common cause of hypothyroidism worldwide. Although it's an essential element for enables the thyroid gland to produce triiodothyronine (T3) and thyroxine (T4) hormones (ATA, 2012b). Moreover, excessive iodine intake can also cause hypothyroidism due to a failure to escape from the Wolff–Chaikoff effect, by a mechanism of inhibiting the thyroid from synthesizing large quantities of thyroid hormones (Lee et al., 2010).

3.9.2 Selenium

Several studies suggest that selenium plays an essential role in prevent the development of hypothyroidism. The role of selenium on thyroid gland incorporated as selenoproteins, which participate in the protection of thyrocytes from damage by H_2O_2 produced for thyroid hormone biosynthesis. In addition, selenium constitutes an essential part of iodothyronine deiodinase enzymes which catalyze thyroid hormone by activation and inactivation convert of thyroxine (T4) to triiodothyronine (T3) (Rasmussen et al., 2011). Furthermore, selenium has also an important impact on immune function which impact on inflammatory activity in thyroid-specific autoimmune disease (Gartner and Gasnier, 2003).

3.9.3 Smoking

Epidemiological studies found that smoking has either no associated or an increased risk of hypothyroidism. The mechanism by which smoking effect on thyroid gland include interfering with thyroid gland hormonogenesis and with peripheral thyroid hormone action (Belin et al., 2004).

3.9.4 Alcohol consumption

Recent studies found that moderate alcohol consumption is associated with a decreased development of overt autoimmune hypothyroidism. The mechanism that alcohol effect on thyroid autoimmunity remains unclear (Laurberg et al., 2006). While other studies in the past have shown that alcohol dependence cause reduction in peripheral thyroid hormones and/or

blunted thyroid stimulating hormone (TSH) response to deregulation in the central hypothalamic–pituitary–thyroid (HPT) axis (Ozsoy et al., 2006). The reduction in serum thyroid hormones was explained due to direct and irreversible toxic effect of alcohol on the thyroid gland (Valeix et al., 2008).

3.9.5 Physical activity

Studies suggest that moderate exercise is an important factor in treatment of hypothyroidism. Exercise has a greater effect on the thyroid gland and its level of circulating thyroid hormones (Ciloglu et al., 2005b), moreover it can also help in combat with the major symptoms of hypothyroidism such as weight gain, fatigue and depression (Thyroid Guide, 2011).

3.9.6 Weight

Obesity is associated with an increased risk of hypothyroidism and vice versa. Both types of hypothyroidism (subclinical and overt hypothyroidism) are frequently associated with weight gain, due to the increased TSH level which decreased thermo genesis and metabolic rate (Biondi, 2010). While obesity increases the susceptibility to harbor autoimmune hypothyroidism due to the effects of adipocytokine leptin on the pituitary gland (Marzullo et al., 2010).

3.10 Genetic factors and family history

A genetic factor is known to be an important risk factor of hypothyroidism. Genetic factors play a role in developing hypothyroidism through effects on the causes of hypothyroidism which include autoimmune thyroid disease AITD (Hashimoto's thyroiditis), congenital hypothyroidism, and chromosomal disorders (e.g. Down syndrome & Turner syndrome).

Hashimoto's thyroiditis is one of the most prevalent causes of hypothyroidism, its influenced by both genetic and environmental factors (Erkan Sar et al., 2011). Several genes are susceptible to Hashimoto's thyroiditis such as human leukocyte antigen (HLA), cytotoxic T lymphocyte antigen-4 (CTLA-4), protein tyrosine phosphatase nonreceptor-type 22, thyroglobulin, vitamin D receptor, and cytokines gene (Zaletel and Gaberscek, 2011).

Congenital hypothyroidism is defined as thyroid hormone deficiency present at birth. It may causes by mutations in PAX, TSHR, DUOX2, SLC5A5, TG, TPO, and TSHB gene. These mutations can cause loss of thyroid function in one of two ways: disrupt the normal development of the thyroid gland (dysgenesis) before birth, or a disorder of thyroid hormone biosynthesis (dyshormonogenesis) (Rastogi and LaFranchi, 2010).

3.10.1 Family history of autoimmune diseases (AITD):

Family history of autoimmune thyroid disease AITD (Hashimoto's thyroiditis) is associated with increased risk of hypothyroidism. The risk increased if you have a close relative such as a parent or grandparent with an autoimmune disease (MC, 2012). Family history of autoimmune thyroid disease may occur in one member or multi member of the same family as a result of random chance, extrinsic (environmental) factors, intrinsic (genetic) factors, or a combination of these factors. (Tomer and Davies, 2003).

3.11 Hypothyroidism and medical conditions

Abundant studies documented that certain medical conditions are risk for developing hypothyroidism. These conditions include:

3.11.1 Autoimmune diseases

Multiple autoimmune diseases including: diabetes type 1, autoimmune thyroid disease, systemic lupus erythematosus, pernicious anemia, rheumatoid arthritis, Sjögren's, vitiligo & autoimmune adrenal insufficiency (Addison's disease). These autoimmune diseases have a tendency to coexistence within individuals, which lead to developing hypothyroidism. Explanations for the coexistence of autoimmune disorders involve immunological disturbances (in B and T lymphocytes), a trend to react abnormally in the presence of an antigen and a genetic susceptibility (Raterman and Nurmohamed, 2012a).

3.11.2 Down syndrome

Down syndrome is associated with primary hypothyroidism with a prevalence rate ranging from 3% and 54% (Shaw et al., 2006). Down's syndrome may associated with high levels of thyroid antibodies (Karlsson et al., 1998). There are several hypotheses that described an

association between down syndrome and primary hypothyroidism, one of these hypotheses suggested that over expression of the gene DYRK1A in those with trisomy 21 chromosome may have an effect on development hypothyroidism (Thiel and Fowkes, 2007).

3.11.3 Turner syndrome

Turner syndrome especially in females is associated with a higher prevalence rate of hypothyroidism with ranges from 0 - 40% (Jorgensen et al., 2010) . The higher risk of hypothyroidism in females with Turner syndrome has been addressed by several studies, one of these studies thought that a gene on the long arm of X chromosome (Xq) may play an important pathogenic role in the development of autoimmune hypothyroidism (Elsheikh et al., 2001).

3.9.7 Goiter

Goiter is associated with increased risk of hypothyroidism, which known to be associated with disturbance of thyroid iodine metabolism (Aminorroaya et al., 2009).

3.12 Hypothyroidism and medications

Several studies demonstrated that medications such as: interferon, amiodarone, lithium, radioactive iodine, thyroid surgery and Thionamides (e.g. methimazole, propylthiouracil & carbimazole) were associated with increased risk of developing hypothyroidism.

3.12.1 Interferon-α

Interferon-α is a standard therapy for hepatitis C virus infection and the most frequent side effect is hypothyroidism (Pavan et al., 2011). The mechanisms of Interferon-α on thyroid gland include activated immune system through induced cytotoxicity, direct inhibitory effects on thyroid hormone synthesis, release and metabolism (Carella et al., 2004).

3.12.2 Amiodarone

Amiodarone is an effective anti-arrhythmic drug, iodine-rich structure, and may either induce thyrotoxicosis or induced hypothyroidism (Piga et al., 2008). The mechanism

of amiodarone-induced hypothyroidism through inhibits the thyroid gland to escape from the Wolff–Chaikoff effect (Lee et al., 2010).

3.12.3 Lithium

Lithium is widely used in the treatment of mood disorders and it has been associated with increased risk of hypothyroidism (Kibirige et al., 2013). The mechanism by which lithium induces hypothyroidism include inhibition synthesis and release of thyroid hormone, and promotes thyroid autoimmunity (Johnston and Eagles, 1999).

3.12.4 Radioactive iodine (131I)

Radioactive iodine (131I) is mostly used in the treatment of Graves's hyperthyroidism, toxic multi-nodular goiter and thyroid cancer. The most common side effect of radioactive iodine is hypothyroidism (Ahmad et al., 2002). The mechanism of radioactive iodine involves destroying all or part of the thyroid gland (ATA, 2012c).

3.12.5 Thyroid surgery

Thyroid surgery is used to treat a variety thyroid conditions including both cancerous, and benign thyroid nodules, goiter, thyroid cancer and Graves hyperthyroidism. Thyroid surgery mainly follows with hypothyroidism with rates between 6.5 and 45% (Cho et al., 2011c). The most common cause of hypothyroidism after surgery is subtotal resection of Graves disease or multi-nodular goiter, and autoimmune destruction of the thyroid tissue (Lankarani et al., 2008).

3.12.6 Thionamides

Thionamides (e.g. Methimazole, Propylthiouracil & Carbimazole) are a major antithyroid drugs used for treatment of Graves hyperthyroidism, or as preparation therapy before radiotherapy or surgery. The primary mechanism of these drugs is inhibiting thyroid hormone synthesis by inhibiting thyroid peroxidase (Cooper, 2005). Antithyroid drug is associated with hypothyroidism in which a study thought that association result from overly aggressive dosing in mild hyperthyroidism or failure to adjust the ATD dosage (Choo et al.,

2010), while another study suggested that the association may due to concomitant autoimmune thyroiditis (Wood and Ingbar, 1979).

3.13 History of diagnosis

The diagnosis of hypothyroidism is based on physical examination, medical & family history, and laboratory investigation (Garber et al., 2012) . Previous studies revealed that a delayed in the diagnosis of hypothyroidism can lead to retardation of physical and mental growth (Malik and Butt, 2008a).

3.14 Summary

In summary, the literature showed that several risk factors associated with hypothyroidism, which are divided into: socio-demographic factors (age and sex), environmental factors (iodine intake in food and smoking), family history (have a close relative with an autoimmune disease), medical conditions (e.g. diabetes mellitus, vitiligo, pernicious anemia and down syndrome), medication (e.g. radioactive iodine or anti-thyroid medication) and history of diagnosis. These factors were used to build this study conceptual framework. This chapter is the base for analysis in the coming results chapter and the study results discussion and conclusion.

Chapter Four: Study Methodology

4.1 Introduction

In this chapter, the research methodology is presented. The study area, study population, study type, design, tools, the sampling method, statistical analysis, ethical consideration, and variables operational definitions are presented.

4.2 Study area geographic and population characteristics

The study was carried out in the Hebron governorate. Hebron area covers northern part of Hebron governate and Dura covers the southern part of Hebron governate.

Hebron governorate is the largest governorate in Palestine located in the southern part of the West Bank, 30 kms south of Jerusalem and lies 930 meters above sea level (Wikipedia, 2013). It contains in addition to the city of Hebron 28 villages and 2 refugee camps.

Demographic trends in Hebron governorate is almost like the other governorates in the West Bank. According to the population statistics estimated by the Palestinian Central Bureau Statistics (PCBS) the total population was estimated 641,170 thousand citizens, of which 314,174 are females and 326,996 are males (PCBS, 2011).

Dura area is located in the south-west of Hebron Governorate (Wikipedia, 2012). The total area of Dura is estimated to be 17,600 dunums, of which 7,100 dunums are built-up areas, 8,220 dunums are agricultural lands, and 1,270 dunums are forests, uncultivated areas, or public lands (ARIJ, 2009).

The demographic trends in Dura is closely related to the economic and political situation like the other governorates in the West Bank. According to the population statistics estimated by the Palestinian Central Bureau Statistics (PCBS), the total population of Dura in 2013 is estimated to be 33,914 citizens (PCBS, 2013).

4.3 Primary health services in the North and South of Hebron governorate

The main health care providers for patient in the Hebron governorate are the Ministry of Health, UNRWA, NGOs, Palestinian Military Medical Services (PMMS) and the private sector.

The MOH is considered the major provider of primary health care services as it operates 126 PHC out of 146 PHC facilities, NGO's operates 16 PHC, UNRWA operates three PHC, and PMMS operates one PHC (MOH, 2011b).

Karantina, the main primary health care clinic in Hebron, has six specialist sub-clinics, including an endocrinology clinic that started recently to operate by providing several services for inhabitants in the northern part of Hebron, including diagnosis, treatment and follow up of referred patients (Abu Rmeileh, 2013).

In the southern part of Hebron there are 94 primary health care clinics (PHC), of which 84 are sponsored by the MOH, six by NGOs , four by UNRWA , and one by PMRS (MOH, 2011b).

The main health bodies in Dura town are: the Dura clinic, the UNRWA clinic, the Maternity & Pediatric Centre, and the Emergency Centre for Military Medical Services (ARIJ, 2009).

Dura clinic, the main MOH clinic in the Southern part of Hebron, has six specialist sub-clinics and including an endocrinology clinic that provides diagnosis, treatment and follow up of the referred patients (MOH, 2011a).

4.4 Health services for hypothyroidism

Karantina and Dura clinics are the only MOH centers that provide endocrinology care services in Hebron governorate. These services include the diagnosis, treatment and follow up of endocrine referred patients (Abu Rmeileh, 2013).

4.5 Study settings

The study was conducted at Karantina and Dura endocrinology clinics:

Karantina clinic provides service for the central and the northern areas of Hebron area

Dura clinic provides services for the central and the southern areas of Dura areas.

4.6 Study design

The study design was a case- control study.

4.7 Study stages:

The study was done in two stages:

4.7.1 Stage 1: Descriptive analysis

4.7.1.1 Source of data:

The data was collected from patients' files

4.7.1.2 Data collection from patients' files

All files presented in the two selected clinics were included in the study. Patients' files were read by the study researcher at the endocrinologist clinic to be sure of what is written in these files. Medical information was clarified for the researcher, so he can coded in the sheet of data collection.

The collected data from these files were: patients' file numbers, gender, place of residence, hypothyroidism diagnosis date and type of diagnosis. For patients diagnosed with hypothyroidism, the researcher extracted as well: the cause, type of hypothyroidism, diagnosis history, TSH level, and treatment & its dosage.

4.7.2 Stage 2: a case-control study

4.7.2.1 Study population:

All patients visiting the two targeted clinics for thyroid problems between June 2012 and June 2013 were targeted and asked to participate in the study. During this period 103 patients who met the study inclusion criteria were approached and invited to participate. Also an equal number of patients attending the other primary care clinics, for reasons other than endocrine problem were invited to participate. The study sample included 206 participants

(i.e. 103 study cases and 103 controls, 1:1). These characteristic were used for inclusion and exclusion for both cases and controls.

4.7.2.2 Selection criteria

1- Selection of study cases

The study cases from Karantina and Dura endocrinology clinics were distributed as follows:

- 42 patients with hypothyroidism were registered at the Karantina endocrinology clinic.
- 61 patients with hypothyroidism were registered at Dura endocrinology clinic.

2-Selection of controls:

The controls were patients attending other specialized clinics in Karantina and Dura clinics e.g. gynecology clinic and internal medicine clinic. Those controls were invited to participate in the study. The control group were :

- 37 participants from Karantina clinic.
- 66 participants from Dura clinic.

3-Exclusion criteria for controls:

1- Any patient who refused to do blood drawing for TSH level measurement.
2- Any patients who has a TSH level above 3 at the time of survey.
3- Patients previously diagnosed with autoimmune diseases: Thyroid dysfunction, goiter, diabetes mellitus, vitiligo, pernicious anemia.
4- Patients using medications: Surgery or radiotherapy, lithium carbonate and iodine-containing compounds.
5- Pregnant women.

4.7.2.3 Case-control study tools:

In stage two, a study questionnaire and TSH measurement were done.

1- Structured Questionnaire

The structured questionnaire was based on previous studies questionnaire, American Thyroid Association guidelines for detection of thyroid dysfunction (Ladenson et al., 2000c), Thyroid Foundation of Canada (TFOF, 2013), University of Wisconsin Integrative Medicine(WISC, 2011) and WHO (WHO, 2006).

For lifestyle category, we used Steps Arabic questionnaire of WHO for smoking and physical activity (WHO, 2006). Also, we used integrative treatment of hypothyroidism of University of Wisconsin Integrative Medicine (WISC, 2011) and common source of dietary iodine of American Thyroid Association (ATA, 2012b).

For medical conditions and medications , we used the questionnaire of the health study of Nord –Trondelage (HUNT) in Norway (Bjoro et al., 2000) and the American Thyroid Association guidelines for detection of thyroid dysfunction (Ladenson et al., 2000c).

For family history of thyroid diseases and autoimmune diseases, we used the questionnaire of a study in UK (Parle et al., 1991b) and the American Thyroid Association guidelines for detection of thyroid dysfunction (Ladenson et al., 2000c).

For women's health, we used the thyroid assessment questionnaire of the Thyroid Foundation of Canada (TFOF, 2013).

Data were collected from subjects through personal face-to-face interview. Each interview took about 45 minutes. The questionnaire contained a set of questions relevant to each risk factor of the conceptual framework including: (See Annex 2 for the questionnaire copy).

1. Personal socio-demographic data such as age, gender, marital status, family size, living area, educational years, work and household average monthly income. Questions (1-23)
2. Lifestyle, which included questions about smoking habit, alcohol drinking, weight, physical activity, food intake and supplements intake. Questions (24-106)
3. Medical conditions, which included questions about chronic diseases and autoimmune diseases. Questions (39-89)

4. Medications, which included questions about the usage of medication such as propylthiouracil, thyroidectomy, radioactive iodine, lithium, amiodarone, interferon, carbimazole and methimazole. Questions (131-136)
5. Women's health, which included question about menstrual cycle and pregnancy. Questions (138-142).
6. Family history, which included questions about family history of autoimmune diseases. Questions (150-160)
7. Diagnose history for cases, which included questions (only for case) about the date of diagnosis, age, weight, diagnosed hypothyroidism, person who did the diagnoses, treatment and dosage. Questions (143-149).

Questionnaire validation and piloting

The questionnaire was sent to three specialist endocrinologists, Dr. Aref Abu Remileh, Dr. Abdel Latif Shawar and Dr. Raed AL Alami. Two of them answered and suggested to add one question to the medical condition. After that, pilot study was done on 10 patients with hypothyroidism attending private endocrinology clinic. The interview was held with patients after explaining to them about of the study aim. Refining of the questionnaire was done according to the results of the pilot study, and the results were excluded from the whole study. At the end, we did Cronbach's Alpha coefficient to check the reliability of questionnaire. The result of Cronbach's Alpha coefficient was as follows: 67% for food & supplements, 65% for medical conditions, 27% for medication, 43% for women health and 46% for family history of autoimmune diseases.

2- TSH test

TSH tests were done to all control participants in order to exclude the probability of having undiagnosed hypothyroidism and included only participants with TSH between 0.4- 4.0 µIU/ml.

Samples collection and handling:

1. A laboratory technician collected 2.0 ml of venous blood samples obtained from the control participants who agreed to participate in the study by signing a consent form specially designed for this study.
2. Blood was collected in plain vial tube and allowed to clot and centrifuged at 5000 RPM for 10 minutes.
3. Separated serum was stored in appropriate conditions, avoiding exposure to high or low temperature. After that, serum was transferred using appropriate condition (ice box) to "Horus" specialized medical laboratories in Hebron where TSH tests were performed.
4. TSH tests were assayed by IMMULITE / IMMULITE 1000 rapid TSH immunometric assay method.

After patients verbal consent form (Annex 1) to participate in the study, each patient had to sign a special consent form. In addition, a laboratory technicians collected blood samples which was transferred in ice box to specialized medical laboratory in Hebron.

4.8 Data analysis

The collected data was coded manually then entered, cleaned and analyzed by using the Statistical Package for Social Sciences (SPSS version 17.0).

Data analysis included:

- Descriptive analysis for patients' files data, and study subjects. Frequencies were calculated for all variables and presented as percentages.
- Univariate analysis was presented showing the association between hypothyroidism and the studied determinants with the socio-demographic factors, lifestyle factors, medical conditions, medications, women health, and family history of autoimmune diseases. Frequencies and Chi-squared test were calculated, and *p*-values were calculated for ordinal level measures ($P<0.05$)
- T-test was done to examine the difference of TSH levels between the study cases and control groups.
- Multiple logistic regressions was done to all statistically significant variables in the univariate analysis to obtain the odds ratio (OR) and 95% confidence interval. The

model includes: participants BMI; household monthly income; education level; age; gender; living area; working status; rate of daily physical activity; smoking by other in closed places; smoking by other at home; consumption of fruits; consumption of vegetables; consumption of carrots; consumption of canned tuna; consumption of canned sardines; consumption of coffee; consumption of red meat; consumption of yogurt; taking iron supplement; taking vitamin B_{12} supplement; taking calcium supplement; and frequency of eating banana and strawberry.

4.9 Ethical consideration

The Faculty of Public Health committee accepted to do the research; and the approval to carry out the study was obtained from the Graduate Studies Committee at Al-Quds University. Moreover, we obtained permission to conduct this study from the Ministry of health.

All study cases and control group received a full explanation about the details of the study, its aim, objective and benefit. The researcher asked them to sign a consent form to show their approval (See Annex 1). The written consent form was attached to each questionnaire explaining the aim and objectives of the study and confidentiality controls had to sign their agreement to have a blood test for TSH level. We found that 4 of participants in the study have high TSH level and they were referred to an endocrinologist. In addition, we considered them as cases.

4.10 Operational definition of variables

Clinics: (Karantina or Dura).

Gender: (male or female).

Age category: composed of three categories (≤18 years, 19-40 years, >40 years).

Marital status: composed of two categories (single or married).

Family size: composed of two categories (≤ 5 persons, >5 persons).

Place of residence: Place in which participant live (urban, or rural)

Educational level: composed of four categories (**≤** 6 years, 7-9 years, 10-12 years, >12 years).

Occupation: composed of two categories (working, not working).

Household average monthly income: composed of four categories (< 1000 NIS, 1000-2000 NIS, 2001-3000 NIS, 3001-5000 NIS).

Smoking: composed of two categories (smoking , not smoking).

BMI: weight in kilogram divided by the height in meter square, and composed of four categories (underweight < 18.5, normal 18.5-24.99, overweight ≥ 25-29.99, Obese ≥ 30).

Rate of daily activity: composed of three categories (high, medium, low)

Physical activity : composed of four types of exercise (walking, running, exercises with equipment and exercises without equipment).

Frequency of exercise per hour: composed of four categories (< half an hour, half an hour, 1-2 hours, > 2 hours**).**

Frequency of exercise per week: composed of four categories **(** less <1, 3-2, 4-5, >6)

Food groups: composed **(** fruits, vegetables, milk and milk products, animal products, beverages, water**,** bread, nuts and salty snacks)

Frequency of food intake: composed of four categories (<1 per week, 1-4 per week, 5-7 per week, 2-3 times daily**).**

Supplements: composed **(**multivitamins with iodine**,** multivitamins without iodine, vitamin B complex, vitamin B12, vitamin B6, calcium, calcium + vitamin D, iron supplements and folic acid **).**

Chronic diseases: composed (diabetes , pituitary disease, thyroid disease heart disease, liver disease, kidney disease, mental illness, diabetes type 1, Down syndrome, anemia, Sjögren's, Addison's disease and celiac disease)

Medication: composed (thyroidectomy, propylthiouracil lithium, amiodarone, interferon, carbimazole and methimazole)

Euthyroid: (TSH level within the normal range, 0.4 – 4 mIU/L).

Overt hypothyroidism: (TSH>4 mIU/L and low FT4I).

Subclinical hypothyroidism: (TSH level>4 mIU/L and normal serum FT4I).

4.11 Summary

This chapter presents an overview of the methodology that was used in this research. It provides study justification, design. Moreover, it provides description of the study setting and sample, and the pilot testing of the data. The study tool and instruments that were used in the data collection were explained. Descriptive statistics was used in data analysis and univariate analysis & multivariate analysis was done to compare the relationship between the dependant and independent variables.

Chapter 5: Results

5.1 Introduction

In this chapter, results are presented in 3 parts. The first part presents a descriptive analysis of patients' files and study cases. The second part presents a descriptive analysis of the study subjects. And in the third part the univariate and multivariate analysis model are shown.

5.2 Part one: Descriptive analysis

5.2.1 Descriptive analysis of the patients' files

In this study, the researcher investigated all patients' files registered at the two main governmental clinics (Karantina and Dura clinic) between years 2008 and April 2012 in Hebron governorate. Figure 5.1 reveals that hypothyroidism was the most diagnosed endocrine disorder with the prevalence of 17.1% among patients attending the clinics (16.9% Karantina and 17.5% in Dura).

As shown in figure 5.2, the types of hypothyroidism were: 87.0% primary hypothyroidism, 5.2% secondary hypothyroidism and 7.8% congenital hypothyroidism.

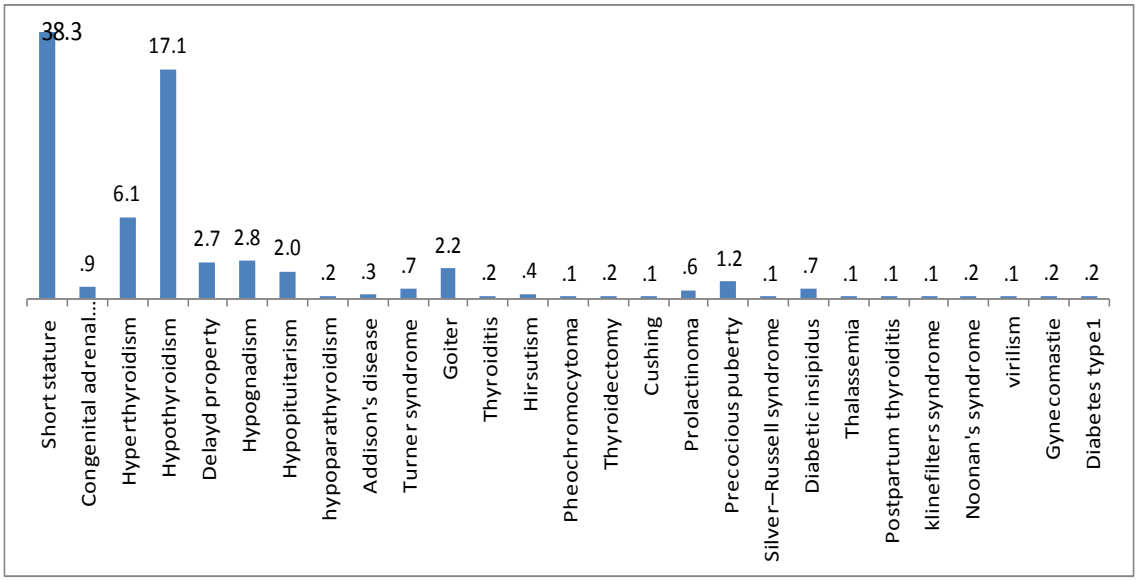

Figure 5.2: Distribution of endocrine disorders in the clinics

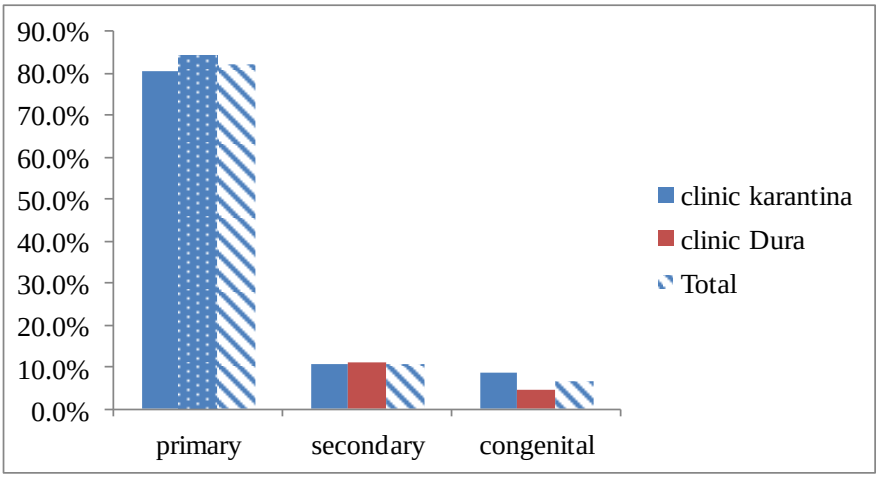

Figure 5.2 : Distribution of type of hypothyroidism in the clinics

Figure 5.3 shows the first diagnosis of endocrine disorder at the registration of the patient before having primary hypothyroidism. Primary hypothyroidism and medical conditions were 0.5% hyperthyroidism associated, 0.5% turner syndrome associated, 2.2% thyroid cancer associated, 1.6% goiter associated, 0.5% thyroids associated, 1.1% thyroidectomy associated, 0.5% postpartum thyroiditis associated and 1.1% diabetes type 1 associated. While between secondary hypothyroidism and medical conditions were 54.2% hypopituitarism associated and 4.2% thalassemia associated.

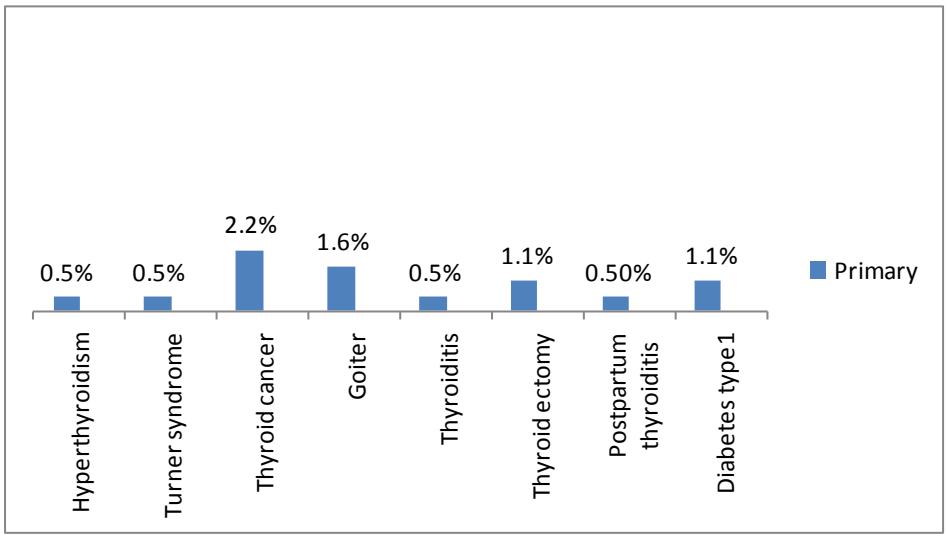

Figure 3.3: Association between types of hypothyroidism and endocrine disorders in the clinics

5.3 Study cases description

5.3.1 History of diagnosis

Table 5.1 shows that the mean age at the time of diagnosis of the study cases was 33.3 ± 14.5 years (mean ± S.D). Of them, 68.9% were diagnosed with hypothyroidism. The diagnosis was based on the presence of hypothyroidism symptoms and blood TSH, T3 and T4 levels and 50% were diagnosed done by an endocrinologist. All study cases uses thyroxine with a maximum dose of 250 µg and a minimum dose of 25 µg to treat and control their thyroid gland activity.

Table 5.1: Characteristic of the study cases

		N (%)	Mean ±SD	Minimum	Maximum
Years of diagnosis			4.58 ± 4.87 years	0.49	23.76
Age			33.3 ± 14.5 years	0.15	64.00
Diagnosed hypothyroidism	**By chance**	22 (21.4%)			
	Periodic inspection	10 (9.7%			
	The presence of symptoms	71 (68.9%)			
Who diagnosed?	**General practitioner**	31 (30.1%)			
	Endocrinologist	51 (49.5%)			
	Internists	11 (10.7%)			
	Gynecologist	9 (8.7%)			
	Nephrologist	1 (1.0%)			
Thyroxine dose	**First treatment**	103 (100%)	63.65 ± 38.86	25.00	200.00
	Current treatment	103 (100%)	86.94 ± 48.25	25.00	250.00

5.3.2 BMI for study cases

Table 5.2 shows that the mean BMI of the study cases ≥18 years at study time was 29.67 ± 5.73 and 28.54 ± 6.59 at diagnosis, indicating that the BMI of study cases decreased after diagnosis. Height at time of diagnosis is not present in all patients' files. While the mean BMI of the study cases aged less than 18 years at study time was 19.07± 6.24.

Table 5.2: BMI of the study cases at study time and diagnosis

	N	Mean ±SD	Minimum	Maximum
BMI (≥18 years) at study time	92	29.67±5.73	14.79	43.70
BMI (≥18 years) at diagnosis	92	28.54±6.59	1.32	43.96
BMI (<18 years) *at study time	11	19.07±6.24	13.33	33.53

5.3.3 Family history of autoimmune diseases

Table 5.3 shows that study cases had significantly more family history of autoimmune diseases including vitiligo, thyroid diseases (hypothyroidism and hyperthyroidism) compared to the control group (P <0.05). Other variables such as diabetes type 1, down syndrome, pernicious anemia, sjögren's, addison's disease and celiac disease did not show any significant differences between the two groups (P > 0.05 see annex 3).

Having a family history of vitiligo, thyroid diseases, hyperthyroidism were significantly different among study cases and control group (p<0.05). However, having a family history of hypothyroidism did not show such significant difference between the two groups (table 5.3.3).

Table 5.3: Associations between study cases and control groups by family history of autoimmune diseases

		Study cases N=103	Control group N= 103	Total (%) N=206	Chi Square
		N (%)	N (%)	N (%)	P value
Vitiligo	**Yes**	5 (4.9%)	0 (0.0%)	5 (2.4%)	0.024
	No	98 (95.1%)	103 (100.0%)	201 (97.6%)	
Family history	**First degree relative**	4 (80.0%)	0 (0.0%)	4 (1.9%)	NA
	Second degree relative	1(20.0%)	0 (0.0%)	1 (0.5%)	
Thyroid diseases	**Yes**	45 (43.7%)	26 (25.2%)	71 (34.5%)	0.005
	No	58 (56.3%)	77 (74.8%)	135 (65.5%)	
Family history	**First degree relative**	31 (68.9%)	10 (43.5%)	41 (19.9%)	0.043
	Second degree relative	14 (31.1%)	13 (56.5%)	27 (13.1%)	
Hypothyroidism	**Yes**	45 (43.7%)	23 (22.3%)	68 (33.0%)	0.001
	No	58 (56.3%)	80 (77.7%)	138 (67.0%)	
Family history	**First degree relative**	31 (70.5%)	10 (47.6%)	41 (19.9%)	0.074
	Second degree relative	13 (29.5%)	11 (52.4%)	24 (11.7%)	
Hyperthyroidism	**Yes**	4 (3.9%)	0 (0.0%)	4 (1.9%)	0.043
	No	99 (96.1%)	103 (100.0%)	202 (98.1%)	
Family history	**First degree relative**	2 (50.0%)	0 (0.0%)	2 (1.0%)	NA
	Second degree relative	2 (50.0%)	0 (0.0%)	2 (1.0%)	

*NA: not available

5.4 Part 2: Univariate analysis

5.4.1 Socio-demographic factors difference between study cases and control group

Table 5.4 shows that the majority of the study population were females and in the age group 19-40 years, and 79.6% were married. Also, 65.5% had a family size of more than 5 members, and about half were living in urban areas. Of the study population, 35.0% completed 10-12 years of education and 78.6% were not working. More than a third of the study population had a monthly income "between" 1000-2000 NIS.

When comparing study cases and control group, study cases were significantly living in urban areas, less educated, not working and their family income was lower compared to control group ($P<0.05$). Other variables in the table did not show significant differences between the two groups ($P>0.05$) (see table 5.2).

Table 5.4: Associations between study cases and control groups by socio-demographic factors

		Study cases N=103	Control group N=103	Total (%) N=206	Chi Square
		N (%)	N (%)	N (%)	P value
Clinic	**karantena**	42 (40.8%)	37 (35.9%)	79 (38.3%)	0.474
	Dura	61 (59.2%)	66 (64.1%)	127 (61.7%)	
Gender	**Male**	8 (7.8%)	3 (2.9%)	11 (5.3%)	0.121
	Female	95 (92.2%)	100 (97.1%)	195 (94.7%)	
Age	**≤18 years**	11 (10.7%)	6 (5.8%)	17 (8.3%)	
	19-40 years	52 (50.5%)	69 (67.0%)	121 (58.7%)	0.050
	>40 years	40 (38.8%)	28 (27.2%)	68 (33.0%)	
Marital status	**Married**	85 (82.5%)	79 (76.7%)	164 (79.6%)	0.299
	Single	18 (17.5%)	24 (23.3%)	42 (20.4%)	
Family size	**≤ 5 persons**	41 (39.8%)	30 (29.1%)	71 (34.5%)	0.107
	>5 persons	62 (60.2%)	73 (70.9%)	135 (65.5%)	
Living area	**Urban**	44 (42.7%)	76 (73.8%)	120 (58.3%)	0.000*
	Rural	59 (57.3%)	27 (26.2%)	86 (41.7%)	
Educational	**≤ 6 years**	25 (24.3%)	9 (8.7%)	34 (16.5%)	
	7-9 years	27 (26.2%)	16 (15.5%)	43 (20.9%)	0.000*
	10-12 years	34 (33.0%)	38 (36.9%)	72 (35.0%)	
	>12 years	17 (16.5%)	40 (38.8%)	57 (27.7%)	
Working status	**Yes**	7 (6.8%)	37 (35.9%)	44 (21.4%)	0.000*
	No	96 (93.2%)	66 (64.1%)	162 (78.6%)	
Household average monthly income	**< 1000 NIS**	34 (33.0%)	15 (14.6%)	49(23.8%)	
	1000-2000 NIS	46 (44.7%)	33 (32.0%)	79 (38.3%)	0.000*
	2001-3000 NIS	18 (17.5%)	36 (35.0%)	54 (26.2%)	
	3001-5000 NIS	5 (4.9%)	19 (18.4%)	24 (11.7%)	

5.4.2 Lifestyle factors

5.4.2.1 Weight, physical activity and smoking

Table 5.5 shows that 34 % of the study subjects were overweight and obese. Study cases were significantly more obese than control group, but control group was more overweight ($p<0.05$).

Although 70% of the study subjects believed they are physically active, but they mainly considered walking as being their main daily physical activity. About 27% reported walking almost daily. However, no significant difference in physical activity were found between study cases and control group ($p>0.05$). Other reported physical activity methods

such as running and physical training with or without using machines did not show any significant differences (see annex, table 4).

Most of the study sample were not smokers, but, study cases reported that they are more affected by passive smoking ($p<0.05$).

Table 5.5: Association between study cases and control groups' BMI, physical activity and smoking status.

		Case N=103	Control group N=103	Total (%) N=206	Chi Square
		N (%)	N (%)	N (%)	P value
BMI	Underweight < 18.5	8 (7.8%)	3 (2.9%)	11 (5.3%)	0.001
	Normal 18.5-24.99	21 (20.4%)	34 (33.3%)	55 (26.7%)	
	Overweight ≥25-29.99	26 (25.2%)	44 (43.1%)	70 (34.0%)	
	Obese ≥30	48 (46.6%)	22 (21.4%)	70(34.0%)	
Rate of daily activity	High	20 (19.4%)	41 (39.8%)	61 (29.6%)	0.001
	Medium	64 (62.1%)	59 (57.3%)	123 (59.7%)	
	Low	19 (18.4%)	3 (2.9%)	22 (10.7%)	
Physical activity	Yes	68 (66.0%)	76 (73.8%)	144 (69.9%)	0.224
	No	35 (34.0%)	27 (26.2%)	62 (30.1%)	
Walking per week	Less <1	8 (11.8%)	3 (3.9%)	11 (5.3%)	0.004
	3-2	35 (51.5%)	24 (31.6%)	59 (28.6%)	
	4-5	4 (5.9%)	15 (19.7%)	19 (9.2%)	
	>6	21 (30.9%)	34 (44.7%)	55 (26.7%)	
Frequency walking	Less half an hour	35 (51.5%)	32 (42.1%)	67 (32.5%)	0.375
	Half an hour	20 (29.4%)	31 (40.8%)	51 (24.8%)	
	1-2 hours	13 (19.1%)	12 (15.8%)	25 (12.1%)	
	> 2 hours	0 (0.0%)	1 (1.3%)	1 (0.5%)	
Smoking	Yes	4 (3.9%)	1 (1.0%)	5 (2.4%)	0.174
	No	99 (96.1%)	102 (99.0%)	201 (97.6%)	
Smoking while you at home	Yes	64 (62.1%)	48 (46.6%)	112 (54.4%)	0.025
	No	39 (37.9%)	55 (53.4%)	94 (45.6%)	
Smoking by others in closed places	Yes	56 (54.4%)	38 (36.9%)	94 (45.6%)	0.012
	No	47 (45.6%)	65 (63.1%)	112 (54.4%)	

5.4.2.2 **Food intake**

Table 5.6 shows that all study subjects use iodized salt in their houses. The consumption of fruits was mostly taken by participants 1-4 times per week (60.2%) and 37.4% consumed it at least once daily. The rate of consumption was significantly different between the 2 groups ($p<0.05$). In most of the studied fruits (see annex table 5) no significant difference was found in all fruits consumption, except for strawberry and banana where controls reported more frequently intake it per week (table 5.3).

About 75% of participants consume vegetables 5-7 times weekly, but carrots intake was significantly different between the 2 groups. Other vegetables did not show any significant different (see annex, table 5).

Among study population, 51% consumed yogurt 1-4 times weekly and was significantly more frequently intake by control group ($p<0.05$), and study cases intake of red meat was more frequent ($p<0.0\%$).

regarding fish intake, only 18.4% and 24.8% of the study population consumes canned sardine and canned tuna 1-4 times weekly, respectively. The intake was significantly different between the 2 study groups ($p<0.05$).

In addition to food intake, 29.6% of the study population drink coffee two to three times daily, which was significantly more frequent among the control group ($p<0.05$).

5.4.2.3 Supplements intake

Table 5.7 shows that vitamin B12, calcium, and iron supplements were consumed mainly by less than 15% of the study subjects. This consumption was statistically significantly different between the 2 study groups ($p<0.05$), where study cases reported more use of calcium, but control group reported more use of vitamin B12 and iron supplement. Other supplements intake did not show significant differences between the two groups ($P >0.05$, see annex, table 6)

Table 5.6: Differences between study cases and control group in food intake

		Study cases N=103	Control group N=103	Total (%) N=206	Chi Square
		N (%)	N (%)	N (%)	P value
Iodized salt	**Yes**	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Fruits	**<1 per week**	3 (2.9%)	2 (1.9%)	5 (2.4%)	0.005
	1-4 per week	67 (65.0%)	57 (55.3%)	124 (60.2%)	
	5-7 per week	26 (25.2%)	44 (42.7%)	70 (34.0%)	
	2-3 times daily	7 (6.8%)	0 (0.0%)	7 (3.4%)	
Strawberry	**<1 per week**	69 (67.0%)	47 (45.6%)	116 (56.3%)	0.002
	1-4 per week	34 (33.0%)	56 (54.4%)	90 (43.7%)	
Bananas	**<1 per week**	33 (32.0%)	23 (22.3%)	56 (27.2%)	0.001
	1-4 per week	63 (61.2%)	50 (48.5%)	113 (54.9%)	
	5-7 per week	7 (6.8%)	30 (29.1%)	37 (18.0%)	
Vegetables	**1-4 per week**	26 (25.2%	14 (13.6%)	40 (19.4%)	0.001
	5-7 per week	60 (58.3%)	89 (86.4%)	149 (72.3%)	
	2-3 times daily	17 (16.5%)	0 (0.0%)	17 (8.3%)	
Carrots	**<1 per week**	59 (57.3%)	42 (40.8%)	101 (49.0%)	0.034
	1-4 per week	33 (32.0%)	51 (49.5%)	84 (40.8%)	
	5-7 per week	11 (10.7%)	10 (9.7%)	21 (10.2%)	
Yogurt	**<1 per week**	37 (35.9%)	25 (24.3%)	62 (30.1%)	0.036
	1-4 per week	53 (51.5%)	52 (50.5%)	105 (51.0%)	
	5-7 per week	13 (12.6%)	26 (25.2%)	39 (18.9%)	
Red meat	**<1 per week**	72 (69.9%)	85 (82.5%)	157 (76.2%)	0.033
	1-4 per week	31 (30.1%)	18 (17.5%)	49 (23.8%)	
Canned sardines	**<1 per week**	78 (75.7%)	90 (87.4%)	168 (81.6%)	0.031
	1-4 per week	25 (24.3%)	13 (12.6%)	38 (18.4%)	
Canned tuna	**<1 per week**	70 (68.0%)	85 (82.5%)	155 (75.2%)	0.015
	1-4 per week	33 (32.0%)	18 (17.5%)	51 (24.8%)	
Coffee	**<1 per week**	41 (39.8%)	39 (37.9%)	80 (38.8%)	0.010
	1-4 per week	17 (16.5%)	7 (6.8%)	24 (11.7%)	
	5-7 per week	24 (23.3%)	17 (16.5%)	41 (19.9%)	
	2-3 times daily	21 (20.4%)	40 (38.8%)	61 (29.6%)	

Table 5.7: Association between study cases and control group by using supplements.

		Study cases N=103	Control group N=103	Total N=206	Chi Square
		N (%)	N (%)	N (%)	P value
Vitamin B12	**Yes**	6 (5.8%)	15 (14.6%)	21 (10.2%)	0.038
	No	97 (94.2%)	88 (85.4%)	185 (89.8%)	
Calcium	**Yes**	7 (6.8%)	0 (0.0%)	7 (3.4%)	0.007
	No	96 (93.2%)	103 (100.0%)	199 (96.6%)	
Iron	**Yes**	8 (7.8%)	18 (17.5%)	26 (12.6%)	0.036
	No	95 (92.2%)	85 (82.5%)	180 (87.4%)	

5.4.3 Medical conditions

5.4.3.1 TSH levels at study time

TSH mean levels did not show a significant difference between study cases and control group as measured at the time of the study (T test *p value =0.066* >0.05). For details see table 5.8 and figure 7.

Table 5.8: Distribution of TSH levels (uIU/L) between study cases and control group at study time

	Study cases	Control group
Mean (95% confidence interval)	15.9 (8.9-23)	1.7 (1.5-1.8)
Standard error	3.6	0.06
Median	5.8	1.53
Variance	1316	0.471
Standard deviation	36	0.68
Range	272	4.40

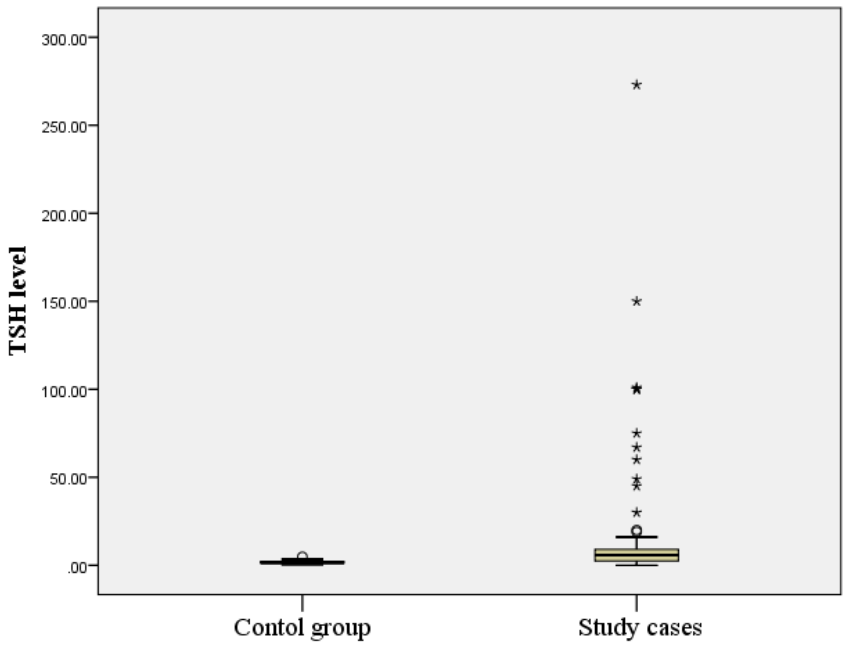

Figure 4 : Distribution of TSH levels (uIU/L) between study cases and control group at study time

*We found that four of participants in the study have high TSH level and we considered them as cases.

5.4.3.2 Chronic diseases

Table 5.9 shows that 7.3 % of the study subjects had diabetes type 2 and 2.9% suffer from pituitary disease, while 50% were diagnosed with thyroid disease.

When comparing study cases and control group, the study cases were statistically significantly suffered more from diabetes type 2, pituitary disease, thyroid disease (hyperthyroidism, goiter and congenital hypothyroidism) compared to study control group (P <0.05). Other variables such as heart disease, liver disease, kidney disease, mental illness, diabetes type 1, down syndrome, anemia, sjögren's, Addison's disease and celiac disease did not show significant differences between the two groups (P >0.05, see annex, table 7).

Table 5.9: Differences between study cases and control group by their medical conditions.

		Study cases N=103	Control group N=103	Total (%) N=206	Chi Square
		N (%)	N (%)	N (%)	P value
Diabetes type 2	**Yes**	15 (14.6%)	0 (0.0%)	15 (7.3%)	0.001*
	No	88 (85.4%)	103 (100.0%)	191 (92.7%)	
Pituitary Diseases	**Yes**	6 (5.8%)	0 (0.0%)	6 (2.9%)	0.013*
	No	97 (94.2%)	103 (100.0%)	200 (97.1%)	
Thyroid disease	**Yes**	103 (100.0%)	0 (0.0%)	103 (50.0%)	0.001*
	No	0 (0.0%)	103 (100.0%)	103 (50.0%)	
Hyperthyroidism	**Yes**	5 (4.9%)	0 (0.0%)	5 (2.4%)	0.024*
	No	98 (95.1%)	103 (100.0%)	201 (97.6%)	
Goiter	**Yes**	32 (31.1%)	0 (0.0%)	32 (15.5%)	0.001*
	No	71 68.9%	103 (100.0%)	174 (84.5%)	
Congenital hypothyroidism	**Yes**	6 (5.8%)	0 (0.0%)	6 (2.9%)	0.013*
	No	97 (94.2%)	103 (100.0%)	200 (97.1%)	

5.4.4 Women's health

Table 5.10 shows that 15.0% (n=31 of women) of the women subjects (23) were over 45 years and more had no menstrual cycle in the past 12 months. Also 68.4% of them were pregnant at least once, and 22.8% of them were affected with postpartum thyroiditis.

Of study cases, 22% had no menstrual cycle in the past 12 months and 75% with regular periods compared to 11% and 89%, respectively in the control group (P <0.05). Also, 8.8%

of study cases had postpartum thyroiditis compared to none in the control group (P <0.05). Other variables such as abortion and bleeding postpartum did not show any significant differences between the two groups (P >0.05, see annex, table 8).

Table 5.10: Differences between study cases and control group in their menstrual cycle and pregnancy among women

		Study cases N=95	Control group N=100	Total (%) N=195	Chi Square
		N (%)	N (%)	N (%)	P value
During the past 12 months menstrual period completely gone	Yes	20 (22.2%)	11 (11.1%)	31 (15.0%)	0.039
	No	70 (77.8%)	88 (88.9%)	158 (76.7%)	
Regular menstrual cycle	Yes	51 (75.0%)	78 (89.7%)	129 (62.6%)	0.015
	No	17 (25.0%)	9 (10.3%)	26 (12.6%)	
Pregnant at least once	Yes	68 (85.0%)	73 (98.6%)	141 (68.4%)	0.002
	No	12 (15.0%)	1 (1.4%)	13 (6.3%)	
Postpartum Thyroiditis	Yes	6 (8.8%)	0 (0.0%)	47 (22.8%)	0.009
	No	62 (91.2%)	73 (100.0%)	106 (51.5%)	

5.4.5 Medications use

Table 5.11 shows that 3.4% of the study subjects had thyroidectomy. Also, 2.4% of them take Propylthiouracil.

When comparing study cases and control group, 6.8% of study cases had thyroidectomy and 5% take Propylthiouracil compared to none in the control group (P <0.05). Other medications such as radioactive iodine, lithium, amiodarone, interferon, carbimazole and methimazole did not show any significant differences between the two groups (P >0.05 see annex, table 9).

Table 5.11: Association between study cases and control group by medication

		Case N=103	Control N=103	Total (%) N=106	Chi Square
		N (%)	N (%)	N (%)	P value
Thyroidectomy	Yes	7 (6.8%)	0 (0.0%)	7 (3.4%)	0.007*
	No	96 (93.2%)	103 (100.0%)	199 (96.6%)	
Propylthiouracil	Yes	5 (4.9%)	0 (0.0%)	5 (2.4%)	0.024*
	No	98 (95.1%)	103 (100.0%)	201 (97.6%)	

5.5 Part Three: Multivariate analysis:

Logistic regression models included all statistically significant variables in the univariate analysis in the above section. The variables are participants BMI; household monthly income; education level of participant; age of participant; gender of participant; living area; working status; rate of daily physical activity; smoking by other in closed places; smoking by other at home; consumption of fruits; consumption of vegetables; consumption of carrots; consumption of canned tuna; consumption of canned sardines; drinks coffee; consumption of red meat; consumption of yogurt; taking iron supplement; taking vitamin B_{12} supplement; taking calcium supplement; frequency of eating banana and strawberry; diabetes type 2; pituitary disease; thyroid disease (hyperthyroidism, goiter and congenital hypothyroidism); thyroidectomy; Propylthiouracil; family history of autoimmune diseases including vitiligo and thyroid diseases.

From the regression analysis; table 5.12 shows that being unemployed and living in rural areas significantly increase the risk to have hypothyroidism compared to those working or living in urban areas. Also; there is a statistically significant increased risk to have hypothyroidism in persons with lower monthly income compared those with higher monthly income. Also; the risk to develop hypothyroidism is also increased among those present in closed place where others smoke (3 folds) and are less physically active compared to those living in a non smoking environment and are more physically active. For food intake; those who consume more bananas weekly are at lower risks to develop hypothyroidism compared to those who consumed less banana. While, those who consume more carrot and more red meat weekly are at higher risks to develop hypothyroidism compared to those who consumed less amounts weekly. For supplements intake; the risk to develop hypothyroidism is increased among those taking iron supplements compared to those not taking it.

Table 5.12: Logistic regression analysis for hypothyroidism.

		Sig.	Adjusted odds ratio (AOR)	95% confidence interval for AOR	
				Lower	Upper
Working status	**Yes**	0.000	0.036	0.008	0.163
	No		1.00		
Living area	**Urban**	0.000	0.115	0.047	0.282
	Rural		1.00		
Monthly income	**Less than 1000 NIS**	0.051	5.976	0.991	36.030
	1000-2000 NIS	0.015	8.409	1.516	46.632
	2001-3000 NIS	0.412	2.060	0.367	11.565
	3001-5000 NIS		1.00		
Smoking by others in closed places	**Yes**	0.002	3.821	1.614	9.047
	No		1.00		
Physical activity rate	**High**	0.000	0.042	0.007	0.245
	Medium	0.001	0.064	0.013	0.309
	Low		1.00		
Bananas consumption	**<1/week**		1.00		
	1-4/ week	0.672	1.224	0.481	3.117
	5-7/week	0.004	0.122	0.029	0.520
Carrots consumption	**<1/week**		1.00		
	1-4/ week	0.125	0.507	0.213	1.208
	5-7/ week	0.057	5.814	0.952	35.497
Red meat	**<1/ week**		1.00		
	1-4/ week	0.000	15.259	4.585	50.781
Iron supplement intake	**Yes**	0.004	0.123	0.029	0.519
	No		1.00		

Chapter 6: Discussion

6.1 Introduction

This case-control study aimed to determine the risk factors associated with hypothyroidism among patients attending the primary health care clinics in Hebron governorate. In this chapter, the main study findings are interpreted and discussed. In the last part of this chapter, the study's conclusion and recommendations will be presented.

6.2 Study main findings

In the first stage of the study, data from patients file showed that that hypothyroidism was the most diagnosed endocrine disorder with the prevalence of 17.1% among patients attending the clinics (16.9% Karantina and 17.5% in Dura). Also, the sub types of hypothyroidism were 87.0% the primary hypothyroidism, 5.2% the secondary hypothyroidism and 7.8% the congenital hypothyroidism. These types of hypothyroidism were shown to be associated with diabetes type 1, turner syndrome, thyroid cancer, goiter, thyroidectomy, postpartum thyroiditis, hypopituitarism and thalassemia.

In the second stage of the study, which included 103 study cases and 103 controls, the multiple regression model showed that living area; working status and household monthly income were associated with hypothyroidism. Also, rate of daily physical activity and smoking by others in closed places were significantly associated with hypothyroidism. In addition, consumption of carrots, banana and red meat were associated with hypothyroidism. Moreover, iron supplement was the only vitamin intake that was associated with hypothyroidism.

6.3 Part 1: Hypothyroidism descriptive analysis

6.3.1 Prevalence of hypothyroidism

The prevalence of hypothyroidism among patients attending the two main governmental clinics (Karantina and Dura) was 17.1%. Hypothyroidism prevalence varies around the world and it depends on ethnic and geographical factors and especially on iodine intake (Yadav et al., 2013). No previous study in Palestine investigated the epidemiology of hypothyroidism. The prevalence of hypothyroidism in the general population in USA, UK

and Scotland ranges from 3.8%–4.6% (Chakera et al., 2012). Also, previous studies around the world reported that the prevalence of subclinical hypothyroidism ranges from 1% to higher than 20% and 1-2% for overt hypothyroidism (Aminorroaya et al., 2009). This study shows that the Palestinian hypothyroidism prevalence is higher compared to some selected previous studies worldwide (table 1), except Bangladesh.

Possible explanation for this high rate of hypothyroidism in Palestine could be iodine deficiency but also might congenital factors like autoimmune diseases is a potential reason too. As shown in literature, the most common causes of hypothyroidism in iodine sufficient area such as the United states of America is most probably due to chronic autoimmune (Hashimoto's), and in iodine insufficiency area could be due predominantly to iodine deficiency (Vanderpump, 2011).

Table 6.1: Prevalence rate of hypothyroidism in selected epidemiological studies.

Author, Country of study	Type of study	Sample	Prevalence of hypothyroidism
(Aoki et al., 2007b),USA	National Health and Nutrition Examination Survey (NHANES)	4392 participants ≥12 years	-3.7% in general population
(Bjoro et al., 2000), Norway	A health study of Nord-Trùndelag (HUNT)	94009 participants ≥12 years	-0.9% in males - 4.8% in females
(Mao et al., 2010b), China	Population-based study	11067 participants ≥20 years	- 1.7% in females - 0.3% in males
(Aminorroaya et al., 2009), Iran	A cross-sectional survey	2523 men and women >20 years	- 4.8% in men - 12.8% in women
(Nouh et al., 2008), Libya	A cross-sectional study	356 subjects 20-65 years	-Overt hypothyroidism was (1.12%) -Subclinical hypothyroidism was (6.18%)
(Yadav et al., 2013), Nepal	A hospital based study	1504 cases	-Hypothyroidism was (2.26%) -Subclinical hypothyroidism (10.50%)
(Mannan et al., 2010), Bangladesh	A hospital based study	498 endocrine patients	-Hypothyroidism was 18.5%

6.3.2 Prevalence of subtypes of hypothyroidism

This study showed that hypothyroidism was the main primary type of thyroid dysfunction. This study result is in agreement with previous studies, which found that primary hypothyroidism is the most common subtype of hypothyroidism, and it composes about 95% of hypothyroidism types (Jayakumar, 2011). In addition, studies worldwide demonstrate that secondary hypothyroidism rarely occurs, and it composes about 5% of hypothyroidism sub types (Jayakumar, 2011), similar to our study (5.2%). In concordance with our findings, a

cross sectional study in Pakistan showed that primary hypothyroidism was found in 63.3% of thyroid cases, but only 1.4% had secondary hypothyroidism (Mansoor et al., 2010). Also, a prospective population-based study in Denmark reported that the nosological type of hypothyroidism was 84.4% spontaneous (presumably autoimmune) and 1.6% was congenital hypothyroidism (Carle et al. 2006).

6.4 Part II: Case control study

In this section all variables in the case-control study results will be presented

6.4.1 Hypothyroidism and socio-demographic

In this subsections, age, gender, place of residence and others results will be discussed.

6.4.1.1 Hypothyroidism and patients' age and gender

Our results showed that hypothyroidism was more prevalent (50.5%) in age group 19-40, which is contrary to previous findings that the incidence of thyroid dysfunction increases with advancing age (Hollowell et al., 2002). However, a study in Scotland showed that the tendency to develop thyroid disorders occurs comparatively among younger age group (Hunter et al., 2000). In Pakistan, a study found that primary hypothyroidism was more common in the age group 16-40 years (Mansoor et al., 2010). Also, in Nepal, a study reported that higher prevalence of hypothyroidism was observed in the age group 15-30 years (Aryal et al., 2010). However, the National Health and Nutrition Examination Survey (NHANSE) in the USA reported that individuals aged 80 years and older had five times greater odds for having hypothyroidism compared to younger aged individuals (12- 49 years)(Aoki et al., 2007b). Possible explanation of our study finding was that most of patients were adults and only 6 patients were less than 10 years of age, which might reflect a sample bias.

This study showed that the prevalence of diagnosed hypothyroidism was 92.2% in females (n=95), and 7.8% in males (n=8). In Denmark, a prospective population-based study showed that hypothyroidism was three times predominance in women than in men (Carle et al., 2006). In China, a population-based study, found that the prevalence of hypothyroidism was 1.7% in females and 0.3% in males. Subclinical hypothyroidism was more common in females (males 2.4% versus females 5.8%, $P < 0.001$) and with increasing age ($P < 0.001$)

(Mao et al., 2010b). In Pakistan, a cross sectional study, found that primary hypothyroidism was 4.5 times more common in female than in male (Mansoor et al., 2010). In Saudi Arabia, a hospital based study showed that patients 196 (54 males and 142 females) from 391 had hypothyroidism (Lamfon, 2008). There is no clear explanation why females are at greater risk to have hypothyroidism compared to males. But pregnancy, genetic factors (skewed X chromosome inactivation patterns, and defects in the sex chromosomes), medical condition, and sex hormones are believed to play an important role in this association (Jorgensen et al., 2010,Prummel et al., 2004).

6.4.1.2 Hypothyroidism and patients residency: rural versus urban

Our results showed that living in rural areas significantly increases the risk (10 times) to have hypothyroidism compared to those living in urban areas. A study in India found that the prevalence of thyroid disease is more in the city compared to town (James and Kumar, 2012). Another study in the United Kingdom reported that a 2-fold excess of subclinical hypothyroidism was seen in patients resident in the most deprived quartile compared with those in the most affluent quartile (Wilson et al., 2006). In addition, a study performed in Canada revealed that lower socioeconomic status associated with more advanced thyroid cancer stage (Siu et al., 2013).

6.4.1.3 Hypothyroidism and working status

Our study results showed that jobless persons significantly increases the risk to have hypothyroidism compared to those who work (OR= 0.036, 95% CI=0.008-0.163). The majority of our study population were females, married and not working, which suggests that being less physically active might indirectly affect their thyroid gland activity. In Bangladesh, a clinical based study found that the majority of female patients with endocrine diseases were housewives, while most of male patients with endocrine diseases were businessmen (Mannan et al., 2010). Also, work shift was found to be associated with a number of serious health problems. Contradicting our results, a study in Italy found a significant association between shift work and autoimmune hypothyroidism (Magrini et al., 2006).

6.4.1.4 Hypothyroidism and household average monthly income

Our study results showed that there is a statistically significant increased risk to have hypothyroidism in persons with lower monthly income compared to those with higher monthly income**.** A study in Canada, revealed that lower socioeconomic status was associated with more advanced thyroid cancer stage (Siu et al., 2013). Low income might affect the people ability to buy fish, as a source of iodine, since it is expensive and unavailable in the low price market in Palestine.

6.4.2 Hypothyroidism and lifestyle factors

6.4.2.1 Weight

Our results showed that 34% of the study subjects were overweight and obese. And they were significantly more obese than control group ($p<0.05$), However weight was not statistically significant after adjustment. Many studies found that thyroid dysfunction contribute to the development of regional obesity and tendency to gain weight (Biondi, 2010). Moreover, obesity was found to be a risk factor for developing hypothyroidism (Verma et al., 2008). Our study results is consistent with a study done in Norway which found that hypothyroidism correlated with higher BMI and higher prevalence of obesity in both smokers and nonsmokers (Asvold et al., 2009). Another study in India found that primary hypothyroidism was more prevalent in individuals with extreme obesity when compared with moderate obese patients (56% versus 41%) (Verma et al., 2008). This is due to both types of hypothyroidism (subclinical and overt hypothyroidism) which are frequently associated with weight gain, as a result of high TSH level which decreased thermogenesis and metabolic rate (Biondi, 2010). Obesity increases the susceptibility to harbor autoimmune hypothyroidism due to the effects of adipocytokine leptin on pituitary gland (Marzullo et al., 2010).

6.4.2.2 Physical activity

Our study results showed that 70% of the study subjects stated are physically active, but they mainly considered walking as being their main daily physical activity. About 27% reported walking almost daily. After adjustment for age and gender, those who are physically active were less at risk to develop hypothyroidism by 6 times compared to those who were less to physically active.

Evidence is growing that physical activity in the form of regular exercise has a positive effect on thyroid gland. However, a double-blind, randomized study in Brazil revealed that sub-maximal cardiopulmonary exercise performance improved after six months of TSH normalization which helped in enhancing the ability to carry out daily life activities in patients with subclinical hypothyroidism (Mainenti et al., 2009). Another double-blind, randomized, placebo-controlled fashion in Italy found that exercise altered both the tolerance and pattern of blood glucose, lactate, pyruvate, free fatty acid and glycerol concentrations in subclinical hypothyroidism patients compared to healthy subjects (Caraccio et al., 2005b). This is due to exercise that has a greater effect on the thyroid gland and the level of circulating thyroid hormones (Ciloglu et al., 2005a). Moreover, it can also help in combat with the major symptoms of hypothyroidism such as weight gain, fatigue and depression (Thyroid Guide, 2011).

6.4.2.3 Smoking

Our results indicate that most of all the study subjects were not smokers, but the cases reported that they are more affected by passive smoking ($p<0.05$). After adjustment for age and gender, the risk to develop hypothyroidism was 3 folds more among those who are present in smoking environment "passive smokers" compared to others.

Studies evaluating tobacco smoking and thyroid disorders have yielded conflicting results with either negative or positive association between smoking and hypothyroidism. A meta analysis of 25 studies on the association between smoking and thyroid diseases found that smoking was significantly associated with Graves' disease, while the association with hypothyroidism did not reach statistical significance (Vestergaard, 2002). In Norway, a population-based study showed that smoking was negatively associated with hypothyroidism but positively associated with hyperthyroidism (Asvold et al., 2007). In contrast, a retrospective study in Japan suggested that smoking may increase the risk of hypothyroidism in patients with Hashimoto's thyroiditis (Fukata et al., 1996). In Greece, a study found that one hour of passive smoking at bar/restaurant levels is accompanied by significant increases in metabolism and thyroid hormone levels (Metsios et al., 2007). In USA, a study found that active and passive exposure to cigarette tobacco smoke is associated with a mild inhibitory effect on the thyroid reflected in higher serum T4 and T3 in nonsmokers compared (Soldin et al., 2009). The effect of passive smoking on hypothyroidism is still of concern and further studies are needed to clarify this association.

6.4.2.4 Food intake

Our findings showed that consuming more bananas weekly lower the risk for developing hypothyroidism by 15 times compared to fewer consumers.

Previous studies suggested that consumption of banana may lead to reduce the risk of chronic diseases including cancer, cardiovascular, Alzheimer's, depression, and diabetes (Kumar et al., 2012). However, banana is the best source of vitamin B6, and it's provide 41% of vitamin B6 that we need on a daily basis (Kumar et al., 2012). Vitamin B6 is important for thyroid function because it's involved in manufacturing T4, and it's deficiency can lead to hypothyroidism (Sworczak and Wisniewski, 2011). Also, banana is an excellent source of vitamin C (Kumar et al., 2012). Vitamin C is an essential antioxidants that help the thyroid gland to neutralize the oxidative stress that promoted by hypothyroidism (Sworczak and Wisniewski, 2011). In addition, bananas contain L tyrosine and iodine, which are essential for thyroid hormone, and both were used as integrative treatment of hypothyroidism (WUSC, 2011). Therefore, these studies supported our results that consumption of bananas may reduce the risk of hypothyroidism.

Another finding in our study showed that consuming more carrots weekly increase the risk to develop hypothyroidism by 15 times compared to those consuming less amounts weekly. Carrot is the best source of beta carotene which is converted to vitamin A (Lee et al., 2011). Contradicting our results, a previous studies, revealed that vitamin A is necessary to regulate thyroid hormone metabolism (Farhangi et al., 2012). In addition, vitamin A supplements was also found to improve thyroid function without a change in iodine nutrition (Zimmermann et al., 2007). A cross-sectional study of African children found that vitamin A deficiency in children with severe iodine deficiency disorders was associated with an increase in TSH stimulation and thyroid size and a reduced risk of hypothyroidism (Zimmermann et al., 2004). Another study performed in Iran, found that vitamin A supplementation might reduce the risk of subclinical hypothyroidism in premenopausal women (Farhangi et al., 2012).

More consumption of red meat weekly in our study was shown to increase the risk for hypothyroidism by 15 times compared to those consuming less amounts weekly. The available epidemiologic evidence between red meat or processed meat intake and hypothyroidism is limited. Also, few epidemiologic studies investigated the association between red meat and thyroid cancer and showed conflict results. A case-control study in

Uruguay found that total meat intake was associated with increased risk of thyroid cancer (OR = 2.38; p <0.039) (Aune et al., 2009). Also, another case-control study in Italy found marginally significant increased risk of thyroid cancer among high consumers of red meat (OR = 1.5, 95% CI: 1.0-2.1) (Tavani et al., 2000). In contrast, a prospective study in USA showed a negative association between red meat intake and thyroid cancer (Cross et al., 2007). Another study in Netherlands found that a diet consisting of green vegetables, beef, full fat milk and butter for 3 month decrease significantly the TSH levels among patients with subclinical hypothyroidism risk ratio of 2.8 (Kuiper and Gaag, 2012). Several potential mechanisms could explain the association between red meat intake and increased cancer risk, for example, red meat are sources of saturated fat and iron, which have been an established risk factor for several different cancer sites (Aune et al., 2009)

6.4.3 Hypothyroidism and supplementation

6.4.3.1 Iron supplement

Our results showed that the risk to develop hypothyroidism is lower among those taking iron supplements compared to those not taking it (OR= 0.123, 95% CI=0.029-0.519).

Iron deficiency anemia and thyroid disorders tend to coexist in patients, and influence each others. Previous studies in animals and humans, iron deficiency anemia was shown to impair thyroid metabolism through decreasing plasma total thyroxin (T4) and triiodothyronine (T3) concentrations (Hess et al., 2002). A randomized double-blind study in Iran found that combination of levothyroxine and iron salt is better for patients with subclinical hypothyroidism and iron-deficiency anemia (Ravanbod et al., 2013). Also, a Turkish study results showed that secondary and subclinical hyperthyroid developed in a significant portion of patients with iron deficiency anemia, and these abnormalities can recover after iron replacement therapy without additional thyroid hormone replacement (Gokdeniz et al., 2010).

6.4.4 Hypothyroidism and patients' chronic diseases

6.4.4.1 Turner syndrome

Our prevalence study results (stage 1) showed that 0.5% of patients with turner syndrome had hypothyroidism, which is lower than reported by other studies. A study in the UK found that 15% of women with turner syndrome were hypothyroidism (Elsheikh et al., 2001). In Sweden, a follow-up study showed that 37% of women with turner syndrome had hypothyroidism after five years follow-up. (El Mansoury et al., 2005a). Possible explanation is that a gene on the long arm of X chromosome (Xq) may play an important pathogenic role in the development of autoimmune hypothyroidism in patients with turner syndrome (Elsheikh et al., 2001).

6.4.4.2 Diabetes type 1 and type 2

Our study results found that 1.1% of patients with diabetes type 1 had hypothyroidism, while, in the case-control study(stage 2), 2.9% of study cases had diabetes type 1 compared to none in the control group ($P > 0.05$). Our results are lower than that reported by other studies. In Germany, a cross-sectional analysis showed that the prevalence rate of subclinical hypothyroidism was 7.2% in children, adolescents, and young adults (age <25 years) with type 1 diabetes (Denzer et al., 2013). In the USA, a longitudinal study found that hypothyroidism was more common in female (41%) than in male (19%) with type 1 diabetes (Umpierrez et al., 2003). In Iran, a cross-sectional study showed that children and adolescents with diabetes type 1 had higher prevalence of subclinical hypothyroidism than nondiabetic (Ardestani et al., 2011). In Saudi Arabia 15.8% of children and adolescents with type 1 diabetes had hypothyroidism (Al-Agha et al., 2011). Explanations for the coexistence of diabetes type 1 and hypothyroidism involve immunological disturbances in B and T lymphocytes, a trend to react abnormally in the presence of an antigen and a genetic susceptibility (Raterman and Nurmohamed, 2012b).

Our prevalence study results (stage 1) found that no patients had diabetes type 2, while in the case-control study (stage 2) 14.6 % of study cases had diabetes type 2 compared to none in the control group ($P < 0.05$), but the association is not statistically significant after adjustment. A study in Mexico found that hypothyroidism was 5.7% in type 2 diabetic patients (Tamez-Perez et al., 2012). In Greece, a study showed the prevalence of subclinical

hypothyroidism was 5.2% in males and 8.4% in females with type 2 diabetes (Papazafiropoulou et al., 2010). Our study results are lower compared with study in India that showed that 23.7 % of type 2 diabetic patients had hypothyroidism (Singh et al., 2011). In Kuwait, a study found that the prevalence rate of hypothyroidism in type 2 diabetic patients was 20.1% (Al wazan et al., 2010). Hypothyroidism have been associated with insulin resistance which was reported to be the major cause of impaired glucose metabolism in diabetes type 2 (Wang, 2013).

6.4.4.3 Pituitary disease

Our prevalence results (stage1) showed that 54.2% of patients with hypopituitarism developed central hypothyroidism, while the case-control results (stage 2) showed that 5.8% of study cases suffered from pituitary disease compared to none in the control group ($P < 0.05$). But the association is not statistically significant after adjustment.

According to the American thyroid association (ATA), damage of pituitary by radiation, surgery, or especially tumor are the most common causes of central "secondary' hypothyroidism (ATA, 2012a). Several studies found that 15% of patients with pituitary adenoma had central hypothyroidism (Yamada and Mori, 2008). In India, 83.2% of patients with hypopituitarism had hypothyroidism (Gundgurthi et al., 2012). The discrepancy between our study 2 stages could be related to the under-reporting of patients with other diseases in their files which was our source of information in the prevalence study (stage 1), and could be an over-reporting by patients in the interviews.

6.4.4.4 Thalassemia

Our prevalence study results (stage 1) found that 4.2% of patients with beta thalassemia major had hypothyroidism. However, the frequency of hypothyroidism in thalassemic patients ranges from 6% to 30% among different countries depending on chelating regimens (De, V et al., 2004). It gives impression that hypothyroidism is rare in thalassemic patients and its prevalence was lower than that reported by others. Our results is comparable to cohort study in Greece, which reported low prevalence of hypothyroidism (4.0%) in beta-thalassemia (Zervas et al., 2002). Also, in Oman primary hypothyroidism was 3.3% in thalassemic patients (Mula-Abed et al., 2008). However, in Iran the prevalence of hypothyroidism among patients with beta-thalassemia was 14.6% (Eshragi et al., 2011).

This is due to iron overload which causes tissue damage of the thyroid gland, that affects thyroid hormones production and manifests varying degrees of primary hypothyroidism (Malik et al., 2010).

6.4.4.5 Hyperthyroidism

Our prevalence study results (stage 1) showed that 0.5% of patients with hyperthyroidism developed hypothyroidism, while the case-control study (stage 2) showed that 4.5% of the study cases suffered from hyperthyroidism compared to none in the control group ($P < 0.05$), but the association is not statistically significant in the logistic regression model. In comparison, our results seem far lower than reported by other studies. Umra et. al found that approximately 15-20% patients with Graves' hyperthyroidism develop spontaneous hypothyroidism after discontinuation of anti-thyroid treatment or following subtotal thyroidectomy (Umar et al., 2010). This is due to the fact that patients are no more having thyroxin which led to hypothyroidism (Umar et al., 2010).

6.4.4.6 Goiter

Our prevalence study results (stage 1) showed that 1.6% of patients with goiter developed hypothyroidism, while the case-control study (stage 2) showed that 31.1% of the study cases had goiter compared to none in the control group ($P < 0.05$), but the association is not statistically significant after adjustment. In India, a study found that hypothyroidism (subclinical and clinical) was 3.2% in children with goiter and 2.4% in children without goiter (Das et al., 2011). In Iran, a study showed the prevalence of subclinical hypothyroidism in goiter grade 1 and grade 2 in children was 9.9% and 16.3% respectively (Aminorroaya et al., 2010). In Palestine, a cross-section study showed the prevalence of goiter among primary school students aged 8-10 years in the West Bank and Gaza Strip (grade 1 and 2) was 14.9% (Ramlawi and Abdeen, 1997). The discrepancy between our two study stages could be related to the under-reporting of patients with other diseases in patients file which was our source of data in the prevalence study (stage 1). Also, could be an over-reporting by patients in the interviews.

6.4.4.7 Thyroid cancer

Our prevalence study results (stage 1) showed that 2.2% of patients had thyroid cancer. A recent study in the USA found that history of hypothyroidism was associated with significantly increased risk of thyroid cancer (Balasubramaniam et al., 2012). A meta-analysis of ten studies showed a 2.77-fold increased incidence of thyroid cancer in patients with antibody evidence of Hashimoto's thyroiditis, compared to controls (Singh et al., 1999). A study in Saudi Arabia reported that malignant thyroid cancer among patients with hypothyroidism was 7.4 % in males, and 4.9% in females (Lamfon, 2008). Moreover, several studies demonstrated that hypothyroidism developed after radiation therapy or surgical treatment for thyroid cancer (Lankarani et al., 2008).

6.4.4.8 Congenital hypothyroidism

Our prevalence results (stage 1) showed the prevalence of congenital hypothyroidism was 7.8%, while our case-control study (stage 2) showed that 5.8% of the study cases had congenital hypothyroidism compared to none in the control group ($P < 0.05$), but the association was not statistically significant after adjustment. Our study results was higher than reported by a study performed in Denmark, which reported the prevalence of congenital hypothyroidism was 1.6% (Carle et al., 2006), and lower than study in Saudi Arabia that found congenital hypothyroidism rate was 14.8% among males and 9.8% among females (Lamfon, 2008). Another study in Sudan found that patients with congenital hypothyroidism constitute 26.3% of the clinic thyroid cases (Mohd et al., 2012). The variation between prevalence our two study stages could be under-reporting in patients' files. Also, could be an over-reporting by patients in the interviews.

6.4.5 Women's health

Our results in stage 2 found that 15.0% of the study subjects had no period in the past 12 months (22% of study cases and 11% of control group, $p<0.05$). But, 23 women of the 31 women were 45 years and more. Also 68.4% of women were pregnant at least once, and 22.8% of them were affected with postpartum thyroiditis.

Our study is in consistent with results from hospital based study in India which showed irregular menstrual cycles in 31% of cases with hypothyroidism (Binita et al., 2009). Another

study in Greece found that 23.4% of hypothyroid patients had irregular periods before 6 months of the discovery of the hypothyroidism (Krassas et al., 1999).

Our prevalence study results (stage 1) found that 0.5% of women with postpartum thyroiditis developed hypothyroidism, while in case-control part (stage 2), 8.8% of the study cases had postpartum thyroiditis compared to none in the control group ($P < 0.05$). According to a publication of the American thyroid association, postpartum thyroiditis occurs in approximately 5-10% of women, and approximately 20% of those women with postpartum thyroiditis that go into hypothyroidism phase will remain hypothyroid (ATA, 2012d). Furthermore, another report showed that 20–40% of women with postpartum thyroiditis developed permanent hypothyroidism over the ensuing 3–12 years (Stagnaro-Green, 2012). A study in Australia found that hypothyroidism was present in 38% (71 women) who had postpartum thyroiditis (PPTD) at baseline with a significant adjusted odds ratio 9.7 for postpartum hypothyroidism (Stuckey et al., 2010). Moreover, a follow up study in Iran found that 64% of women with hypothyroid postpartum thyroid dysfunction became permanent hypothyroid when thyroxin treatment was subsequently withdrawn (Azizi, 2005). A study performed in Jordan, found that 20.8% of women during early pregnancy were diagnosed with sub-clinical hypothyroidism (Alkafajei et al., 2012).

6.4.6 Family history of autoimmune thyroid diseases (AITD) and hypothyroidism

Our study cases indicated more family history of autoimmune diseases including vitiligo and thyroid diseases (hypothyroidism and hyperthyroidism) compared to the control group. Furthermore, the study cases had more first-degree relatives with thyroid diseases than second-degree relatives with thyroid diseases compared to the control group. That means, study cases with history of first-degree relatives who have thyroid diseases significantly differ from those having second-degree relatives of AITD, but the association was not statistically significant after adjustment to age and gender. A familial study in Germany showed an increased familial risk of developing autoimmune thyroid disease (AITD), especially for first-degree relatives with (AITD) in comparison with the general population (Dittmar et al., 2011). Moreover, a prospective cohort study in the Netherlands found that the prevalence of autoimmune thyroid disease AITD was 27% among first- and second-degree relatives of AITD patients (Strieder et al., 2003). In addition, a study performed in

Egypt demonstrated that associated factors for the development of neonatal hypothyroidism included positive family history of hypothyroidism and hypothyroidism of the mother (Abdel-Rasoul et al., 2011).

6.4.7 Thyroidectomy, medication use and hypothyroidism

Our prevalence study results (stage 1) found that 1.1% of patients had thyroidectomy and developed hypothyroidism, while in the case-control study (stage 2) 6.8% of the study cases had thyroidectomy compared to none in the control group ($P < 0.05$).

Our results are lower than that reported by others. Several studies showed that hypothyroidism following lobectomy or hemi-thyroidectomy, with rates between 6.5 and 45% (Cho et al., 2011b). A study in Australia found that hypothyroidism was diagnosed in 10.9% of 294 patients after hemi-thyroidectomy (Su et al., 2009). But, a retrospective study in Korea found that the incidence of hypothyroidism following thyroid lobectomy was 21.1% within 35.7 months of follow-up (Cho et al., 2011a). Another study in Iran reported that 35.2% of cases of thyroidectomy developed hypothyroidism on average 5 ± 3.2 months (mean ± S.D) after surgery (Lankarani et al., 2008).

6.4.7.1 Propylthiouracil medication and hypothyroidism

In our study, 5% of the study cases take Propylthiouracil compared to none in the control group ($P < 0.05$).

According previous studies, Thionamides (Methimazole, Propylthiouracil, Carbimazole) is a major anti-thyroid drug used for treatment of Graves hyperthyroidism, and these anti-thyroid drugs are associated with the development of hypothyroidism (Cho et al., 2011e). A prospective randomized study in Thailand found that the incidence of hypothyroidism among hyperthyroidism patients treated with a fixed-15 mg daily dosage of Methimazole for 12 weeks was 31.4% (Homsanit et al., 2001).

6.4.8 History of diagnosis: age of diagnosis

In our study, the mean age at diagnosis of the study cases was 33.3 ± 14.5 years (mean ± S.D) and 68.9% of the study cases were diagnosed with hypothyroidism. The diagnosis was based on the presence of hypothyroidism symptoms and blood TSH, T3 and T4 levels and 50% was diagnosed by an endocrinologist

The mean age of our study diagnosis is higher than reported by a study performed in Turkey, which found 24.5% of patients with Hashimoto's thyroiditis had subclinical hypothyroidism with the mean age at diagnosis 11.5±2.2 years, and 29% of patients with Hashimoto's thyroiditis had overt hypothyroidism with the mean age 10.4±2.6 years (mean ± S.D) (Demirbilek et al., 2007). Another study in Pakistan that included 100 consecutive cases of hypothyroidism from birth to twelve years, found that delayed diagnosis was among 42% (n=100) of cases and were between 1-5 years, and 66% of these cases had developmental delay (Malik and Butt, 2008b). A study in Turkey, revealed that height prognosis in late diagnosed congenital hypothyroidism (Kandemir and Yordam, 2001).

6.5 Study bias and limitation

1. Recall bias might be a major bias in our study. A lot of questions answered by patients about their health status, medication, family history, life style as well as types of food consumed. This type of design has its limitations and possible not to give the correct information

2. The present study was case control- clinical based study; and does not represent the whole population.

3. The present study was based on TSH only. Therefore, the present study could have been strengthened if free T_3, free T_4, Total T_4, Total T_3, anti-thyroperoxidase (anti-TPO) and anti-thyroglobulin (anti Tg) were included.

4. A possibility that TSH cut-offs values which was used in the present study may have underestimated health risk. The values used were those recommended by the manufacturer of the kit and other studies because Palestine does not have its own reference interval for thyroid function test panel.

5. Our study cases were not homogenizes (because included primary hypothyroidism, secondary hypothyroidism and congenital hypothyroidism).

6.6 Conclusion

The present study was a case control- clinical based study and cannot represent the whole Palestinian population. The study identified possible risk factors associated with hypothyroidism among patients attending the primary health care clinics in Hebron governorate and can be used as baseline for future work on thyroid diseases. Also, the study revealed that hypothyroidism appears to be quite common in Palestine. Although the prevalence of hypothyroidism was based on files presented in endocrinology clinics, however 17.4% is considered high in comparison to other endocrine disorders. This could be associated to iodine deficiency because of the lower consumption of iodized salt, and other congenital factors like autoimmune diseases a potential reason too. Moreover, the present study demonstrated that living area, working status household monthly income, rate of daily physical activity, smoking by others in closed places, consumption of carrots, banana, and iron supplement intake were associated with hypothyroidism. Better understanding of these factors and how they impact on hypothyroidism manifestation may allow preventive measures or better tailoring of therapies. Therefore, our results are important for future planning of policies such as setting a national screening program that will prevent and/or delay the complication of hyperthyroidism related disabilities.

6.7 Recommendations

Recommendations for policy makers

1. A national screening program for thyroid disorders is needed to help in preventing and/or delaying thyroid disorders and its complication or any of its other related disabilities recommended for high risk individuals who might have goiter, iodine deficiency disorder, family history of autoimmune disease……etc.

2. A comprehensive health education program is needed to educate people on the importance of using iodized salt and the importance to care for eating foods that help preventing such disorder, in addition to the role of physical activity in preventing it occurrence.

3. To incorporate the TSH, T3, and T4 measurement at the MOH laboratory testing.

Recommendations for doctors and health staff

1. To participate in increasing the awareness of their patients on the role of changes in lifestyle in delaying the occurrence of hypothyroidism and its complications.

2. To encourage and order the TSH blood level for patients at risk to develop thyroid diseases, and to refer these patients to endocrine clinic if needed.

3. More focus in reporting and filing information in patients files about patients health situation and follow up.

Recommendations for future research and researchers

1. Further population based epidemiological studies are needed to establish the accurate prevalence and predominant etiological factors of thyroid disorders.

2. Additional studies will be needed to determine the iodine level spectrum for the Palestinian population.

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Annex: 1

كلية الصحة العامة

يعد مرض قصور الغدة الدرقية من الأمراض الشائعة، وهو يصيب النساء أكثر من الرجال، ويزداد المرض مع تقدم العمر، وهو حالة مرضية يكون فيها إنتاج هرمونات الغدة الدرقية (هرمونات الثايروید) أقل من المعدل الطبيعي، وهناك أسباب عدة تؤدي للإصابة بقصور الغدة الدرقية من أهمها: أمراض المناعة الذاتية، والاستئصال الجراحي للغدة الدرقية، والعلاج الإشعاعي للغدة الدرقية، وقصور الغدة الدرقية يؤدي إلى العديد من المضاعفات منها: قصور الذاكر زيادة الوزن أو صعوبة فقدان الوزن الاكتئاب اضطراب مواعيد الدورة الشهرية و/أو مشاكل الخصوبة، والآم المفاصل أو العضلات.

ومن هنا يهدف هذا البحث إلى معرفة العوامل المرتبطة بقصور الغدة الدرقية بين المرضى الذين يراجعون عيادات الرعاية الصحية الاولية في محافظة الخليل من أجل العمل على الوقاية والحد من انتشار مضاعفات هذا المرض عند هؤلاء المرضى .

تأتي هذه الاستبانة استكمالاً لدرجة الماجستير؛ لذا نرجو من حضرتكم الإجابة على الأسئلة كافة، آملين أن تكون إجابتكم بموضوعية وحسب التعليمات الواردة قبل كل سؤال، علما إن المعلومات الواردة في الاستبيان ستستخدم لأغراض البحث العلمي فقط، وسيتبقى سرية تماماً، كما نرجو من حضرتكم التوقيع بالموافقة على إجابة أسئلة هذه الاستبانة.

شاكرين لكم حسن تعاونكم

الباحث: مصطفى برهم

اطلعت على جميع التعليمات الواردة في هذا الاستبيان وعليه قررت المشاركة في هذه الدراسة، وان وجود اسمي وتوقيعي هو دليل على قبولي للمشاركة في هذه الدراسة.

التاريخ_____

الساعة_____

اسم المشارك : **التوقيع**_____

اسم الباحث : مصطفى برهم **التوقيع**_____

Annex: 2

القسم الاول: بيانات المبحوث

Q.1	تاريخ تعبئة الاستمارة	|___|___|___|___|___|___| يوم / شهر / عام			
Q.2	اسم العيادة:				
Q.3	رقم الملف الطبي:	|___|___|___|___|___|			
Q.4	الاسم الشخصي الرباعي:				
Q.5	التلفون	الجوال			
Q.6	العنوان				
Q.7	المقابل	1- حالة	2- ضابطة		
Q.8	الجنس	1- ذكر	2- أنثى		
Q.9	العمر	|___| سنة			
Q.10	تاريخ الميلاد	|___|___|___|___|___|___| يوم / شهر / عام			
Q.11	الطول سم	|___|___|			
Q.12	الوزن كغم	|___|___|			
Q.13	TSH level	|___|___|,|___|___|	Q.14التاريخ|___|___|___| ___|___|___|___|___|___| يوم / شهر / عام		
Q.15	Free T4 level	|___|___|,|___|___|	Q.16التاريخ|___|___|___| ___|___|___|___|___|___| يوم / شهر / عام		
Q.17	الحالة الاجتماعية	1-متزوج	2-أعزب	3-أرمل	4-مطلق
Q18	هل تعمل (ي)	1- نعم	2- لا		
Q.19	المهنة خلال عشرة الأعوام الماضية				
Q.20	عدد سنوات الدراسة	|___|___| سنة			
Q.21	مكان السكن	1-مدينة	2-قرية	3-مخيم	4-خربة او بيت شعر
Q.22	الدخل الشهري للعائلة بالشيكل	1-أقل من 1000 شيكل	2-1000-2000	3-2001-3000	4- 3001-5000
Q.23	عدد افراد الاسرة المقيمين في المنزل حاليا	|___|___| فرد			
Q.24	هل أنت مدخن	1-نعم	2-لا		
	ماذا تدخن يوميا؟ (متعدد الاجابات)	1- سيجارة مع فلتر	2-سيجارة بدون فلتر	3-سيجار	4-غليون	5-ارجيلة

	ماهو معدل تدخينك اليومي لأي من هذه الأنواع	|___|___|	|___|___|	|___|___|	|___|___|	|___|___|
Q.25	ما هو عدد سنوات التدخين	|___|___| سنة				
Q.26	هل يدخن أحد من اسرتك في البيت اثناء وجودك؟	1-نعم	2-لا			
Q.27	هل يدخن أحد اثناء وجودك في مكان مغلق مثل مكان العمل؟	1-نعم	2-لا			
Q.28	هل سبق وأن تناولت مشروبا كحوليا مثل البيرة أو النبيذ او الويسكي خلال حياتك؟	1-نعم	2-لا			
Q.29	هل تناولت المشروبات الكحولية مثل البيرة أو النبيذ او الويسكي:	1. يوميا	2. 5 -6 مرات في الأسبوع	3. 1-4 مرات في الأسبوع	4. 1-3 مرات في الشهر	5 - أقل من مرة في الشهر
Q.30	عندما تشرب الكحول في المتوسط كم كأسا تشرب يوميا؟	العدد |___|___|	لا أعلم			
Q.31	منذ كم سنة وأنت تشرب الكحول؟	سنوات |___|___|	لا أعلم			

Q.32	حسب تقييمك ما هو مستوى نشاطك اليومي (مشي، ركض، اعمال منزلية..	1-عالي	2-متوسط	3-منخفض	4-غير ذلك حدد
Q.33	هل تمارس الرياضة؟	1-نعم	2-لا		

	نوع الرياضة	كم مرة في الأسبوع تمارس هذه الرياضة				مدتها في كل مرة			
		مرة أو اقل	2-3 مرات	4-5 مرات	6 أو أكثر	نصف ساعة أو اقل	نصف ساعة- ساعة	ساعة- ساعتين	أكثر من ساعتين
Q.34	المشي								
Q.35	الركض								
Q.36	تمارين عامة بدون أجهزة								
Q.37	تمارين باستخدام أجهزة رياضية								
Q.38	غير ذلك:								

القسم الثاني: لائحة الاغذية

Q.39	هل تتناول ملح الطعام المضاف باليود	1-نعم	2-لا

		الوحدة	لا يتناول	التحضير: 1.طازجة 2.معلبة 3.مجففة	+6 لليوم	4 - 6 لليوم	2-3 لليوم	مرة لليوم	5-6 في الأسبوع	2-4 في الأسبوع	مرة في الأسبوع	1-3 في الشهر
Q.40	الفواكة بشكل عام	حبة										
Q.41	المشمش	حبة										
Q.42	الأناناس	حبة										
Q.43	الفراولة	حبة										
Q.44	الموز	حبة										
Q.45	الخوخ	حبة										
Q.46	الخضروات بشكل عام	½ ك										
Q.47	الملفوف	½ ك										
Q.48	الزهرة (القرنبيط)	½ ك										
Q.49	بروكلي	½ ك										
Q.50	البندورة	حبة										
Q.51	الخس	حبة										

Q.52	الجزر	حبة											
Q.53	بطاطا	حب											
Q.54	الفول السوداني	½ ك											
Q.55	فول الصويا	½ ك											
Q.56	حليب كامل الدسم	1ك											
Q.57	حليب منزوع الدسم	1ك											
Q.58	لبن رائب كامل الدسم	1ك											
Q.59	لبن رائب منزوع الدسم	1ك											
Q.60	جبنة بيضاء بلدية	100 غم											
Q.61	جبنة بيضاء مصنعة	100 غم											
Q.62	زبدة بلدية	100 غم											
Q.63	زبدة مصنعة	100 غم											
Q.64	بوظة	1ك											
Q.65	لبن مخيض	1ك											

Q.66		الوحدة	لا يأخذ	1.طازجة 2.مقلية 3.مشوية 4.مغلية	+6 لليوم	4 - 6 لليوم	2-3 لليوم	مرة لليوم	5-6 في الأسبوع	2-4 في الأسبوع	مرة في الأسبوع	1-3 في الشهر
Q.67	البيض	بيضة										
Q.68	اللحوم الحمراء (الخروف، العجل)	150غم										
Q.69	لحم الدجاج	150غم										

Q.70	لحم الحبش	150 غم										
Q.71	اللحوم المصنعة المطبوخة مثل السلامي، المرتديلا، البسطرمة	شريحة										
Q.72	النقانق أو السجق	حبة										
Q.73	اللحوم المدخنة	شريحة										
Q.74	السمك الطازج	150 غم										
Q.75	السمك المملح	150 غم										
Q.76	السلمون	150 غم										
Q.77	الجمبري	150 غم										
Q.78	السردين المعلب	علبة										
Q.79	التونا المعلبة	علبة										
Q.80	الطحالب والأعشاب البحرية	150 غم										
Q.81	المشروبات الغازية (الكولا)	كأس										
Q.82	المشروبات الغازية بدون سكر	كأس										
Q.83	القهوة	فنجان										
Q.84	الشاي العادي	كأس										
Q.85	الشاي الأخضر	كأس										
Q.86	الماء	كأس										
Q.87	المكسرات (لوز)	½ ك										
Q.88	الخبز ومشتاقتة	رغيف										
Q.89	الموالح (شيبس , بسكويت مالح)	بكيت										

القسم الثالث :لائحة المكملات الغذائية

	هل تتناول التالي:	2-لا	1 -نعم	كم حبة بالأسبوع	كم ابرة بالاسبوع	في العام الماضي كم شهر تقريبا استخدمته	هل تعرف نوعها
Q.90	الفيتامينات (Multi-Vitamins) المضافة باليود						
Q.91	Multivitaminsعادي						
Q.92	potassium iodine						
Q.93	فيتامين B complex						
Q.94	فيتامين B12						
Q.95	فيتامين B6						
Q.96	فيتامين A						
Q.97	فيتامين c						
Q.98	فيتامين E						
Q.99	فيتامين D						
Q.100	البوتاسيوم						
Q.101	الكالسيوم						
Q.102	السيلينيوم						
Q.103	الزنك						
Q.104	حامض الفوليك						
Q.105	الحديد						
Q.106	Calcium + vit D						

القسم الرابع: الوضع الصحي

	المرض	2.لا	1.نعم	3. لا اعرف	اذا نعم، تاريخ التشخيص
Q.107	أمراض المناعة الذاتية				
Q.108	مرض السكري				
Q.109	أمراض القلب				
Q.110	السرطان				
Q.111	أمراض الغدة الدرقية				
Q112	أمراض الغدة النخامية				
Q.113	أمراض الكبد				
Q.114	امراض الكلية				
Q.115	أمراض نفسية				
Q.116	هل تم تشخيصك أوعلاجك لأمراض الغدة الدرقية ؟				
Q.117	هل تم تشخيصك بقصور الغدة الدرقية (hypothyroidism) ؟				
Q.118	هل تم تشخيصك بفرط نشاط الغدة الدرقية (hyperthyroidism) ؟				
Q.119	هل كان لديك تضخم في الغدة الدرقية goiter؟				
Q.120	هل كان لديك في أي وقت مضى التهاب الدرقية المنيع الذات Autoimmune Thyroiditis؟				
Q.121	هل كنت تعاني من قصور الغدة الدرقية الخلقي congenital hypothyroidism منذ بداية الحياة ؟				
Q.122	مرض السكري نوع 1				

Q.123	فقر الدم				
Q.124	البلاهة المنغولية				
Q.125	البهاق				
Q.126	متلازمة شيجرن				
Q.127	الاعتلال المعوي				
Q.128	مرض اديسون				

القسم الخامس : الأدوية

Q.129	هل قمت بعملية إزالة الغدة الدرقية	1-نعم	2-لا	
Q.130	هل تم علاجك باليود الإشعاعي Radioactive iodine	1-نعم	2-لا	
	هل تتناول أي من هذة الادوية؟	نعم	لا	المدة الزمنية
Q.131	الليثيم Lithium			
Q.132	أمايوداروون Amiodarone			
Q.133	الإنترفيرون Interferon			
Q.134	كاربيمازول Carbimazole			
Q.135	الميتازول Methimazole			
Q.136	بروبيلثيوراسيل Propylthiouracil			
Q.137	أخرى			

القسم السادس: للنساء فقط

		1-نعم	2-لا	3-أحيانا
Q.138	خلال 12 شهر الماضية هل انقطعت دورتك الشهرية كاملا؟			
Q.139	هل الدوره الشهرية منتظمة ؟			
Q140	هل كنت حامل على الأقل مرة واحدة ؟			
Q.141	هل حصل لك نزيف بعد الولادة؟			
Q.142	هل حصل لك اجهاض ؟			

القسم السابع: اسئلة للحالات فقط

Q.143	تاريخ تشخيص قصور الغدة	|___|___|/|___|___|/|___|___||___|___| يوم / شهر / عام			
Q.144	كم عمرك عندما تم تشخيصك بقصور الغدة	|___|___| سنة			
Q.145	كم وزنك عندما تشخيصك بقصورة الغدة				
Q.146	كيف تم اكتشاف قصور الغدة لديك؟	1-بالصدفة	2-الفحص الدوري	3-وجود أعراض	4-لا أذكر
Q.147	من قام بتشخيصك؟	1-طبيب عام	2-أخصائي غدد	3-أخصائي باطني	4-غير ذلك / 5-لا أذكر
Q.148	اول علاج تم اعطاؤه لك		Q.148_1 الجرعة: _____		
Q.149	العلاج الحالي		Q.149_1 الجرعة: _____		

القسم الثامن :التاريخ العائلي المرضي:

صلة القرابة:
1. احد الوالدان
2. كلا الوالدان
3. أخ او/و أخت
4. عم, او/و عمة
5. خال او/و خالة
6. أحد الجدان او كلاهما
7. آخرون من

		1.نعم	2.لا	صلة القرابة: استخدام الارقام اعلاه
Q.150	يعاني من أمراض المناعة الذاتية Autoimmune disease			
Q.151	مرض السكري نوع 1			
Q.152	فقر الدم			
Q.153	البلاهة المنغولية			
Q.154	البهاق			
Q.155	متلازمة شيجرن			
Q.156	الاعتلال المعوي			
Q.157	مرض اديسون			
Q.158	مصاب بأمراض في الغدة الدرقية			
Q.159	مصاب بمرض بقصور الغدة الدرقية hypothyroidism؟			
Q.160	مصاب بمرض بفرط الغدة الدرقية hyperthyroidism؟			
Q.161	أمراض اخرى			

هل تود (ي) اضافة اي معلومة لم اسألها لك

_____

_____

_____

_____

Annex: 3

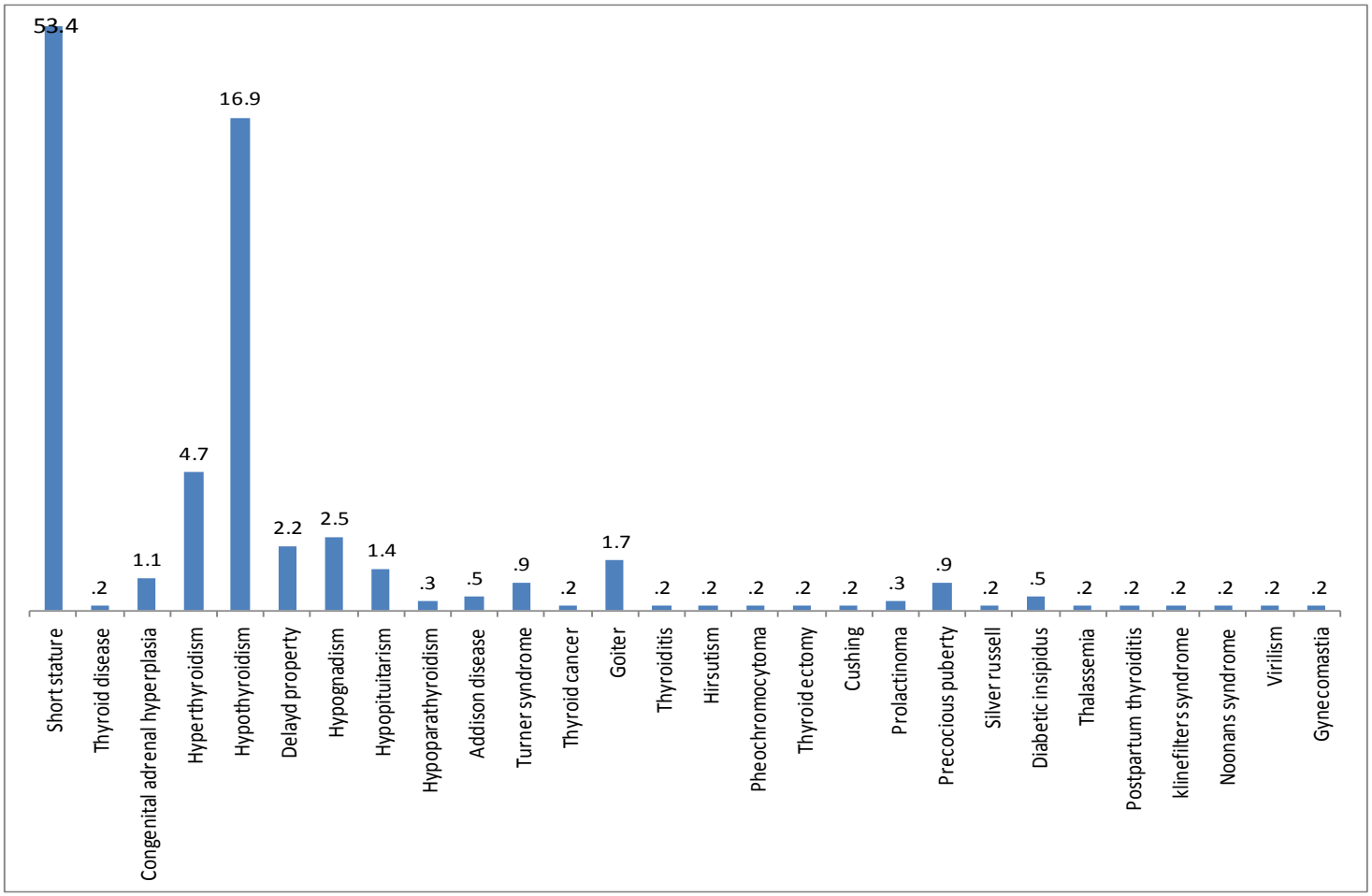

Figure 1: distribution of patients attending Karantina endocrinology clinic

Annex: 4

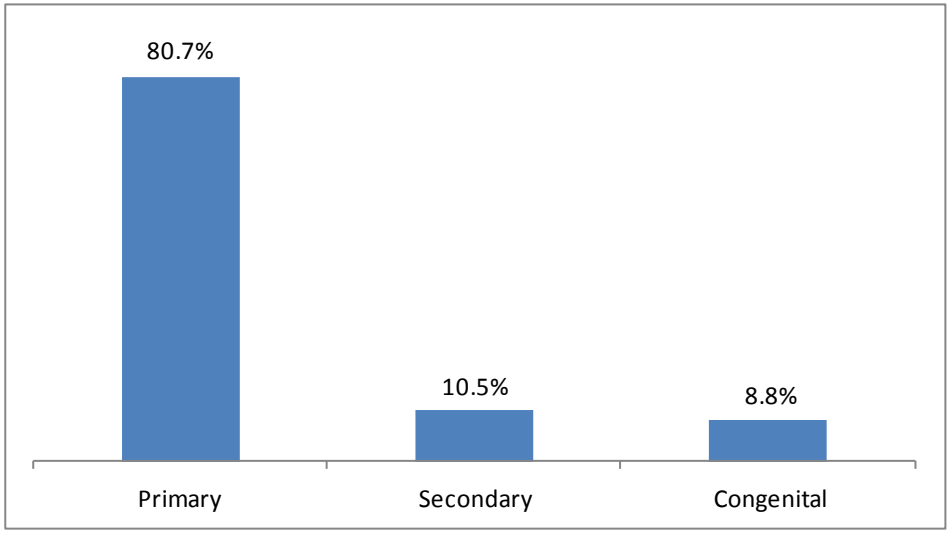

Figure 1: distribution of patients attending Karantina endocrinology clinic

Annex: 5

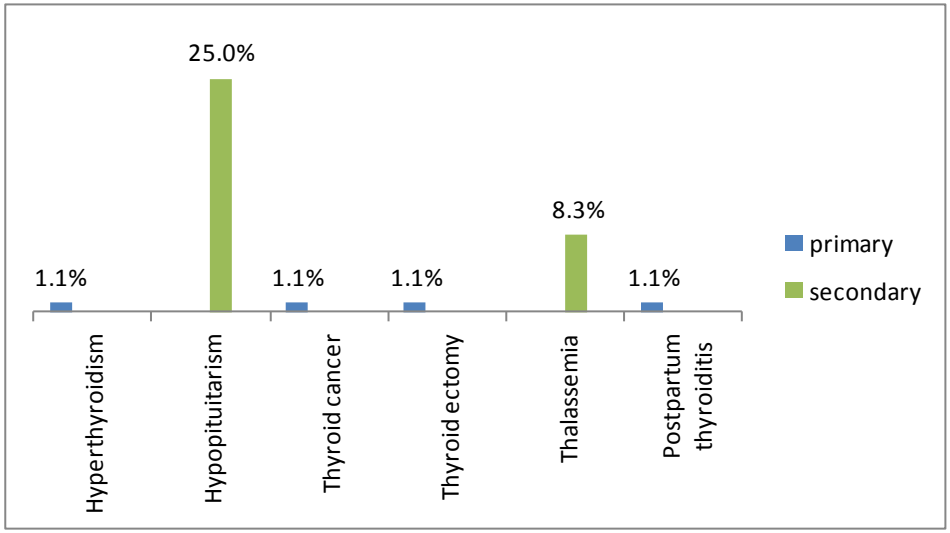

Figure 5.5: Association between types of hypothyroidism and endocrine disorders in Karantina endocrinology clinic

Annex: 6

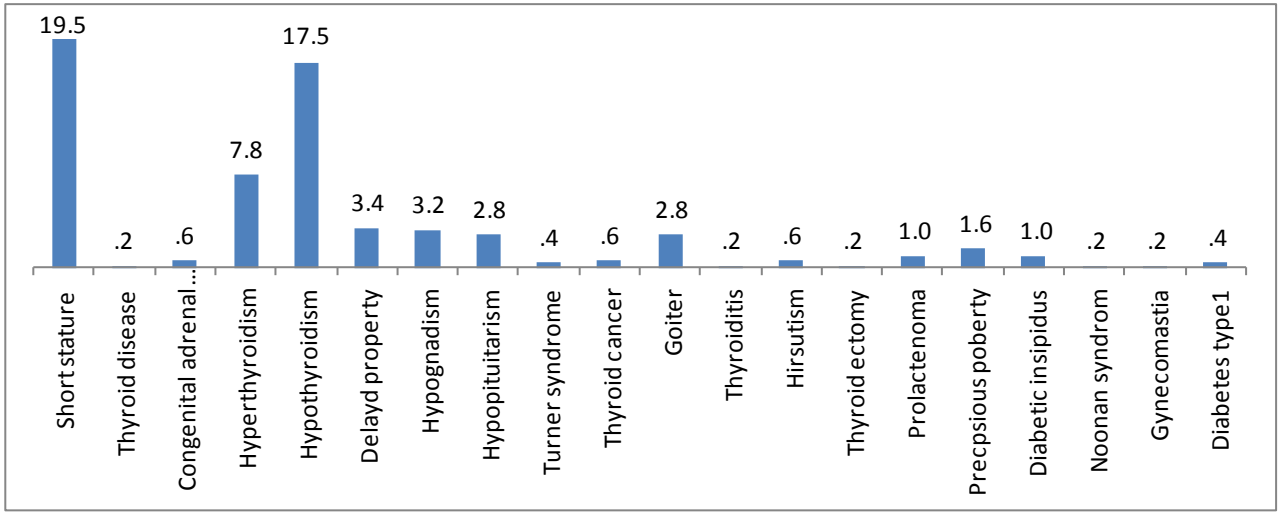

Figure 4: Distribution of patients attending Dura endocrinology clinic

Annex: 7

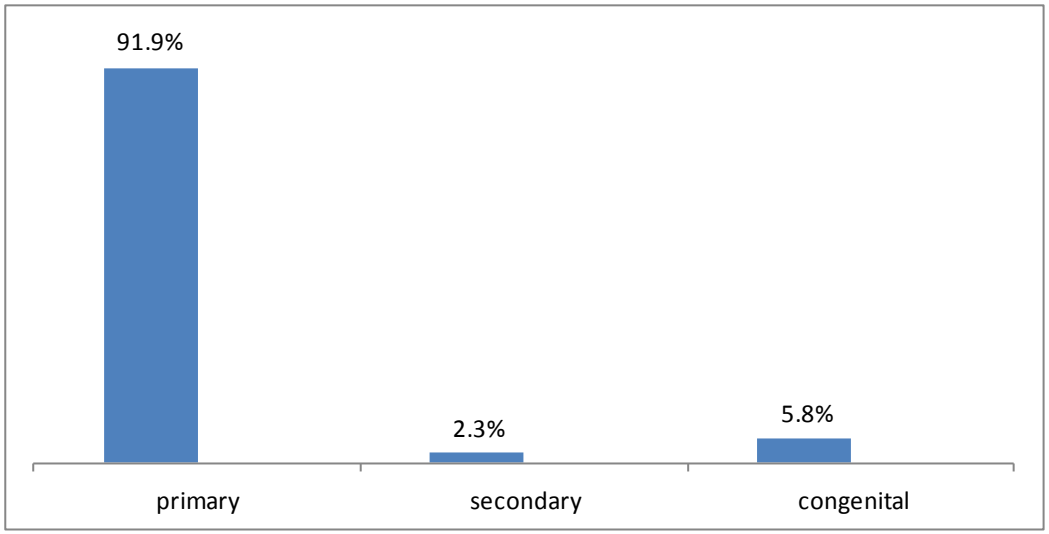

Figure 4: Distribution of patients attending Dura endocrinology clinic

Annex: 8

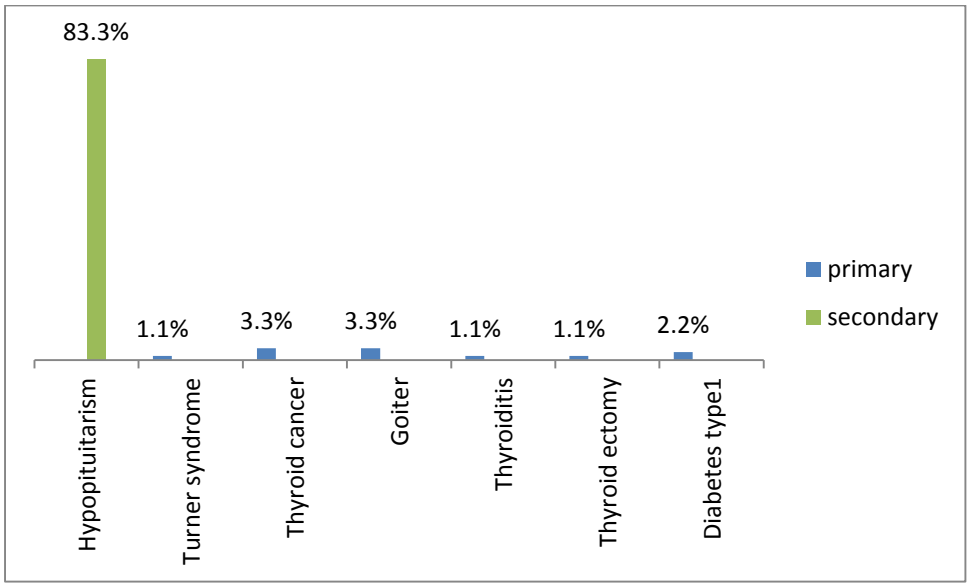

Figure 5.6: Association between types of hypothyroidism and endocrine disorders in Dura endocrinology clinic

Annex: 9

Table 5.2: Association between study cases and control groups' BMI, physical activity, smoking status and alcohol consumption.

		Case N=103	Control group N=103	Total (%) N=206	Chi Square
		N (%)	N (%)	N (%)	P value
BMI	**Underweight < 18.5**	8 (7.8%)	3 (2.9%)	11 (5.3%)	0.001
	Normal 18.5-24.99	21 (20.4%)	34 (33.3%)	55 (26.7%)	
	Overweight ≥25-29.99	26 (25.2%)	44 (43.1%)	70 (34.0%)	
	Obese ≥30	48 (46.6%)	22 (21.4%)	70(34.0%)	
Rate of your daily activity	**High**	20 (19.4%)	41 (39.8%)	61 (29.6%)	0.001
	Medium	64 (62.1%)	59 (57.3%)	123 (59.7%)	
	Low	19 (18.4%)	3 (2.9%)	22 (10.7%)	
Physical activity	**Yes**	68 (66.0%)	76 (73.8%)	144 (69.9%)	0.224
	No	35 (34.0%)	27 (26.2%)	62 (30.1%)	
Walking per week	**Less <1**	8 (11.8%)	3 (3.9%)	11 (5.3%)	0.004
	3-2	35 (51.5%)	24 (31.6%)	59 (28.6%)	
	4-5	4 (5.9%)	15 (19.7%)	19 (9.2%)	
	>6	21 (30.9%)	34 (44.7%)	55 (26.7%)	

Frequency walking	**Less half an hour**	35 (51.5%)	32 (42.1%)	67 (32.5%)	0.375
	Half an hour	20 (29.4%)	31 (40.8%)	51 (24.8%)	
	1-2 hours	13 (19.1%)	12 (15.8%)	25 (12.1%)	
	> 2 hours	0 (0.0%)	1 (1.3%)	1 (0.5%)	
Running per week	**less <1**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	3-2	3 (100.0%)	1 (100.0%)	4 (1.9%)	
	4-5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	>6	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Frequency running	**Less half an hour**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	Half an hour	3 (100.0%)	1 (100.0%)	4 (1.9%)	
	1-2 hours	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	> 2 hours	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Exercises without equipment per week	**less <1**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	3-2	2 (100.0%)	0 (0.0%)	2 (1.0%)	
	4-5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	>6	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Frequency exercises without equipment	**Less half an hour**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	Half an hour	1 (50.0%)	0(0.0%)	1 (0.5%)	

	1-2 hours	1 (50.0%)	0 (0.0%)	1 (0.5%)	
	> 2 hours	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Exercises with equipment per week	**less <1**	0 (0.0%)	0 (0.0%)	0(0.0%)	NA
	3-2	1 (100.0%)	0 (0.0%)	1 (0.5%)	
	4-5	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	>6	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Frequency exercises with equipment	**Less half an hour**	1 (100.0%)	0 (0.0%)	1 (0.5%)	0.157
	Half an hour	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-2 hours	0 (0.0%)	1 (100.0%)	1 (0.5%)	
	> 2 hours	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Smoking	**Yes**	4 (3.9%)	1 (1.0%)	5 (2.4%)	0.174
	No	99 (96.1%)	102 (99.0%)	201 (97.6%)	
Smoking while you at home	**Yes**	64 (62.1%)	48 (46.6%)	112 (54.4%)	0.025
	No	39 (37.9%)	55 (53.4%)	94 (45.6%)	
Smoking by others in closed places	**Yes**	56 (54.4%)	38 (36.9%)	94 (45.6%)	0.012
	No	47 (45.6%)	65 (63.1%)	112 (54.4%)	
Alcohol consumption	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	

***NA: not available**

Annex: 10

Table 5.3: Differences between study cases and control group in food intake

		Study cases N=103	Control group N=103	Total (%) N=206	Chi Square
		N (%)	N (%)	N (%)	P value
Iodized salt	**Yes**	103 (100.0%)	103 (100.0%)	206 (100.0%)	NA
	NO	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Fruits (Preparation)	**Fresh**	103 (100.0%)	103 (100.0%)	206 (100.0%)	NA
	Bottled	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Dried	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Fruits	**<1 per week**	3 (2.9%)	2 (1.9%)	5 (2.4%)	0.005
	5-7 per week	26 (25.2%)	44 (42.7%)	70 (34.0%)	
	2-3 times daily	7 (6.8%)	0 (0.0%)	7 (3.4%)	
	1-4 per week	67 (65.0%)	57 (55.3%)	124 (60.2%)	
Apricot	**<1 per week**	32 (31.1%)	24 (23.3%)	56 (27.2%)	0.441
	5-7 per week	8 (7.8%)	10 (9.7%)	18 (8.7%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	63 (61.2%)	69 (67.0%)	132 (64.1%)	
Pineapple	**<1 per week**	98 (95.1%)	93 (90.3%)	191 (92.7%)	0.180
	5-7 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	5 (4.9%)	10 (9.7%)	15 (7.3%)	
Strawberry	**<1 per week**	69 (67.0%)	47 (45.6%)	116 (56.3%)	0.002
	5-7 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	34 (33.0%)	56 (54.4%)	90 (43.7%)	
Banana	**<1 per week**	33 (32.0%)	23 (22.3%)	56 (27.2%)	0.001
	5-7 per week	7 (6.8%)	30 (29.1%)	37 (18.0%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	63 (61.2%)	50 (48.5%)	113 (54.9%)	
Vegetables (Preparation)	**Fresh**	103 (100.0%)	103 (100.0%)	206 (100.0%)	
	Bottled	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Dried	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Vegetable	**<1 per week**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.001
	5-7 per week	60 (58.3%)	89 (86.4%)	149 (72.3%)	
	2-3 times daily	17 (16.5%)	0 (0.0%)	17 (8.3%)	
	1-4 per week	26 (25.2%)	14 (13.6%)	40 (19.4%)	
Cabbage	**<1 per week**	65 (63.1%)	71 (68.9%)	136 (66.0%)	0.377
	5-7 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2-3 times daily	0 (0.0%)	0(0.0%)	0 (0.0%)	
	1-4 per week	38 (36.9%)	32 (31.1%)	70 (34.0%)	
Cauliflower	**<1 per week**	23 (22.3%)	22 (21.4%)	45 (21.8%)	0.866
	5-7 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	80 (77.7%)	81 (78.6%)	161 (78.2%)	
Tomato	**<1 per week**	2 (1.9%)	1(1.0%)	3 (1.5%)	0.082
	5-7 per week	72 (69.9%)	83 (80.6%)	155 (75.2%)	

	2-3 times daily	5 (4.9%)	0 (0.0%)	5 (2.4%)	
	1-4 per week	24 (23.3%)	19 (18.4%)	43 (20.9%)	
Lettuce	**<1 per week**	64 (62.1%)	64 (62.1%)	128(	0.840
	5-7 per week	8 (7.8%)	6 (5.8%)	14 (	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	31 (30.1%)	33 (32.0%)	64 (	
Carrot	**<1 per week**	59 (57.3%)	42 (40.8%)	101 (49.0%)	0.034
	5-7 per week	11 (10.7%)	10 (9.7%)	21 (10.2%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	33 (32.0%)	51 (49.5%)	84 (40.8%)	
Potato	**<1 per week**	24 (23.3%)	16 (15.5%)	40 (19.4%)	0.088
	5-7 per week	17 (16.5%)	29 (28.2%)	46 (22.3%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	62 (60.2%)	58 (56.3%)	120 (58.3%)	
Full fat milk	**<1 per week**	64 (62.1%)	58 (56.3%)	122 (59.2%)	0.344
	5-7 per week	14 (13.6%)	22 (21.4%)	36 (17.5%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	25 (24.3%)	23 (22.3%)	48 (23.3%)	
Yogurt	**<1 per week**	37 (35.9%)	25 (24.3%)	62 (30.1%)	0.036
	5-7 per week	13 (12.6%)	26 (25.2%)	39 (18.9%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	53 (51.5%)	52 (50.5%)	105 (51.0%)	
Local cheese	**<1 per week**	67 (65.0%)	67 (65.0%)	134 (65.0%)	0.262
	5-7 per week	8 (7.8%)	3 (2.9%)	11 (5.3%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	28 (27.2%)	33 (32.0%)	61 (29.6%)	
Local butter	**<1 per week**	84 (81.6%)	94 (91.3%)	178 (86.4%)	0.088
	5-7 per week	5 (4.9%)	1 (1.0%)	6 (2.9%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	14 (13.6%)	8 (7.8%)	22 (10.7%)	
Ice-cream	**<1 per week**	46 (44.7%)	42 (40.8%)	88 (42.7%)	0.850
	5-7 per week	9 (8.7%)	10 (9.7%)	19 (9.2%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	48 (46.6%)	51 (49.5%)	99 (48.1%)	
Shake milk	**<1 per week**	74 (71.8%)	62 (60.2%)	136 (66.0%)	0.204
	5-7 per week	7 (6.8%)	11 (10.7%)	18 (8.7%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	22 (21.4%)	30 (29.1%)	52 (25.2%)	
Animal product (Preparation)	**Boiled**	101 (99.1%)	103 (100.0%)	204 (99.0%)	
Animal product	**<1 per week**	9 (8.7%)	3 (2.9%)	12 (5.8%)	0.154
	5-7 per week	5 (4.9%)	8 (7.8%)	13 (6.3%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	89 (86.4%)	92 (89.3%)	181 (87.9%)	
Egg	**<1 per week**	28 (27.2%)	19 (18.4%)	47 (22.8%)	0.121
	5-7 per week	15 (14.6%)	25 (24.3%)	40 (19.4%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	60 (58.3%)	59 (57.3%)	119 (57.8%)	
Red meat	**<1 per week**	72 (69.9%)	85 (82.5%)	157 (76.2%)	

	5-7 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.033
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	31 (30.1%)	18 (17.5%)	49 (23.8%)	
Chicken	**<1 per week**	9 (8.7%)	3 (2.9%)	12 (5.8%)	0.085
	5-7 per week	4 (3.9%)	9 (8.7%)	13 (6.3%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	90 (87.4%)	91 (88.3%)	181 (87.9%)	
Turkey meat	**<1 per week**	59 (57.3%)	60 (58.3%)	119 (57.8%)	0.369
	5-7 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	44 (42.7%)	43 (41.7%)	87 (42.2%)	
Processed meats (Salami, Mortadella)	**<1 per week**	73 (70.9%)	76 (73.8%)	149 (72.3%)	0.831
	5-7 per week	8 (7.8%)	6 (5.8%)	14 (6.8%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	22 (21.4%)	21 (20.4%)	43 (20.9%)	
Sausage	**<1 per week**	92 (89.3%)	95 (92.2%)	187 (90.8%)	0.338
	5-7 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	11 (10.7%)	8 (7.8%)	19 (9.2%)	
Smoked meats	**<1 per week**	101 (98.1%)	102 (99.0%)	203 (	0.561
	5-7 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	2 (1.9%)	1 (1.0%)	3 (1.5%)	
Fish	**<1 per week**	56 (54.4%)	59 (57.3%)	115 (55.8%)	0.674
	5-7 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	47 (45.6%)	44 (42.7%)	91 (44.2%)	
Canned sardines	**<1 per week**	78 (75.7%)	90 (87.4%)	168 (81.6%)	0.031
	5-7 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	25 (24.3%)	13 (12.6%)	38 (18.4%)	
Canned tuna	**<1 per week**	70 (68.0%)	85 (82.5%)	155 (75.2%)	0.015
	5-7 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	33 (32.0%)	18 (17.5%)	51 (24.8%)	
Soft drinks	**<1 per week**	48 (46.6%)	48 (46.6%)	96 (46.6%)	0.617
	5-7 per week	13 (12.6%)	19 (18.4%)	32 (15.5%)	
	2-3 times daily	2 (1.9%)	1 (1.0%)	3 (1.5%)	
	1-4 per week	40 (38.8%)	35 (34.0%)	75 (36.4%)	
Coffee	**<1 per week**	41 (39.8%)	39 (37.9%)	80 (38.8%)	0.010
	5-7 per week	24 (23.3%)	17 (16.5%)	41 (19.9%)	
	2-3 times daily	21 (20.4%)	40 (38.8%)	61 (29.6%)	
	1-4 per week	17 (16.5%)	7 (6.8%)	24 (11.7%)	
Tea	**<1 per week**	5 (4.9%)	12 (11.7%)	17 (8.3%)	0.269
	5-7 per week	28 (27.2%)	21 (20.4%)	49 (23.8%)	
	2-3 times daily	59 (57.3%)	58 (56.3%)	117 (56.8%)	
	1-4 per week	11 (10.7%)	12 (11.7%)	23 (11.2%)	
Water	**<1 per week**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.367
	5-7 per week	13 (12.6%)	9 (8.7%)	22 (10.7%)	
	2-3 times daily	90 (87.4%)	94 (91.3%)	184 (89.3%)	
	1-4 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	

Nuts	**<1 per week**	60 (58.3%)	49 (47.6%)	109 (52.9%)	0.231
	5-7 per week	8 (7.8%)	7 (6.8%)	15 (7.3%)	
	2-3 times daily	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	1-4 per week	35 (34.0%)	47 (45.6%)	82 (39.8%)	
Bread	**<1 per week**	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.818
	5-7 per week	11 (10.7%)	10 (9.7%)	21 (10.2%)	
	2-3 times daily	92 (89.3%)	93 (90.3%)	185 (89.8%)	
	1-4 per week	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Salty snacks	**<1 per week**	50 (48.5%)	35 (34.0%)	85 (41.3%)	0.165
	5-7 per week	13(12.6%)	21 (20.4%)	34 (16.5%)	
	2-3 times daily	6 (95.8%)	7 (6.8%)	13 (6.3%)	
	1-4 per week	34 (33.0%)	40 (38.8%)	74 (35.9%)	

***NA: not available**

Annex: 11

Table 5.4: Association between study cases and control group by using supplements.

		Study cases N=103	Control group N=103	Total N=206	Chi Square
		N (%)	N (%)	N (%)	P value
Multi-Vitamins added iodine	**Yes**	1 (1.0%)	0 (0.0%)	1 (0.5%)	0.316
	No	102 (99.0%)	103 (100.0%)	205 (99.5%)	
Multivitamins	**Yes**	7 (6.8%)	3 (2.9%)	10 (4.9%)	0.195
	No	96 (93.2%)	100 (97.1%)	196 (95.1%)	
Vitamin B complex	**Yes**	2 (1.9%)	3 (2.9%)	5 (2.4%)	0.651
	No	101 (98.1%)	100 (97.1%)	201 (97.6%)	
Vitamin B12	**Yes**	6 (5.8%)	15 (14.6%)	21 (10.2%)	0.038
	No	97 (94.2%)	88 (85.4%)	185 (89.8%)	
Vitamin B6	**Yes**	1 (1.0%)	0 (0.0%)	1 (0.5%)	0.316
	No	102 (99.0%)	103 (100.0%)	205 (99.5%)	
Vitamin A	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Vitamin C	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA

	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Vitamin E	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Vitamin D	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Potassium	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Calcium	**Yes**	7 (6.8%)	0 (0.0%)	7 (3.4%)	0.007
	No	96 (93.2%)	103 (100.0%)	199 (96.6%)	
Selenium	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Zink	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Folic acid	**Yes**	9 (8.7%)	7 (6.8%)	16 (7.8%)	0.603
	No	94 (91.3%)	96 (93.2%)	190 (92.2%)	
Iron	**Yes**	8 (7.8%)	18 (17.5%)	26 (12.6%)	0.036
	No	95 (92.2%)	85 (82.5%)	180 (87.4%)	
Calcium + vit D	**Yes**	9 (8.7%)	19 (18.4%)	28 (13.6%)	0.042
	No	94 (91.3%)	84 (81.6%)	168 (86.4%)	

***NA: not available**

Annex: 12

Table 5.15: Differences between study cases and control group by their medical conditions.

		Study cases N=103	Control group N=103	Total (%) N=206	Chi Square
		N (%)	N (%)	N (%)	P value
Diabetes type 2	**Yes**	15 (14.6%)	0 (0.0%)	15 (7.3%)	0.001*
	No	88 (85.4%)	103 (100.0%)	191 (92.7%)	
Heart Disease	**Yes**	12 (11.7%)	5 (4.9%)	17 (8.3%)	0.076
	No	91 (88.3%)	98 (95.1%)	189 (91.7%)	
Cancer	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Thyroid disease	**Yes**	103 (100.0%)	0 (0.0%)	103 (50.0%)	0.001*
	No	0 (0.0%)	103 (100.0%)	103 (50.0%)	
Pituitary Diseases	**Yes**	6 (5.8%)	0 (0.0%)	6 (2.9%)	0.013*
	No	97 (94.2%)	103 (100.0%)	200 (97.1%)	
Liver disease	**Yes**	0 (0.0%)	1 (1.0%)	1 (0.5%)	0.316
	No	103 (100.0%)	102 (99.0%)	205 (99.5%)	
Kidney disease	**Yes**	2 (1.9%)	1 (1.0%)	3 (1.5%)	0.561
	No	101 (98.1%)	102 (99.0%)	203 (98.5%)	
Mental illness	**Yes**	1 (1.0%)	0 (0.0%)	1 (0.5%)	0.316
	No	102 (99.0%)	103 (100.0%)	205 (99.5%)	
Hyperthyroidism	**Yes**	5 (4.9%)	0 (0.0%)	5 (2.4%)	0.024*
	No	98 (95.1%)	103 (100.0%)	201 (97.6%)	
Goiter	**Yes**	32 (31.1%)	0 (0.0%)	32 (15.5%)	0.001*
	No	71 68.9%	103 (100.0%)	174 (84.5%)	
Congenital hypothyroidism	**Yes**	6 (5.8%)	0 (0.0%)	6 (2.9%)	0.013*
	No	97 (94.2%)	103 (100.0%)	200 (97.1%)	
	Yes	3 (2.9%)	0 (0.0%)	3 (1.5%)	

Diabetes type 1	**No**	100 (97.1%)	103 (100.0%)	203 (98.5%)	0.081
Anemia	**Yes**	9 (8.7%)	3 (2.9%)	12 (5.8%)	0.074
	No	94 (91.3%)	100 (97.1%)	194 (94.2%)	
Down syndrome	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Vitiligo	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Sjögren's syndrome	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Addison's disease	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Celiac disease	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	

***NA: not available**

Annex: 13

Table 5.7: Differences between study cases and control group in their menstrual cycle and pregnancy among women

		Study cases N=95	Control group N=100	Total (%) N=195	Chi Square
		N (%)	N (%)	N (%)	P value
During the past 12 months menstrual period completely gone	**Yes**	20 (22.2%)	11 (11.1%)	31 (15.0%)	0.039
	No	70 (77.8%)	88 (88.9%)	158 (76.7%)	
Regular menstrual cycle	**Yes**	51 (75.0%)	78 (89.7%)	129 (62.6%)	0.015
	No	17 (25.0%)	9 (10.3%)	26 (12.6%)	
Pregnant at least once	**Yes**	68 (85.0%)	73 (98.6%)	141 (68.4%)	0.002
	No	12 (15.0%)	1 (1.4%)	13 (6.3%)	
Postpartum Thyroiditis	**Yes**	6 (8.8%)	0 (0.0%)	47 (22.8%)	0.009
	No	62 (91.2%)	73 (100.0%)	106 (51.5%)	
Bleeding after childbirth	**Yes**	30 (37.5%)	17 (23.3%)	47 (22.8%)	0.057
	No	50 (62.5%)	56 (76.7%)	106 (51.5%)	
Abortion	**Yes**	31 (38.8%)	27 (37.0%)	58 (28.2%)	0.822
	No	49 (61.2%)	46 (63.0%)	95 (46.1%)	

Annex: 14

Table 5.8: Association between study cases and control group by medication

		Case N=103	Control N=103	Total (%) N=106	Chi Square
		N (%)	N (%)	N (%)	P value
Thyroidectomy	**Yes**	7 (6.8%)	0 (0.0%)	7 (3.4%)	0.007*
	No	96 (93.2%)	103 (100.0%)	199 (96.6%)	
Radioactive iodine	**Yes**	2 (1.9%)	0 (0.0%)	2 (1.0%)	0.155
	No	101 (98.1%)	103 (100.0%)	204 (99.0%)	
Lithium	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Amiodarone	**Yes**	4 (3.9%)	1 (1.0%)	5 (2.4%)	0.174
	No	99 (96.1%)	102 (99.0%)	201 (97.6%)	
Interferon	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Carbimazole	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Methimazole	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	206 (100.0%)	
Propylthiouracil	**Yes**	5 (4.9%)	0 (0.0%)	5 (2.4%)	.024*
	No	98 (95.1%)	103 (100.0%)	201 (97.6%)	

***NA: not available**

Annex: 15

Table 5.3: Associations between study cases and control groups by family history of autoimmune diseases

		Study cases N=103	Control group N= 103	Total (%) N=206	Chi Square
		N (%)	N (%)	N (%)	P value
Diabetes type 1	**Yes**	19 (18.4%)	15 (14.6%)	34 (16.5%)	0.453
	No	84 (81.8%)	88 (85.4%)	172 (83.5%)	
Family history	**First degree relative**	19 (100.0%)	12 (80.0%)	31 (15.1%)	0.053
	Second degree relative	0 (0.0%)	3 (20.0%)	3 (1.5%)	
Vitiligo	**Yes**	5 (4.9%)	0 (0.0%)	5 (2.4%)	0.024
	No	98 (95.1%)	103 (100.0%)	201 (97.6%)	
Family history	**First degree relative**	4 (800.0%)	0 (0.0%)	4 (1.9%)	NA
	Second degree relative	1(20.0%)	0 (0.0%)	1 (0.5%)	
Sjögren's syndrome	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	106 (100.0%)	
Family history	**First degree relative**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	Second degree relative	103 (100.0%)	103 (100.0%)	106 (100.0%)	
Celiac disease	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	106 (100.0%)	
Family history	**First degree relative**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	Second degree relative	103 (100.0%)	103 (100.0%)	106 (100.0%)	
Addison's disease	**Yes**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	103 (100.0%)	103 (100.0%)	106 (100.0%)	

Family history	**First degree relative**	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	Second degree relative	103 (100.0%)	103 (100.0%)	106 (100.0%)	
Thyroid disease	**Yes**	45 (63.4%)	26 (36.6%)	71 (34.5%)	0.005
	No	58 (43.0%)	77 (57.0%)	135 (65.5%)	
Family history	**First degree relative**	31 (75.6%)	10 (24.4%)	41 (19.9%)	0.043
	Second degree relative	14 (51.9%)	13 (48.1%)	27 (13.1%)	
Hypothyroidism	**Yes**	45 (66.2%)	23 (33.8%)	68 (33.0%)	0.001
	No	58 (42.0%)	80 (58.0%)	138 (67.0%)	
Family history	**First degree relative**	31 (75.6%)	10 (24.4%)	41 (19.9%)	.074
	Second degree relative	13 (54.2%)	11 (45.8%)	24 (11.7%)	
Hyperthyroidism	**yes**	4 (100.0%)	0 (0.0%)	4 (1.9%)	.043
	no	99 (49.0%)	103 (51.0%)	202 (98.1%)	
Family history	**first degree relative**	2 (100.0%)	0 (0.0%)	2 (1.0%)	NA
	second degree relative	2 (100.0%)	0 (0.0%)	2 (1.0%)	

***NA: not available**

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