SYSTEMATIC REVIEW

Subclinical-Hypothyroidism: A Pathology in Evolution

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ABSTRACT

Subclinical-hypothyroidism is identified as suboptimal thyroid hormonal production associated with mild TSH (thyroid stimulating hormone) elevation. Though several non-thyroidal illness in the later stages, medications and dietary supplements may resemble SCH (subclinical-hypothyroidism), but mild persistent subnormal thyroidal pathologies are usually termed as SCH. This review briefly describes the various cardiovascular risk associations with subclinical-hypothyroidism and attempts to provide an insight into the risk and benefit association, which a patient faces once treated for SCH.

Key Words: *Euthyroidism, Subclinical-hypothyroidism (SCH), L-thyroxine (L-T4), Cardiovascular diseases (CVD).*

INTRODUCTION

Subclinical-hypothyroidism (SCH) is defined when TSH values are more than 4.0 mIU/L but less than 10 mIU/L with normal thyroid hormones (fT4 and fT3).[1] Before we make a diagnosis of SCH, it is important to ensure that borderline TSH rise persisted for some time and there are no conditions affecting hypothalamic-pituitary axis, medicines affecting thyroid function and over the counter medications, certain dietary supplements, and non-thyroidal illnesses (NTI). While cut-offs, methodologies, and regional differences can cause differences in TSH measurements, therefore, variance in SCH prevalence, literature review from NHANES III surveys and the Whickam study from UK provides a prevalence from 4.3% and 7.5% alternatively.[2,3] Gender, age, physiological changes (pregnancy) and non-thyroid pathologies do affect the measured thyroid hormones.[4] The entity SCH being commonly prevalent is also questioned as whether being an outlier in the spectrum of TSH physiology or some physiological adjustment of basal metabolic rate (BMR) or a pathology in evolution. Clinically, dilemma starts when questions are raised whether to adopt conservatism or treatment need to be started to address any thyroid complications.

The concept of thyroid well-being could be a broader and seem expanding than our current perception requiring quality data to elaborate SCH. While the etiological aspects and patient population remain unknown in most case, the core concept encompasses an apparently asymptomatic medical condition where the focus is to treat, monitor or not to intervene.[5] The commonest query from both the physicians and the patients is regarding the normality spectrum of TSH hormone with fears emerging from under- and over-treatment. Consequent upon the highlighted issues, the authors planned to review data to provide an insight into the SCH along with guidance towards possible management strategy in the light of risks and benefits.

Literature search strategy: The review was conducted from January 2015 to April 2018. Articles published in only English language or with translation into English were included in the review. We reviewed data with the key words “subclinical-hypothyroidism (SCH)” from Pakmedinet and PubMed. Commentaries, conference proceedings, letters to editors, articles without peer reviews, reports from newspapers from the PubMed group were excluded. The initial search key words “subclinical-hypothyroidism” in adults yielded 2,186 studies on PubMed. Excluding pediatric studies and limiting further to subclinical hypothyroidism and cardiovascular risks in adults provided 289 studies on PubMed. Further limitations in terms of articles published in last 10 years brought the countdown to 200. Limiting further to randomised control trials shortened the list to 8 articles. Seven articles were finally included as they addressed in some way dealing CVD risk association in adults with SCH. Similar search on Pakmedinet provided 24 studies with key words “subclinical-hypothyroidism” or “subclinical thyroid disease”. Studies carried out in children, only in specific diseases like coeliac disease patients or not targeting CVD in any way were excluded. Only 10 studies were analysed further. All studies were observational with only one study evaluated a cohort.

RESULTS

The data from Pakmedinet was exuberant in terms of only scarcity as none of the studies were a randomised control trial or equivalent. Details of 10 studies, which suggested in anyway, the SCH has been mentioned in

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Received: April 24, 2018; Accepted: September 15, 2018

Table I: Local data from pakmedinet.com on subclinical-hypothyroidism and cardiovascular diseases in adults (n=10).

Study	Type of study	Journal	SCH frequency (n)	End point	Comments
Ijaz A *et al.*	Cross-sectional study	J Coll Physicians Surg Pak (Feb 2002)	31%	Frequency of subclinical thyroid diseases	-
Cakmak *et al.*	Comparative cross-sectional study	J Pak Med Assoc (Oct 2011)	-	Reduction in pulmonary function tests	-
Shafit M *et al.*	Case control study	Biomedica (Jan - Mar 2013)	-	Lipid parameters in overt hypothyroidism	Worsening of lipid parameters in subjects with overt disease
Asif M *et al.*	Cross-sectional analytical study	Professional Med J (Aug 2013)	-	eGFR as calculated by Cock-croft-Gualt formula	eGFR worsening with deterioration in thyroid functioning
Shabbir B *et al.*	Descriptive study	Pak J Med Health Sci (Jan - Mar 2012)	5% in diabetic population (n=100)	-	Risk segregation not based upon hypo or hyper thyroid disease
Anwer SM *et al.*	Cohort study	J Ayub Med CollAbottabad (Oct - Dec 2012)	14% (n=100)	Progression to overt hypothyroidism	-
Humerah S *et al.*	Cross-sectional study	J Coll Physicians Surg Pak (Jun 2016)	20% (n=100)	Lipid parameters	Worsening of lipid parameters in subjects with overt disease
Gul N *et al.*	Cross sectional study	J Ayub Med Coll Abottabad (Apr - Jun 2016)	9.78% (n=378)	Frequency of SCH in hospital seting	-
Naib MJ *et al.*	Prospective study	J Med Sci (Oct 2014)	27/320 (n=320 sub-fertile subjects)	Subfertility in SCH group & associated thyroid disorders	Subfertility associated with deranged thyroid profile
Ullah A.	Descriptive cross-sectional study	Khyber Med Uni Med J (Jul - Sep 2013)	6.1% (n=753)	Thyroid disorders in Congestive heart failure	SCH not very common in CHF patients
Ali L *et al.*	Cross-sectional study	Professional Med J (Oct 2015)	9% (n=100)	Generalized risk associations with all CVD disorders	Subclinical thyroid dysfunction are at increased risk of CVD

Table I, along with the frequency of SCH and associated risk factors. Pubmed review yielded seven clinical trials which evaluated post-interventional response in subjects with SCH. Almost all these trials identified worsening of some or all lipid parameters, endothelial dysfunction, insulin resistance, increase in inflammatory markers, CVD risk and higher carotid intima media thickness (CIMT) in subjects with SCH, which responded to clinical intervention. Details are mentioned in Table II.[6-12] Figures 1 and 2 provide suggested algorithms for managing a case with SCH.

DISCUSSION

The evolving evidence provides an insight about the hypothalamic-pituitary-thyroid axis in better ways than before, but still there are grey areas in literature which require further attention. Canaris *et al*. observed in "The Colorado thyroid disease prevalent study" that patients having mildly raised TSH levels had lipid abnormalities and can lead to adverse cardiovascular health issues.[13] These patients with mildly elevated TSH levels, though do not present in clinics, are usually picked up on routine screening and then the physician ends up with a confusion to treat or to adopt a conservative approach. The usual in vogue clinical indication is to treat a raised TSH level beyond 10 mIU/L, *i.e.* overt hypothyroidism. TSH levels, which are above the range of normality but below 10 mIU/L and do cause concern to both physician and patients and leads sometimes to unnecessary interventions and investigations. Furthermore, patients with anti-TPO positivity, lipidemias, or ischemic heart diseases are usually not considered as association to SCH.[14] Finally, there are other conditions like pregnancy, iodine deficiency, celiac disease, history of autoimmune disorders, which are also required to be excluded as they are associated with higher rate of SCH progression towards overt disease.[15,16] Available data highlights a cautious approach highlighting both risks and benefits, which are being discussed.

Treatment with thyroxin (L-T4) once evaluated by TSH normally lags behind the clinical and biochemical response by a margin of 8-12 weeks from the baseline. The apparent concerns arise once a patient with SCH is started with treatment to address mild clinical or biochemical derangements overshoots normality limits to end up having treatment-associated complications along with worsening of any underlying autoimmune disease like adrenocortical deficiency. These over-treatment related concerns have been appreciated below.

Cardiovascular (CVD) risks: Overtreatment with thyroxin can lead to possible hyperthyroidism. Though mild L-T4 treatment for a short duration may not cause any harm, but treatment for a longer duration with inappropriate clinical and biochemical monitoring can lead to CVD issues including diastolic dysfunction, left

ventricular hypertrophy, and fatal atrial arrhythmias.[17] So, even minor over replacement of thyroxin must be avoided in patients to prevent adverse cardiac effects, especially so in geriatric population.[18]

Pregnancy: Casey *et al*. observed that subclinical hyperthyroidism not to be associated with non-desirable pregnancy-related outcomes.[19] Alongside, we do appreciate that the upper range of TSH is suppressed (2.5 mIU/L) in first trimester, only to rise by third trimester. So keeping these differential normality ranges in mind and the data from authors like Atkins *et al*., highlighted legitimate maternal and fetal concerns due to hyperthyroidism associated with anti-thyroid treatments during pregnancy.[20] Therefore, caution needs to be exercised while prescribing L-T4 therapy in pregnant subjects with SCH till further research on the subject is available.

Sympathetic overactivity: Thyroxin stimulates adrenaline surge, thus overtreating subjects with L-T4 may lead to sympathetic overactivity.[21] Studies carried out in subjects with subclinical-hyperthyroidism are characterised by increase in sympathetic activity and parasympathetic imbalances.[21]

Neuromuscular effects: Overt hypothyroidism is associated with decrease in nerve conduction and muscle weakness. Moreover, subclinical-hyperthyroidism is also associated with cognitive decline.[22] Brennan *et al*. have highlighted that strength and cross-sectional area of muscles decrease in patients with subclinical-hyperthyroidism.[23]

Thyroid eye disease and dermopathy: Grave's disease and thyroid dermopathy have mostly been observed with hyperthyroidism. In our opinion, such predispositions to autoimmunity may get aggravated in

Table II: Data from PubMed randomised controlled trials data on subclinical-hypothyroidism and cardiovascular diseases in adults from last 10 years (n=7).

Study	Subject selection	Intervention	Main end points	Comments	Conclusion
Herter-Aeberl I *et al*.[6]	Iodine-deficient, overweight Moroccan women (n=163)	200 ug iodine or placebo x 6 mo	• TSH • Total chol (TC) • LDLc • Plasma glucose	• TSH reduction by 33% in iodine group • TC reduction by 38% in iodine vs 38% in placebo • LDLc reduced (p=0.23)	Iodine prophylaxis in iodine deficient females reduced CVD
AlibazOner F *et al*.[7]	27=SCH cases 22=Health controls	LT4 therapy	• Flow-mediated diameter (FMD) as marker for endothelial function	• Improvement in FMD in SCH cases in comparison to healthy controls	Thyroid hormone replacement therapy may help to prevent atherosclerosis in this group of patients.
Kowalska I *et al*.[8]	13 SCH females 14 euthyroid controls	LT4 therapy	• sICAM-1 • Adiponectin • Insulin sensitivity • LDLc • Plasma glucose	• sICAM-1 decreases (P=0.01) • Adiponectin (NS) • Insulin sensitivity improved (p=0.012) • LDLc • Plasma glucose decreased (p=0.019)	L-thyroxine treatment in patients with subclinicalhypothyroidism might exert a beneficial effect by reducing cardiovascularrisk factors
Sathyapalan T *et al*.[9]	60 SCH cases Cross-over trial	Western diet OR Vegetarian diet	• Progression to overt hypothyroidism • Blood pressure • Insulin resistance • Lipids • hsCRP	Vegetarian diets caused: • Increased progression to overt hypothyroidism phytoestrogens • Blood pressure decreased • HOMA-IR [3.5 ±0.09 *vs*. 2.6 ± 0.08; p < 0.02] • Lipids (NS) • HsCRP(4.9 ±0.04 *vs*. 3.9 ±0.03; p < 0.01)	Vegetarian diets increased progression to Overt hypothyroidism
Shakoor SK *et al*.[10]	SCH= 20 Control=20	LT4 therapy	Endothelial progenitor cells (EPC), representing CV risk as: • EPC count • EPC function	• EPC count increased • EPC function improved	LT4 treatment regressed progression to overt hypothyroidism and reduced CVS risk
Adrees M *et al*.[11]	H=56 Control=56	LT4 therapy	• CIMT • Carotid and brachial artery • eGFR	• CIMT reduce • Carotid and brachial artery diameter increase • eGFR improves	LT4 therapy reduce CIMT, increased carotid and brachial artery diameters and eGFR in subjects with SCH
Mikhail GS *et al*.[12]	LT4 treated SCH=60 LT4 non-treated Controls=60	LT4 therapy	• Total cholesterol LDLc • HDLc • Triglycerides	Improvement in lipid parameter in LT4 treated *vs*. non-treated group were as: • Total cholesterol (P<0.001) • LDLc(p<0.01) • HDLc (NS) • Triglycerides (NS)	LT4 treatment reduced LDLc and total cholesterol

patients who are overtreated with thyroxin. However, research is needed to address this association.

Bone mineral density (BMD): Hyperthyroid subjects have decrease bone mineral density. De Rosa *et al*. have highlighted L-T4 overreplacement resulting in bone mineral density loss in subjects who were treated for non-toxic goitre.[24] This tendency to bone mineral density loss has also been observed by other researchers.[25]

Regarding the association of hyperthyroidism with BMD, few have suggested that BMD and BMD may not decrease after thyroxin treatment.[26] Greenspan *et al*. compared both pre-menopausal and post-menopausal ladies for long-term effect of thyroxin on BMD by keeping thyroid parameters within their physiological range to conclude that L-T4 therapy may not be a contra-indication due to possible concerns affecting skeletal

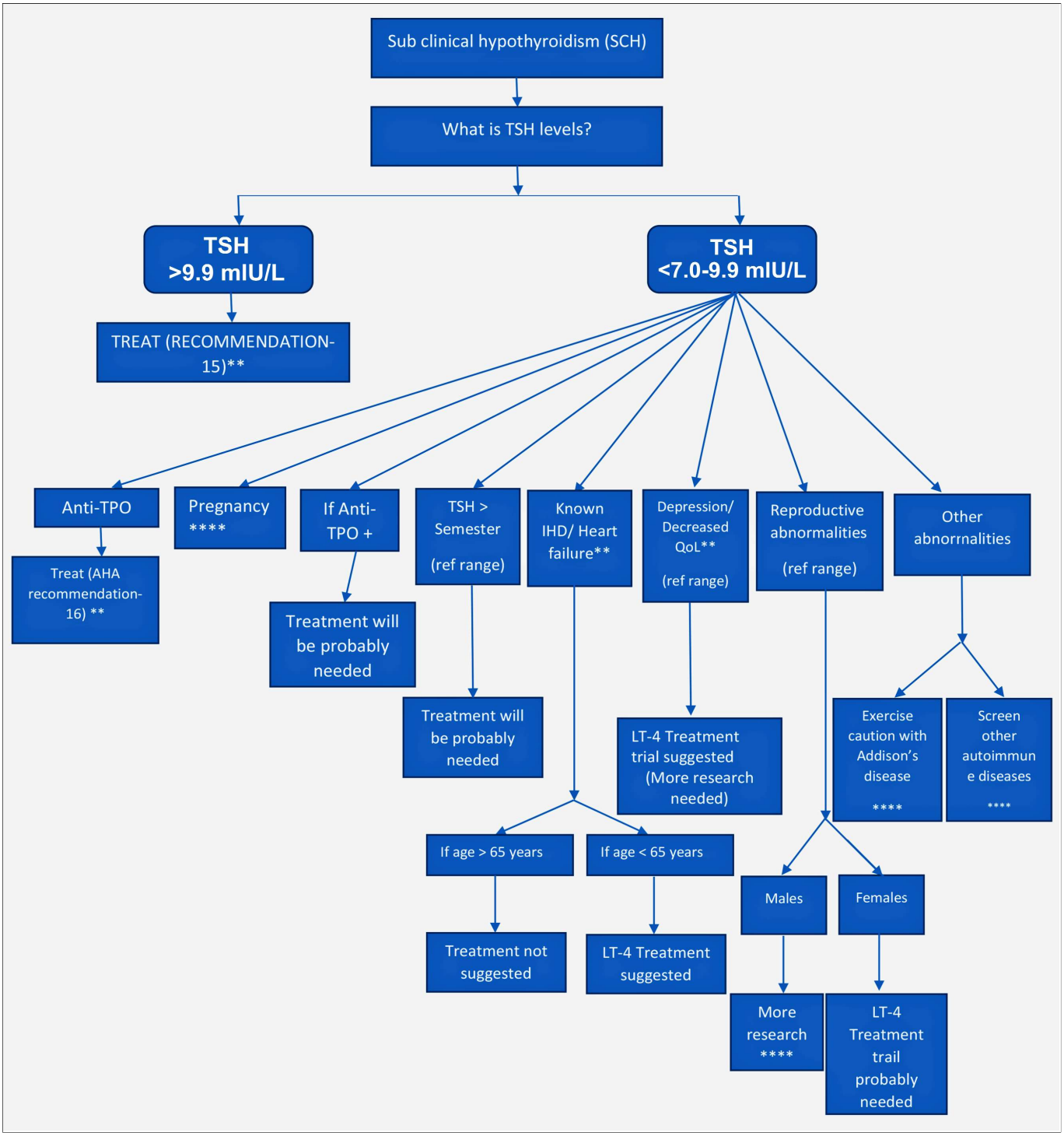

Figure 1: Suggested algorithm for management options with regard to evaluated risks and benefits in subjects having TSH levels from 4.0 to 7.0 mI U/L.
*Confirm the SCH diagnosis by R/O the effects of drugs, NTI, and other factors. **ATA adult treatment guidelines. ***The Whickman survey. ****Treatment assessment based upon combined risk assessment.

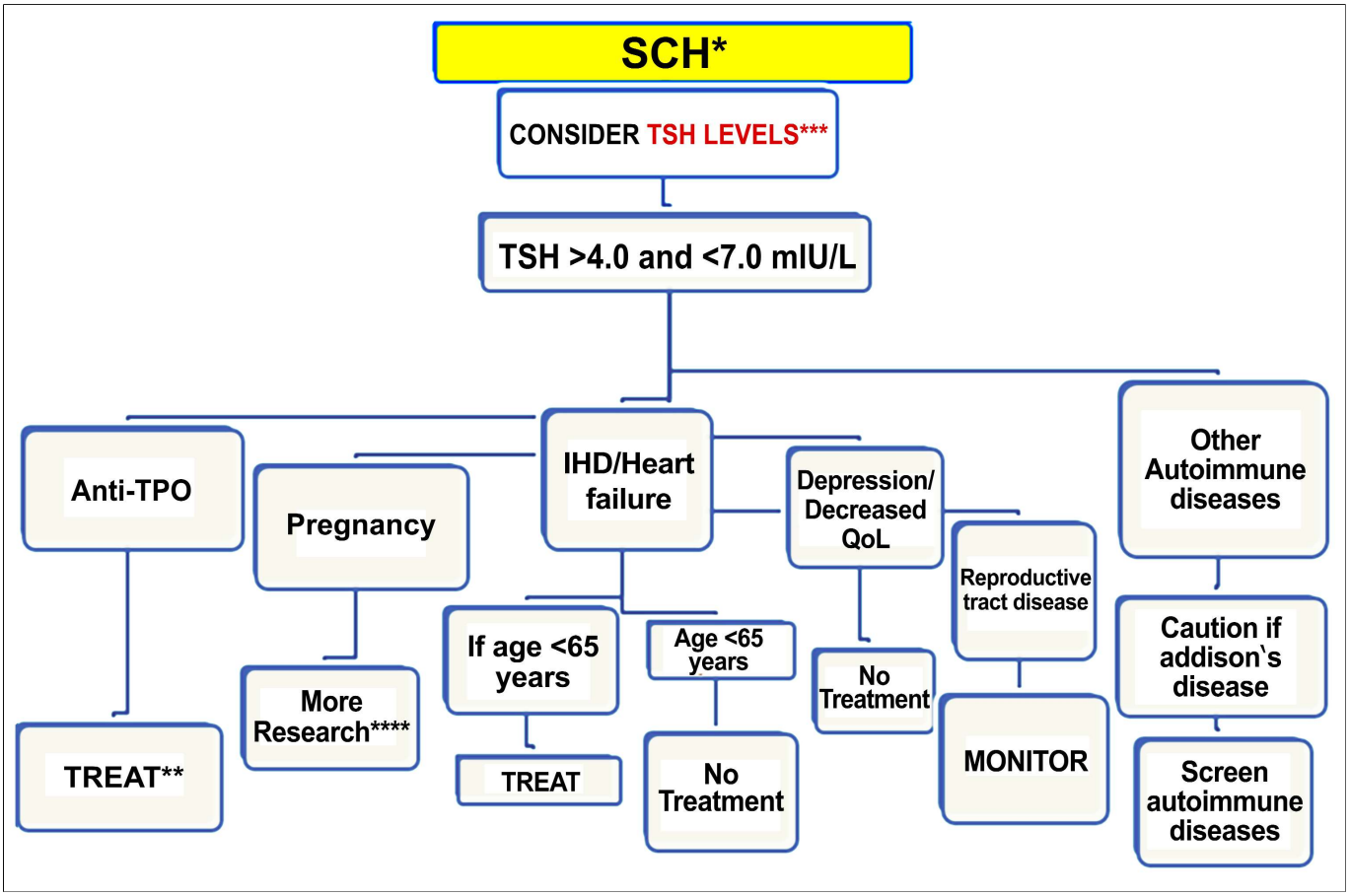

Figure 2: Suggested algorithm for management options with regard to evaluated risks and benefits in subjects with TSH >7.0 ml U/L.
*Confirm the SCH diagnosis by R/O the effects of drugs, NTI, and other factors. **ATA adult treatment guidelines. ***The Whickman survey. ****Treatment assessment based upon combined risk assessment.

integrity.[27] In view of the aforementioned discussion and logical perspective, it may be suggested that decline in BMD can only be expected with over-dosage of thyroxin in subjects with SCH, so treatment may be initiated, keeping TSH levels within target range.

Adrenal deficiency: Managing a patient with SCH or overt hypothyroidism with concomitant adrenocortical deficiency can lead to serious adverse outcomes and thus not suggested. Recent data suggest autoimmunity may cause borderline rise in TSH, especially with autoimmune disorder which may not be in singular and may be associated with polyglandular autoimmune syndrome (PGAS). Thus, SCH association with adreno-cortical deficiency may also be included in differentials before initiating L-T4 therapy.[28] Furthermore, evidence is also there to suggest remission of hypothyroidism once a subject is initiated treatment with steroid for adrenal deficiency.[29,30] Therefore, subjects having SCH or overt hypothyroidism may be clinically screened for possible adreno-cortical deficiency.

Advantages: Though the side effects related with SCH treatment are obvious and related to initial TSH level and dosage, benefits are required to be acknowledged:

CVD benefits: The Whickham survey from United Kingdom evaluated the incidence of CVD events over a 20-year follow-up, and concluded that CVD events were higher among subjects with mildly raised TSH levels (SCH).[31] Gencer *et al*. conducted a prospective controlled trial involving over 25,000 subjects and showed that the hazard ratios for heart failure increase gradually from 1.01 in people with TSH of 4.5 to 6.9 mIU/L to 1.65 at levels between 7.0 of 9.9 mIU/L to 1.86 for levels between 10 to 19.9 mIU/L.[32] Similarly, the PreCIS database study while evaluating multiple risk factors for cardiovascular risk factors concluded that moderate SCH (defined as 6.1-10 μ U/mL) is one of the risks for all-cause mortality including coronary artery disease.[33] Moreover, other studies have identified the association of SCH with coronary artery disease, especially in younger population groups.[32-34] There are markers which were evaluated to determine underlying association of IHD with SCH as:

a: Carotid intima media thickness (CIMT): CIMT is a radiological surrogate marker of endothelial dysfunction and underlying ischemic heart disease. Dardano *et al*. and others have demonstrated markers like CIMT demonstrate deterioration in patients diagnosed to have SCH which improves once therapy normalises the TSH.[12,35]

b: Lipids: There are contrasts in evidence in terms of association between sub-optimal thyroid functioning and dyslipidemias.[9,36] However, others have demonstrated lipid markers to get worsen with rise in TSH.[12] Some like Herter-AeberlI *et al*. have shown only total cholesterol to be reduced with L-T4 therapy and did not show significant reduction in LDLc.[6]

c: Metabolic syndrome: Recent data from Liu *et al*. demonstrate a clear association between components of metabolic syndrome and insulin resistance with SCH.[37] Hence, addressing SCH could be beneficial in reducing insulin resistance in metabolic factor.[6,9]

Pregnany: As mentioned above, the physiology in pregnancy varies from a non-pregnant subject which also includes changes in thyroid hormone levels due to circulating beta-hCG. Higher circulation of Beta-hCG in first trimester leads to hyper-stimulation of thyroid tissue, thus decreasing TSH levels. The upper cut-off of TSH in pregnancy is just 2.5 mIU/L in first trimester and 3.5 mIU/L in last trimester.[38] Most data including ATA's adult treatment guidelines have recommended the use of thyroxin in patients with pregnancy associated SCH or identified adverse pregnancy outcomes.[39-41]

Autoimmunity: Vanderpump *et al*. in one of the Whickham survey follow-up studies highlighted that subjects with SCH, who have positive anti-TPO antibodies, have a higher annual rate of progression to overt hypothyroidism.[42] Walsh *et al*. have also demonstrated higher progression towards overt hypothyroidism in subjects with higher titers of TPO-antibodies, >2.5 mIU/L TSH and female gender.[43] Other studies have identified autoimmunity based upon TPO and TSH antibody positivity and family history of Hashimoto's thyroiditis to be independent risk predictors of overt hypothyroidism.[44] Moreover, the treatment with L-T4 in subjects with in Hashimoto's thyroiditis has been proven to stabilise the inflammation in thyroid disease.[45] However, it seems that the evidence of autoimmunity in patients with euthyroidism or SCH needs further trigger like genetic predispositions and environmental factors to trigger the inflammatory processes leading to thyroid gland destruction.[46]

Cognitive function: Current data do not show any strong association between SCH and cognitive decline. Forti *et al*. in his prospective trial spanning over four-years did not observe an association between TSH levels and cognitive impairment or Alzheimer's disease, but did demonstrate an association with vascular dementia.[47] Some anti-ageing clinics do recommend thyroxin use for even people with minimally deranged or normal thyroid function, but there is no hard evidence to support this association.[48] However, ongoing research about this association may be needed as the frequency of cognitive decline increases with overt hypothyroidism.

Hematological changes: There is a direct relationship between subclinical-hypothyroidism and anemia/ changes in hematological indices.[49] Ravanbod *et al*. in a randomised control trial demonstrated that combined L-T4 treatment with iron therapy was found to be helpful in normalisation of iron deficiency anemia in patients having SCH in comparison to those treated with iron therapy alone.[50] However, further research may be warranted to approve this finding.

GIT function: Evidence is available to suggest that certain upper GI symptoms can be associated with patients having SCH.[51] However, the authors also concluded that the evidence is not strong as normalising TSH levels did not benefit their GI symptomology. More data, therefore, is needed to confirm such associations or otherwise.

Renal changes: Some researchers have shown sub-clinical-hypothyroid function to be associated with functional impairment of renal function. Kim *et al*. have demonstrated that thyroxine replacement attenuates the declining glomerular filtration rate in comparison to control population.[52] Shin *et al*. have identified SCH as an independent predictor of renal outcome in patients with chronic kidney disease.[53]

Reproductive system: Data associated with thyroid dysfunction in the shape of SCH is not associated with decline in reproductive function like reduced semen counts or infertility.[54] Females, on the other hand, have shown a stronger link between SCH with subtle reproductive abnormalities like menstrual abnormalities to infertility.[55] Moreover, studies have also documented an improvement in pregnancy outcomes in subjects after treatment of SCH.[56]

Neuro-psychiatric issues: Some researchers have shown a link between SCH and reduction in quality of life (QoL) and improvement is observed after patient has achieved euthyroid status after therapy.[57] A retrospective analysis by Hickiel *et al*. have shown that patients with treatment resistant depression have a higher prevalence of SCH.[58] In the light of highlighted association of depression/psychiatric disorders with SCH, it may merit a trial of L-T4 therapy with appropriate monitoring.

Future prospects: While this review was focused on thyroid hormone parameters, it is felt that thyroid hormones in particular T3 affects all cells in the body by affecting the functioning of Na+/K+- ATPase pump. Suboptimal function or derangements encountered in function of this pump can lead to either pacing up of the synthetic processes or otherwise by its direct effect on basal metabolic rates. This concept thus also encompasses the effect on thyroid hormones beyond hypothalamic-pituitary-thyroidal axis to cellular and receptor levels where certain genetic changes like polymorphism or mutations can count towards the net TSH levels which could then affect various biochemical and clinical risks.[59] Research in future with regard to

thyroid function will thus possibly be including metabolism and energy consumption. SCH, simply by slowing pace of Na+/K+- ATPase pump due to any genetic change, can lead to SCH causing predisposition to multiple metabolic risks leading to ischemic heart disease, obesity and decline in reproductive function.[59] Therefore, the authors believe that SCH is not simply related to HPA axis abnormality, rather could depict a secondary adjustments to cellular machinery defects like mutations or polymorphic changes along with role of autoimmunity, over the counter supplements, and nutritional habits.

CONCLUSION

Provided the known statistical variability resulting from subject's biological changes, the methodological limitations of available literature and evolving molecular level cellular research on thyroid hormones, it can be suggested that SCH will be taken into clinical practice as pathological entity. However, it remains fundamental here to interpret the TSH and associated thyroid hormone results in the broader clinical perspective of patient, the diet, and associated factors like auto-immunity, metabolic risks, and concerns of over-treatment. Treatment decision must be personalised and evidence-based. Figures 1 and 2 provide a general overview to segregate pathology from physiology where L-T4 therapy may benefit or harm. Fine tuning of TSH is difficult, but must be carried out to achieve physiological ranges by initiating minimal therapy and increase waiting time for clinical and biochemical response. Patients must be followed carefully for various risks mentioned in the review. Finally, it is felt that research is needed to improve our understanding of SCH by quality trials addressing not only harm-benefit perspective of LT-4 therapy, but molecular changes occurring at the cellular levels.

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