Subclinical Hypothyroidism-Shall we treat?Areview article

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Abstract

Introduction :-

Subclinical hypothyroidism (SCHT) is a commonly presenting medical condition with a prevalence of 1-10% in middle age population, with higher incidence in elderly. (1) It should be considered when a patient is found to have mildly elevated thyroid stimulating hormone (TSH), normal free thyroxin (T4) and Tri-iodothyronine (T3), and –usually - the absence of florid signs and/or symptoms of hypothyroidism.

Methodology:-

We conducted internet search in Medline, PubMed , e-medicine websites search more publications found in Google.

.. All relevant topics published during 2000-2017 were reviewed, analyzed and discussed in this review article. Those included abstracts and references, most recent and relevant case controlled studies, cohort studies, some systemic reviews and four interesting meta-analytic studies.
Keywords;- Subclinical hypothyroidism

Conclusions :-

Although subclinical hypothyroidism is the most commonly encountered thyroid function abnormality in every day clinical practice, still the data supporting the association of this thyroid dysfunction with symptoms or adverse clinical outcome, and the risks or benefits of treatment with thyroxin are few and needs further studies.
Keyword ;- Subclincal hypothyroidism, risk, benefit, thyroxin treat.

المقدمة

يعتبر قصور الغدة الدرقية دون السريري (Subclinical hypothyroidism) من الحالات الطبية الشائعة بنسبة انتشار قد تصل الى 1-10٪ من السكان في منتصف العمر، وبنسبة أعلى في كبار السن. يتم تشخيص الحالة عند وجود ارتفاع طفيف في هرمون تحفيز الغدة الدرقية (TSH) و معدلات طبيعية في هرمونات الغدة الدرقية الأخرى وهي الثيروكسين (T4) و هرمون ثُلاثَيُ يودوثيروني(T3)، مع عدم وجود علامات أو أعراض واضحة لقصور الغدة الدرقية

منهجية البحث

قمنا بالبحث في بعض الكتب و المجلات الطبية و في شبكة الإنترنت خاصة المواقع الإلكترونية الطبية ، Medline و PubMed ، ثم لمزيد من المنشورات في محركات البحث (Google).

كانت الكلمات الرئيسية للبحث هي ؛ قصور الغدة الدرقية ، دون السريري ، المخاطر، الفوائد، thyroxin، والعلاج.

تم استعراض جميع المواضيع ذات الصلة التي نشرت في الفترة بين عامي 2000-2017، بما فيها الملخصات والمراجع،و الدراسات الحديثة دراسات الحالات المرضية ذات الصلة ودراسات الأتراب، بعض الملاحظات المنهجية وأربع دراسات تحليل تلوي. ثم قمنا بتحليلها ومناقشتها في هذه المقالة

الاستنتاجات

على الرغم من أن خلل الغدة الدرقية تحت الاكلينيكي هو الخلل الأكثر شيوعاً في وظائف الغدة الدرقية التي نصادفها يوميا في الممارسة السريرية، مازالت الابحاث العلمية و الدراسات التي اجريت لمعرفة وجود اعراض مرضية أو نتائج سريرية ضارة لهذا الخلل في وظيفة الغدة الدرقية محدودة ، وكذلك دراسة الحاجة للمعالجة و المخاطر أو الفوائد من العلاج.

Introduction:-

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormones. Worldwide, iodine deficiency remains the foremost cause of hypothyroidism, while in the United States and other areas of adequate iodine intake; autoimmune thyroid disease (Hashimoto's disease) is the most common cause.

Overt hypothyroidism commonly manifests clinically as a slowing in physical and mental activity. In most cases symptoms and signs are often subtle , neither sensitive nor specific, it is generally suspected when the patient present with Fatigue, loss of energy, lethargy, weight gain, decreased appetite, cold intolerance, dry skin, hair loss and some other manifestations. As most of the symptoms and signs are nonspecific, diagnosis should be confirmed by laboratory results. Thyroid Stimulating Hormone (TSH) assays is the most sensitive screening tool for primary hypothyroidism [1]. If TSH levels are above the reference range, the next step is to measure free Thyroxin (T4) or the free Thyroxin index (FTI), which serves as a surrogate of the free hormone level. Routine measurement of Triiodothyronine (T3) is usually not recommended. Hypothyroidism is diagnosed when there is elevated TSH with decreased T4 or FTI.

When the TSH is found to be slightly elevated (usually at levels of 4.5-10.0 mIU/L) inspite of normal free T4, free T3 or FTI the condition is considered as mild or subclinical hypothyroidism. Subclinical hypothyroidism is defined biochemically as a normal serum free thyroxin (T4) concentration in the presence of an elevated serum Thyrotropin (TSH). Some patients with subclinical hypothyroidism may have vague, non-specific symptoms suggestive of hypothyroidism, but attempts to identify patients clinically have not been successful [1,2]. Thus, this disorder can only

be diagnosed on the basis of laboratory test results. Many studies were conducted worldwide to find out the clinical importance of diagnosing and the possible need for management of subclinical hypothyroidism.

Subclinical hypothyroidism (SCHT) is a commonl presenting medical condition with a prevalence of 1-10% in middle age population, and might be higher in elderly. (1) It should be considered in any person with mildly elevated thyroid stimulating hormone(TSH) (4.5-10 mIU/L), in the presence of normal free thyroxin (T4) and Triiodothyronine (T3) ,and –usually - the absence of florid signs and/or symptoms of hypothyroidism .

In population-based studies, the prevalence of subclinical hypothyroidism ranges from 4 -15% [1,3,7]. This prevalence rises with age, is higher in females than males, and is lower in blacks than in whites [5,8].

The expected-natural- progression of (SCHT) is; (2)

- Persistence of subclinical hypothyroidism or
- Spontaneous reversion to normal (Euthyroid state) ,or
- Progression to overt hypothyroidism

Although this condition is commonly encountered in everyday medical practice , it- still- makes a lot of confusion to the treating doctor when comes to discuss with the patient about the significance of the lab results, progression of his/her condition , possible complications and more critically, if he or she has to be given medications or not.

The argument about importance of early detection and management of SCHT had been proposed by many researchers, denoting that, in spite of normal values of T4 and T3, patients might develop hypothyroid associated complications, specially atherosclerosis and ischemic heart disease if the subclinical thyroid dysfunction left untreated.(1, 2)

Objectives:-

This review was conducted to declare the following argue

- Shall we treat cases of subclinical hypothyroidism or not?
- What are the possible hazards that may happen if patient left untreated?
- Are there any criteria for selection of patient needs treatment?
- What are the risks and benefits of treating patients with SCHT?
- And, if we decided to treat, is there any protocol for treatment?

Methodology:-

We conducted a thorough search in medical journals and specialized internet websites (*Medline*, *PubMed* and *e-medicine*) for the most recent published data regarding our study, then for more publications in Google drive. Key wards for our search were; subclinical hypothyroidism, risk, benefits, thyroxin, treatment.

We reviewed almost all evidenced topics, abstracts and references published during 2000-2018, then concentrated and fully reviewed the most recent and relevant case controlled studies, cohort studies, some systemic reviews and four interesting meta-analytic studies.

Literature Review

Most of the published data reviewed is supporting the possible association of untreated subclinical hypothyroidism with atherosclerosis and cardiovascular events late in life, but the reports or studies regarding the benefits or adverse effects of treatment are very few, and most of the studies did not discriminate the tested groups TSH levels of being (4.5-10 mIU/L) or >10 mIU/L

The argument about importance of early detection and management of SCHT had been proposed by many researchers, denoting that, in spite of normal values of T4 and T3, patients might develop hypothyroid associated complications, specially the atherosclerosis and ischemic heart disease if the subclinical thyroid dysfunction left untreated.1,2

In May 2015, the U.S. Preventive Services Task Force issued a guideline on screening for thyroid disease that included a systematic evidence review and an update of previous recommendations. The review assessed the effect of treating screen-detected subclinical thyroid dysfunction on health outcomes, specifically its effect on cardiovascular disease, blood pressure, body mass index, bone mineral density and lipid levels. They concluded that evidence was inadequate to determine whether screening for thyroid dysfunction reduced morbidity and mortality or improve the quality-of-life. (4)

On the other hand, the American Association of Clinical Endocrinologists and American Thyroid Association advocated aggressive case-finding and recommended screening for persons with certain clinical conditions rather than the general population, arguing that in such people benefits of treating subclinical hypothyroidism with low-dose levothyroxine may outweigh the harms of delaying treatment until the condition has become symptomatic or developing complications. (6)

In the June 6, 2016 issue of the Annals of Internal Medicine experts from Medical Center in Boston offered differing perspectives on the issue, as to whether or not subclinical hypothyroidism should be treated. They admitted that although the condition may resolve or remain unchanged in most of the cases, the likelihood that overt hypothyroidism will develop later with greater TSH elevations and detectable anti-thyroid antibodies. They also discussed that for patients with subclinical hypothyroidism with subtle hypothyroid symptoms and abnormalities of serum lipoproteins and/or cardiac function, in addition to definite and persistent TSH elevation should be considered for thyroxin treatment.(6)

Un expectedly , a very scanty published data – we found – concerning the strategy of use of thyroxin in cases of SCHT, its long term benefits or complications, risks , expected outcome, and the possible hazard of overtreatment , aiming to justify the use of thyroxin in SCHT.

One of the interesting studies we found is the one done by Alice Monzani et al - in their potential trial to study the natural history of SCHT in children and adolescents, and the potential effect of thyroxin therapy in this age group. They reviewed 15 relevant studies and concluded that, as the risk of evolution of SCHT to overt hypothyroidism in children and adolescents is low, and there is no sufficient data or clear evidence of beneficial effect of treatment with Thyroxin in children with SCHT growth or other parameters, the treatment with Thyroxin is unjustified, especially in those with TSH level (5-10 mIU/l), negative anti thyroid antibodies and no goiter (7). On the other hand they found that up to 20% of adults with (SCHT) might progress to overt hypothyroidism , particularly in the presence of a goiter, high TG-Abs , progressively increase TPO-Abs level and high TSH baseline values, or in the presence of marked hypo-echoic thyroid on Ultrasonography. (7), but they didn't recommend clearly if those patients with high risk of progression should be treated or not.

Another Meta-analytic study conducted by *Surks M.I. et al* , the authors collected adequate data supporting the possibility of progression of untreated subclinical hypothyroidism to overt disease , but as they could not prove whether the treatment will prevent this progression or not , they recommended

against the routine treatment of patients with TSH levels within the 4.5 -10 mlU/L , till a strong supporting evidence for treatment could be verified 4 , but they recommended for screening and case finding in pregnant women ,elderly females and other people at high risk of thyroid disease .

Young Joo Park et al 3 almost agreed with these recommendations in their study of the adverse effects of SCHT on patients undergoing cardiac CABG surgery. But –although they found higher incidence of development of post-operative atrial fibrillation in SCHT patients, they could not confirm that preoperative treatment with thyroxin can prevent this complication (8)

The effectiveness of screening and treatment of subclinical thyroid dysfunctions was studied by *Rugge B.et al* (9), who analyzed the data from all relevant and good quality studies published between 2002 -2010. They found that most of the studies agreed that patients with sub clinical hypothyroid who received thyroxin , had significant – in the short term -improvement in lipid profile and left ventricular function , but overall symptoms and quality of life did not improve Unfortunately, none of these trials evaluated the long term cardiovascular outcome, or the harmful effects of treatment with thyroxin , and they did not find any study comparing a well-defined strategy of giving Thyroxin to patients with SCHT ,with a strategy of watchful waiting (9)

Similarly, Cochrane review done by *Villar HC* and his group (published online January 2009) concerning Levothyroxine treatment for SCHT, they analyzed twelve good quality trials (350 patients) , seven of them evaluated the effect of treatment to patients ' symptoms, mood and quality of life. They didn't find a statistically significant changes in those parameters to advice giving or avoiding thyroxin, but in six trials of them there was a considerable improvement in plasma cholesterol and LDL (10)

The recommendations of the joint consensus panel (published in 2005) of the American Association of Clinical Endocrinologists (AACE),The American thyroid association(ATA), and the Endocrine society (TES) , favored doing routine screening for SCHT in adults ,specially pregnant women , and the aggressive approach of case finding in patients presenting with symptoms and /or signs suggestive of thyroid dysfunction , and advised the clinicians to consider each individual's unique situation in determining the need for treatment.(7) These recommendations were reviewed in the 2017 guidelines of the American Thyroid Association, where their committee strongly recommended against the routine treatment of patients with SCHT with serum levels of 4.5-10mIU/L, with the exception of pregnant women with positive thyroid antibodies (TPOAb), when a benefit of treatment is suggested aiming to reduce risk of miscarriage. (11) in such a case, they recommended that they should be treated with oral thyroxin aiming to normalize the TSH level within the referance level of that specific trimester (1st trimester 0.1-2.5 mIU/L,2nd trimester 0.2-3 mIU/L and 3rd trimester 0.3-3 mIU/L.(9)

This special recommendations was anticipated ,as many researchers proved that SCHT during pregnancy is associated with an increased risk of adverse pregnancy complications such as pregnancy induced hypertension ,abruption ,low birth weight, preterm deliveries and possibly an increased risk of neuro–cognitive defects in the developing fetus.(8) but they didn't discuss the risks of over treatment .

On the other hand, in spite of lack of evidence, some of the researchers argued against the use of L.thyroxine in case of SCHT, as they found that up to 50% of those people develop poorly controlled thyroid function, and they might become more prone to develop side effects of overtreatment with thyroxin, subclinical or overt hyperthyroidism with their known complications such as atrial fibrillation, and other cardiovascular events, or bone loss later in life.(8)

Of the recently published reviews and studies- I found- is the one done by *Salman Razvi et al* (14), who collected data from about 320,000 adult participants in the (UK General Practice Research

Database) who had serum TSH of 5-10 mIU/I, then divided them according to their age groups ,then approximately 50% of each group was given L thyroxin ,while the others left untreated , all groups records were followed up between 2001-2008 , then results analyzed . They found that in those ≤ 40 years of age, cardiovascular events and all causes of mortality were about 40 % less over time in the L-thyroxin treated group, compared to the untreated group, but not in the older patients. And, interestingly enough, they found that atrial fibrillation was not more in patients taking L-thyroxin, even in the older age-group. According to this study, they recommended that ; patients with SCHT should be treated with thyroxin if SCHT with TSH>10 mIU/L and in females when SCHT is been diagnosed during pregnancy or pre-pregnancy , and they advised to consider treatment, if patient with SCHT has :

- Patients with symptoms or signs of hypothyroidism (fatigue, dry skin, constipation, muscle cramps …etc)
- Age less than 70 yrs
- TSH level consistently elevated above 10 μU per mL (10 mU per L)
- Goiter
- High cardiovascular risk including ; coronary artery disease, Diabetes and Dyslipidemia
- Greater magnitude and duration of TSH elevation
- High titers of anti-thyroid antibodies

As most of the data published was supporting the possible association of untreated subclinical hypothyroidism with atherosclerosis and cardiovascular events late in life, the conflict about management of subclinical hypothyroidism, especially in elderly, brought about the idea of starting the randomized multicenter placebo-controlled study called TRUST research "Thyroid Hormone Replacement for Untreated adults with Subclinical hypothyroidism Trial". Aiming to improve the health and generally wellbeing of old people with SCHT, and resolving the debates about the best way of management of this condition.(16) Double-blind, randomized, placebo-controlled, parallel-group trial was conducted, they involved 737 adults who were at least 65 years of age and who had persisting subclinical hypothyroidism (Thyrotropin level, 4.60 to 19.99 mIU per liter; free Thyroxin level within the reference range). A total of 368 patients were assigned to receive levothyroxine (at a starting dose of 50 μg daily, or 25 μg if the body weight was <50 kg or the patient had coronary heart disease), with dose adjustment according to the Thyrotropin level; 369 patients were assigned to receive placebo with mock dose adjustment. The two primary outcomes were the change in the Hypothyroid Symptoms score and Tiredness score on a thyroid-related quality-of-life. They found that Levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism who received Thyroxin compared to those received the placebo (17)

Conclusions

Although subclinical hypothyroidism is the most commonly encountered thyroid function abnormality in clinical practice, but the data supporting the association this thyroid dysfunction with symptoms or adverse clinical outcome.

Many studies agreed that SCHT may be a risk factor for atherosclerosis and myocardial infarction, but there is insufficient evidence to support starting thyroxin therapy in asymptomatic patients with TSH level of 4.5-10 mIU/L, especially in children.

Very few researches were conducted to study the long term outcome and side effects of thyroxin in treatment of cases with SCHT but there were no strong evident recommendations with or against its use, except for pregnant ladies with positive thyroxin antibodies, symptomatic patients or those with TSH> 10 mIU/L.

Further studies are needed to clearly evaluate the long term benefits or side effects of Thyroxin therapy on growth, goiter size neuropsychology, and cardiovascular outcomes.

Evidence does not support routine universal screening for hypothyroidism, except for selected populations, especially women, elderlies and those at higher risk, and those present with nonspecific complaints such as depression , fatigue. Presence of elevated TSH level and normal T4 may or may not account for the clinical findings, so, retesting at regular intervals or treatment with low doses of levothyroxine may be warranted.

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