# Impact of Subclinic Hypothyroidism on a Basic Primary Healthcare Area

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**Abstract:** *Objective*: Assess the prevalence of subclinical hypothyroidism in the general population of an urban health area and describe the main clinical and socio-demographic characteristics of patients with subclinical hypothyroidism.

*Method*: A retrospective descriptive observational study. We reviewed case histories from June 2005 to July 2007. We analysed the following variables: General data: age and gender. Family background: thyroid pathology and other diseases. Personal background: cardiovascular, lung, autoimmunity, gynaeco-obsetric alterations, diabetes, hypertension (HT), dyslipidaemia, obesity, alterations of psychiatric haemotologic pathology, other laboratory data: TSH levels, free $T_4$ levels, presence of antiperoxidase antibodies, total and partial cholesterol levels.

*Results*: The prevalence of our sample of 100 patients enrolled in 8 months was 3.8% with a mean of 4.2% ± 1.3 SD in the general population aged over 14 years, of whom 79 were women and 21 were men. The; 13% were associated with type 2 diabetes mellitus, 23% with HT and 40% with dyslipidaemia. Being overweight or obese revealed a mean of 23%, TSH level in 6.92 μU/ml, range from 4,5 to 18,75μU/ml, while the mean free $T_4$ was 1.16 ± 0.16 ng/ml.

*Conclusions*: The prevalence of subclinical hypothyroidism was 3.8%. It was more frequent in women of a mean age of 46 years. Gynaecologic alternations were reported for 17% of females. The incidence of cardiovascular risk factors was relatively high: 13% with DM, 23% with HBP, 40% with dyslipidaemia and 23% with obesity. There are no common guidelines for subclinical hypothyroidism management. Therefore, the implementation and promotion of action guidelines are required in Primary Health Care.

**Keywords:** Subclinical hypothyroidism, primary care, thyroid hormones.

## INTRODUCTION

The introduction of the subclinical hypothyroidism concept and term has meant a genuine revolution in the field of thyroid pathology. In 2002, a committee of experts with representatives from the American Thyroid Association, the American Association of Clinical Endocrinologists and the Endocrinology Society defined the subclinical thyroid dysfunction as the serum TSH concentration above the upper limit of the statistically defined reference range, and when the free thyroxine concentration (free $T_4$, $FT_4$) in serum is within its reference range. Based on a series of studies, this committee established the reference range of TSH levels in serum as between 0.45 and 4.50 μU/ ml (0.45-4.5 mU/L) [1].

In relation to the prevalence of subclinical hypothyroidism (SH), the data of the published series range considerably between 3.4% and 10.8% of the general population [2-7]. This disparity is explained by the age differences of the people included in the samples.

Since then, a good number of authors [2, 3] have attempted to answer a series of questions about their meaning. In this sense, prevention and screening aspects took on new importance since SH could be a previous phase of hypothyroidism, and according to some of these authors [3, 8], preventive treatment could improve these patients' progression.

Therefore, the most frequent reasons for being referred to the Endocrine Service at the Hospital Complex in Albacete have been analysed over the last year. We found that around 40.0% of such referrals are cases of thyroid pathologies as opposed to 18.4% and 16.5% for diabetes and obesity, respectively. Of the 40.0% of referred thyroid pathology cases, 15.5% only correspond to SH, while 25.8% are associated with being overweight or obese and SH.

Nowadays, no consensus exists about treating patients with moderate SH. Both the benefits and risks of SH treatment have been debated for two decades.

The possible advantages of SH treatment have been classified into three categories [9]:

1. Progression to clinical hypothyroidism, with its associated morbidity.
2. Treatment may lower the level of lipids in the blood and may, therefore, potentially lower the risk of death by a cardiovascular cause.
3. Treatment may revert hypothyroidism symptoms, including cognitive and psychiatric alterations.

The reasons against SH treatment are the costs involved and the likelihood of only a few patients benefiting from this

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therapy. We ought not to forget the danger of overtreatment which may lead to iatrogenic hyperthyroidism.

For endogenous SH, and after referring to several references in the literature which are both in favour and against treatment [10-13], treatment with L-Thyroxine is recommended for subjects who present a combination of the following factors:

a) TSH levels >10 μU/ml after repeated analytical tests.

b) Symptoms or signs which are clearly associated with thyroid dysfunction, such as the presence of goitre.

c) Family history of thyroid disease.

d) Pregnancy.

e) Heavy smokers.

f) Severe dyslipidaemia (total cholesterol of > 300 mg/dl).

g) Presence of positive antibodies (ACTPO). Some authors state that the presence of only positive levels of circulating antibodies should not be the only criterion to start treatment with L-Thyroxine [8].

This study has three objectives: to know the prevalence of subclinical hypothyroidism (SH) in the population of the city of Albacete; to confirm whether a relationship exists between the presence of SH and cardiovascular risk factors; finally, to learn how this type of patient is controlled in primary heath care (PHC) consultations.

## METHODOLOGY

### Materials

This study has been conducted within the demographic framework of the city of Albacete with a population of 148,934 inhabitants (Census of 31 December, 2001). The sample was based on an urban medical centre in the city of Albacete (Zone VI) with a mean number of 20,000 inhabitants.

### Methods

We did a descriptive, retrospective study in which we reviewed the case histories of the patients participating in the sample when the study began in June 2005, which continued until July 2007.

We randomly and consecutively selected 100 patients for our study sample with a confidence interval of 95%.

The inclusion criteria were: older than 14 years, present several analytical test results separated by one month with a TSH level of ≥ 4.5 μU/ml and free $T_4$ levels in the normal range (0.8-1.2 ng/dl). Our laboratory uses the following normal reference ranges for THS levels and free $T_4$ levels: 0.27-4.2 μU/ml and 0.8-1.90 ng/dl, respectively. Patients with TSH levels between 4.2-4.4 μU/ml were included in the sample provided their following analytical test results showed a gradual increase in TSH levels.

The exclusion criteria were: normal TSH levels in the second or third tests, the cause of hypothyroidism was primary hypothyroidism infiltrated with substitute thyroid hormones, and thyroid surgery.

Patients' follow-up was done by following the subclinical hypothyroidism management procedure in the regional area of Albacete.

Cardiovascular risk factors were defined as follows: hypertensive patients, in accordance with the World Health Organization (WHO) and the International Hypertension Society (IHS) of 1999, are all those whose medical history shows systolic readings of ≥140 and/or diastolic readings of ≥ 90 mmHg, or those who took anti-hypertension treatments. These readings were taken in the morning nursing consultation with a Morón brand electronic device or with a Riester brand aneroid sphyngnomanometer on the right and left arms while the patient, on an empty stomach, sat 10 minutes.

The hypercholesterolaemia diagnosis was made by determining whether the serum concentration of total cholesterol was equal to or above 200 mg/dl, and/or the Ldl-c values were equal to or above 140 mg/ dl, or if they took hypolipidemic drugs. Our laboratory uses the reference level of 150-220 mg/dl for total cholesterol and 50-130 mg/dl for Ldl-c.

Patients were be defined as diabetic, either diabetes type 1 or 2, if their basal glycaemia level was equal to or above 126 mg/dl or if they took oral anti-diabetes drugs and/or insulin. Body mass index (BMI, $Kg/m^2$) was calculated as follows: subjects were overweight with a BMI above 25 $kg/m^2$ and were obese with a BMI above $30kg/m^2$. Weight and height were measured in the nursing consultation when medical histories were being reviewed.

We used absolute frequencies and percentages for the qualitative data and the mean ± standard deviation.

We used the Chi-squared test to compare the inter-group qualitative data, as well as contingency tables by regrouping the percentages of the various study variables (TSH, total cholesterol, HDL-c, LDL-c).

All the statistical tests with p-values below 0.05 were considered significant.

The statistical analysis was done using the SPSS 11.5b statistical package.

### *Patients*

A retrospective review was done of the case histories of all the patients included in the study sample over the period between June 2005 and January 2006.

The following parameters were analysed in all cases: age, gender, family background of thyroid pathologies and other diseases, a personal background of cardiovascular diseases, pulmonary diseases, autoimmunity, gynaeco-obstetric background, diabetes, hypertension, dyslipidaemia, being overweight/obese, haematological alterations, psychiatric pathology, certain laboratory data (TSH levels (hypophysary thyroid-stimulant hormone), free $T_4$ levels (free thyroxine), presence or absence of ACTPO (antiperoxidase antibodies), levels of total cholesterol and its fractions (HDL-c and LDL-c), an imaging study for which tests to determine thyroid hormones were requested (symptoms for example dry skin, intolerance to cold, constipation, weakness, etc. and/or signs), treatment, years since being diagnosed with subclinical hypothyroidism (SH), being referred to a

specialist, need to subscribe a thyroid hormone replacement treatment, and the percentage of patients who had developed clinical hypothyroidism.

## RESULTS

The case histories of the 100 patients included in the study sample were reviewed. A follow-up was done of their evolution since the study commenced in June 2005 until July 2007. During the follow-up, patients had several tests done, were referred to a specialist and their family doctors' prescribed them a treatment.

### Prevalence of Subclinical Hypothyroidism

Samples of the 100 patients were collected over an 8-month period which presented TSH levels from ≥ 4.5 μU/ml to 18,75 μU/ml and normal free $T_4$ levels after several tests. The prevalence of subclinical hypothyroidism found in one medical centre of the city of Albacete was 3.8% of the general population aged over 14 years.

### General Data and Personal Backgrounds

Of the 100 patients studied, 79 (79%) were women and 21 (21%) were men. The mean age was 46 ± 19 years, although the highest absolute frequency in age was established in the interval (25,35) with 23% of the patients of the 100 subjects included in the study sample.

Regarding the study sample's personal backgrounds, 6% presented auricular fibrillation, 2% also presented another associated autoimmune disease such as fibromyalgia and autoimmune primary hyperparathyroidism. Then 17% of the women studied presented gynaeco-obstetric alterations, among which infertility and having had 2 miscarriages or more were the most frequent. One patient became pregnant during the study and her baby was caesarean-delivered due to preeclampsia.

Of the 100 patients, 40 (40%) had dyslipidaemia, basically pure hypercholesterolaemia, (33 women (41,77%) and 7 men (33,33%). 23 patients (23%) had a medical history of hypertension with 19 women (24,05%) and 4 men (19,04%), and 13 (13%) had a medical background of type 2 diabetes, 9 (11,39%) were women and 4 (19,04%) men (Fig. **1**). Of these 40 patients with hypercholesterolaemia, 19 also had hypertension, which was the most frequent association among the cardiovascular risk factors (Fig. **2**).

Moreover, 23% (23 patients) were overweight or obese, 15 (18,8%) were women and 8 (38%) men. According to the SEEDO 2000 classification, a higher frequency of type I and type II obesity was observed with 30.43% and 17.40%, respectively. Then 7% (7 patients) had a background of anaemia of which microcytic and hypochrome anaemias were the most frequent types (5 subjects).

Of the 100 patients, 22 (22%) suffered psychiatric disorders which were basically related with mood disorders. They were all taking a specific pharmacological treatment for such disorders. Of these 22 patients, 10 had depression, 9 had anxiety, 2 had an adaptive disorder of a mixed kind and 1 had a personality disorder.

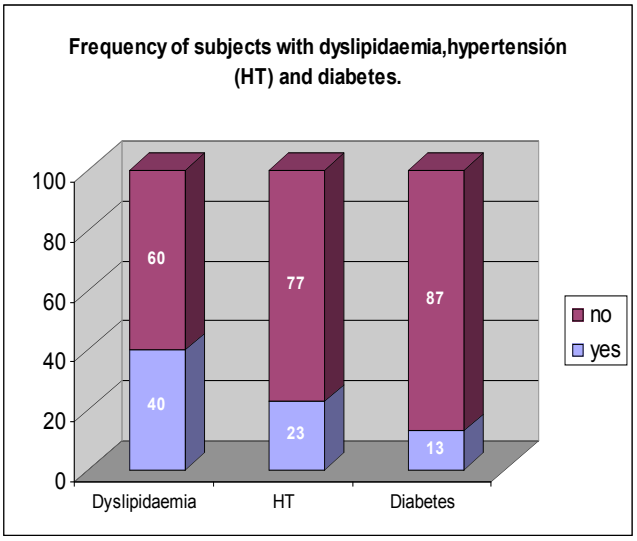


**Fig. (1).** Absolute frequency of subjects with cardiovascular risks.

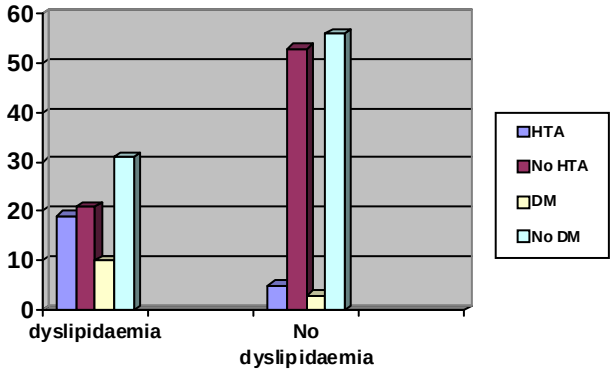


**Fig. (2).** Relationship between the dyslipidaemia factors with the remaining cardiovascular factors.

### Laboratory and Clinical Data

Regarding the TSH levels, the mean was 6.92 μU/ml, range from 4.5 μU/ml to 18,75 μU/ml. In terms of free $T_4$, the mean was 1.16 ng/dl, range from 0.81 ng/dl to 1,64 ng/dl.

By taking into account the classification of Weetman [14] (1997), we found that 91% of the study population presented degree I SH and 9% had grade II SH.

Neither antiperoxidase nor antithyroglobulin antibodies were requested in 89 patients (89%). Of the remaining 11, they were positive in 9 patients (9%) and negative in 2 patients (2%). With regard to the results of the antithyroglobulin antibodies, only 6 patients presented a positive value along with antiperoxidase antibodies.

The mean total cholesterol level was 200 ± 35.6 mg/dl, a value which was conditioned by the fact that most of the subjects (55%) were being treated with statins when the study was done according to their case histories. Nonetheless, the chi-squared test confirmed a statistically significant relationship ($p<0.007$) between the TSH levels

and the presence of total cholesterolaemia, which did not exist between the TSH levels and LDL-c.

In terms of HDL-c, the mean level was 62.3 ± 13.86 mg/dl. With regard to LDL-c, the mean was 116.48 ± 32.8.

Although ultrasound scan imaging tests may be done in the PHC, no ultrasound scan was requested for 81 patients (81%). In the remaining 19 (19%) patients, this scan was normal in 7 patients (7%), but presented alterations in 12 patients (12%). The most frequent alteration was the presence of a level 1-2 goitre in 3 patients (3%).

The case histories provided the reason (symptom or sign) to determine the patient's TSH and free $T_4$ levels. It is most interesting to learn that the main reason was an annual or six-monthly check-up for dyslipidaemia, hypertension or diabetes, all of which are cardiovascular risk factors that do not specify any symptom that might indicate thyroid disease. The most frequently symptom reported was being overweight (15 cases), followed by mood disorders such as depression (8 cases) and anxiety (6 cases), asthenia (8 cases), intolerance to cold (2 cases), constipation (1 case) (Table **1**). The most frequent analytical alteration was pure hypercholesterolaemia, followed by anaemia.

Two cases were diagnosed with chronic autoimmune lymphocyte thyroiditis, and there was one case of subacute De Quervain thyroiditis. Two patients had increased TSH levels of a pharmacological origin since they took amiodarone, which one patient had to stop taking because his/her basal SH worsened.

**Treatment and Follow-Up**

Of the 100 cases, 20 (20%) took neither pharmacological treatment nor followed hygiene-diet measures, and 80% took medication chronically.

The most consumed drugs were antihypertensive drugs (29%) and hypolipidaemiants, for example, statin types (24%), followed by benzodiazepines (23%) and antidepressants (14%).

Of these 80 patients, 29 (29%) took a thyroxine supplement. Doses varied between 25-125 μg/day. Of these, treatment was indicated for 11 of their TSH levels being ≥ 10 μU/ml; there was one case with a goitre, and one case with positive antiperoxidase antibodies; the combined presence of TSH levels ≥ 10 μU/ml and of positive antiperoxidase antibodies was found in two cases, and there were two cases with a goitre and TSH levels ≥ 10 μU/ml. Treatment was established for 11 cases with TSH levels near to 10 μU/ml (7-9.9 μU/ml), but their free $T_4$ levels were on the lower limit of the normal range.

Two patients took amiodarone for auricular fibrillation, but one patient had to stop this treatment as his/her basal SH worsened with TSH levels reaching 17 μU/ml. The other patient's TSH levels slightly increased but returned to normal after a few weeks.

No patient took lithium, interferon or any other treatment that causes thyroidal alterations, except amiodarone.

A follow-up was conducted using the patients' clinical cases to study the tests done in relation to their TSH and free $T_4$ levels in accordance with the Albacete healthcare area Clinical Guidelines criteria.

Besides, 60% of the selected cases had been diagnosed at the start of this study as opposed to the not inconsiderable 38% of the cases having been diagnosed during the study.

Of the 100 patients, 20 (20%) were referred to the Endocrine Service, 4 patients (4%) were referred to the Internal Medicine Department, and 76 (76%) were attended according to the Albacete healthcare area Clinical Guidelines.

**Evolution**

Of the 100 patients, the TSH levels of 14 (14%) returned to normal and the first year after diagnosis.

Besides, the TSH levels of 32% (32 patients) remained between 4.5-10 μU/ml in their successive analyses without taking treatment. Three subjects presented positive antiperoxidase antibodies, but a replacement treatment with thyroxine was not recommended.

Five patients (5%) with TSH levels >10 μU/ml had not started treatment with thyroxine. Of these five, one also presented positive antiperoxidase antibodies.

Of the 29 treated patients, the TSH levels of 11 (38%) patients who were taking a replacement treatment returned to normal. It is interesting to note that the TSH levels of 12 patients (41%) who took thyroxin where above the normal levels.

None of the 100 patients presented any thyroid-related complications, and no case of iatrogenic hyperthyroidism was recorded for any of patients being treated.

One patient stopped thyroxine treatment because she developed symptoms of anxiety, but this patient presented no thyroidal hyperfunction analytical data.

**Progression to Clinical Hypothyroidism**

Of the 100 cases studied, 6 patients (6%) progressed to clinical hypothyroidism. Of these patients, 4 (80%) were younger than 55 years, and 1 woman (20%) was older than 55 years. Of the 6 patients, the TSH levels of 4 patients (67%) were >10μU/ml, 2 of them (34%) had positive antiperoxidase antibodies, and one patient (16.6%) had positive antiperoxidase antibodies and TSH levels >10 μU/ml. Furthermore, 50% of the patients who developed clinical hypothyroidism progressed to SH which took 1 to 2 years, as opposed to the other 50% of subjects who took between 5 and 7 years to progress to clinical hypothyroidism.

Therefore, we observed that 2% of patients progressed to clinical hypothyroidism over a period of 1 to 3 years, while 6% of the subjects are expected to do so over a 7-year period. The most important risk factor was the presence of TSH levels > 10μU/ml.

**DISCUSSION**

**Prevalence of Subclinical Hypothyroidism**

In one of the most recent reviews published in the *American Family Physician,* a prevalence of 4% to 8% was established, which may reach 20% in women over the age of 60 years [5-9]. The prevalence of our study was 3.8% of the

population aged over 14 years, and this result is in agreement with most published series [15, 16].

The study population is mainly female with a mean age of 46± 19 SD years. However, it is interesting to note that approximately 69% of the study population is younger than 55 years. These data correlate with those obtained in several studies, one of which was conducted in our city with a slightly higher mean patient age (53.6± 20), but with a higher number of female patients [17].

**Risk Factors**

Despite type II diabetes mellitus being an endocrine disease, it is present in a lower percentage of subjects with SH when compared with the remaining cardiovascular risk factors (hypertension, hypercholesterolaemia, being overweight). No subject has type I diabetes.

In 2002, a study compared 57 women with SH to 37 women forming a control group. This study demonstrated a higher incidence of diastolic hypertension in women with SH. Our study confirms a percentage of 23% among hypertensive subjects, and 69.56% with systolic hypertension This finding is in agreement with that published in the literature, but a more significant relationship with higher diastolic hypertension figures is not observed.

Although it is known that clinical hypothyroidism causes hypercholesterolaemia, studies done on SH have not always demonstrated lipid alterations [18].

More than half the population studies and, among these, that of Chu and Crapo [2] in 2001, observe no differences in the cholesterol levels of subjects with SH and euthyroidal subjects when figures are gender- and age-adjusted. Other series indicate the increase in total cholesterol and increased LDL-c, particularly in patients with TSH levels over 12μU/ml [19], and they even paradoxically show low total cholesterol levels [17] or borderline normal ones. In this sense, our results show that 40% of the subjects have dyslipidaemia and how this is the main reason for 10% of the study sample having requested tests to check their thyroid hormone levels (TSH and free $T_4$). Besides, there is a significant relationship ($p<0.007$) between the levels of total cholesterol and TSH levels, but not for the LDL-c and HDL-c levels with TSH levels.

If we relating the variables of cardiovascular risk factors and sex in patients with subclinical hypothyroidism can deduce that there are significant differences to be more frequent hypertension (24.5% & 19.05%) and cholesterol (41.77% & 33.33%) in women and moreover diabetes more common in males (19.4% & 11.3%).

Being overweight has always been considered one of the characteristic symptoms of hypothyroidism. In fact, up to 6% of the patients who go to consultations about being obese present thyroid alterations [16].

In our study, we find that 23% of the subjects had been diagnosed with being overweight or obese some years previously. However, obesity does not justify screening all healthy overweight individuals or those who find it hard to lose weight. No such study recommends thyroxin treatment.

We checked that most of the indications for treatment (18%) correspond with the protocols published in the bibliography. In one of the most recent reviews, thyroxine treatment is recommended in patients whose TSH levels are below 10 μU/ml. However, those subjects who present symptoms could try taking thyroxine to see if their symptoms improve. If these subjects clearly improve, treatment should continue while periodically controlling their TSH levels and assessing whether or not symptoms remain. Recommended doses vary between 25 and 125 μg/day.

We observe how a low dose of between 25 and 50 μg/day thyroxine is sufficient to control 50% of the subjects, and how their TSH levels returned to normal without hardly any risk of developing iatrogenic hyperthyroidism.

**Progression to Clinical Hypothyroidism**

In the study of Wickman, the annual rate of new hypothyroidism cases is somewhere between 2% and 5%. Therefore 40% of new cases will appear with a 20-year follow-up. The progression rate is not homogeneous: women with 2.1% with positive ACTPO and normal TSH levels; 2.6% if their TSH levels are equal to the mean level (5-10 μU/ml) with negative antibodies, and 5% in women with TSH levels >10μU/ml; and positive ACTPO [14].

Parle [16] obtained a rate of 17.8% in a geriatric series, which rose to 35.7% with TSH levels > 10μU/ml and positive ACTPO as opposed to 6% with TSH levels below 10.

Therefore after a 2-year follow-up, our annual progression rate (1%) of clinical hypothyroidism is lower to that published. We confirm that one of the most influential factors for this progression is having TSH levels of 10 μU/ml after several tests.

**Controlling Subclinical Hypothyroidism in Primary Health Care**

The 100 patients who participated in this study were diagnosed at the primary health care (PHC) level, and many of them had not been referred to a specialist, neither their antibodies had not been studied nor had they been sent for an ultrasound scan; they had only had tests done to check their TSH and free $T_4$ levels.

Most family doctors had not completed the study, particularly the aspect about determining patients' antithyroid antibodies, an analytical parameter which may indicate whether treatment should be started, just as most scientific societies recommend it in the management of subclinical hypothyroidism. The SH follow-up continues to be clinically performed in the Albacete healthcare area.

After reviewing the patients' case histories, we saw a very irregular SH control pattern when analytically controlling patients who do not need treatment. We notice how some of the doctors of this group of patients do analytical controls on a three-monthly basis, others do annual check-ups, while others do so less regularly. Expert groups recommend analytical controls every 6 to 12 months, unless a subject presents symptoms or the tests repeatedly reveal a TSH level higher than 10 μU/ml.

Most family doctors are well aware that treatment is indicated when a patient's TSH levels are higher than 10 μU/ml, which was confirmed in the case histories. Yet, what

happens to subjects whose TSH levels are not over 10 µU/ml and who present mild or non-specific symptoms? Should they be treated? In the literature, in one of the reviews recently published in the New England Journal of Medicine; David and Cooper [8] leave us with an open possibility, that of treating them with thyroxine and continuing with this treatment if they clinically improve.

In the face of such uncertainty, it is not surprising to discover that these patients have not been diagnosed and have had no treatment for years. Some treatment patterns have been published but there is no general consensus.

## CONCLUSIONS

1. In our study the SH prevalence is same to other studies published. Is more frequently in women with mean age was 46 years.
2. The incidence of cardiovascular risk factors was relatively high in Diabetes and obesity and same in dyslipidaemia and less in hypertension [20].
3. In our study confirmed a statistically significant relationship between the TSH levels and the presence of total cholesterolaemia.
4. The 29% patients started a supplement treatment with L-thyroxine. None presented any thyroid-related complications, and no case of iatrogenic hyperthyroidism was recorded for any of patients being treated.
5. In our study, there is no common pattern in the management of subclinical hypothyroidism. Necessary implementation and promotion of practice guidelines in primary care.

**Table 1. Symptoms of Hypothyroidism in the Studied Patients**

| | Cases N= (100) No.% | | | Cases N= (100) No.% | |
|---|---|---|---|---|---|
| Analytical control | 22 | 22 | Goitre | 1 | 1 |
| Overweight | 15 | 15 | Take OC* | 3 | 3 |
| Dyslipidaemia | 10 | 10 | Infertility | 1 | 1 |
| Depression | 8 | 8 | Menstrual disorders | 3 | 3 |
| Anxiety | 6 | 6 | Anaemia | 3 | 3 |
| Adaptive disorder | 3 | 3 | Myalgias | 2 | 2 |
| Alopecia | 5 | 5 | Dysphonia | 1 | 1 |
| Asthenia | 8 | 8 | Intolerance to cold | 2 | 2 |
| Viriasis | 1 | 1 | Constipation | 2 | 2 |
| Neurological alternations | 2 | 2 | Weight loss | 1 | 1 |
| None | 6 | 6 | Cardiopathy | 1 | 1 |

*OC: Oral contraceptives.

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