Review Article

Uric acid status in subclinical hypothyroidism

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Abstract

Overt hypothyroidism is associated with high levels of serum uric acid (UA) however, the association between UA and thyroid function in patients with subclinical thyroid dysfunction remains unclear. Subclinical hypothyroidism (SCH) is a common endocrine disorder characterized by normal thyroxine (T4) and triiodothyronine (T3), and elevated thyroid stimulating hormone (TSH) levels, usually without clinical manifestations. Therefore, we carried out a study of patients with subclinical thyroid dysfunction to assess the relationship between thyroid function and UA. This lead us to review the literature to find to what extent subclinical hypothyroidism is associated with uric acid. This study adopts the method of retrospective analysis to collect general information and laboratory results aimed at assessing the correlation between uric acid and thyroid hormone levels. We searched 3 databases using different keywords. Literature search was done for articles published in the last ten years, between 2013-2023. All relevant studies were screened. A total of eighteen articles were finalized for the review. Some studies supported T3 supplementation resulting in SCH correction. Our study indicates that it is important to screen for serum uric acid levels routinely in patients with subclinical hypothyroidism.

Introduction

Thyroid gland is one of the largest endocrine gland in the body, it secretes thyroxine (T4) and triiodothyronine (T3). Hypothyroidism is a progressive disorder that presents with diverse degrees of thyroid failure and metabolic consequences. Subclinical hypothyroidism (SCH) is a common endocrine disorder characterized by normal thyroxine (T4) and triiodothyronine (T3), and elevated thyroid stimulating hormone (TSH) levels, usually without clinical manifestations. SCH implies an absence of symptoms; however, it is perhaps better thought of as mild hypothyroidism. Moreover, mild hypothyroidism can progress to overt hypothyroidism. Physiological interactions exist between thyroid hormones and uric acid synthesis and excretion. Minor degrees of hypothyroidism can lead to adverse effects in various tissues, although clinically the patients may be euthyroid. Subclinical hypothyroidism is an early mild form of hypothyroidism, a condition in which the body doesn't produce enough thyroid hormones. Subclinical hypothyroidism is associated with an increased risk of metabolic disorders and cardiovascular events. Although

overt hypothyroidism shows increased levels of uric acid (UA), there is gap in knowledge about the association between uric acid (UA) and subclinical hypothyroidism [1,2]. This study was conducted to determine whether subclinical thyroid dysfunction has deleterious effects on renal function.

Review Methods

We searched three databases (Google scholar, PubMed Central and PubMed) from 2013 to 2023, i.e., last 10 years, for the article published on relationship between hypothyroidism and uric acid levels. The first stage involved screening titles and abstracts to identify and exclude irrelevant articles. All full-text studies that were potentially relevant were then read carefully in relation to the inclusion criteria. Observational and review/systematic review articles except the experiment studies on animal were selected. In total, eighteen articles met the inclusion criteria and were reviewed in the present study. Keywords used were: "Uric acid and hypothyroidism", "uric acid and subclinical hypothyroidism" in three databases separately. Table 1 shows the database searched, keywords used, date of search and the number of relevant publications identified. Reference lists of the articles were checked to identify more studies. Ethical approval was not required.

Table 1: Electronic search result

Database	Keyword	Date of search	Number of articles
Pubmed Central	Uric acid and hypothyroidism	15/11/2023	2717
Pubmed Central	Uric acid and subclinical hypothyroidism	15/11/2023	804
Pubmed	Uric acid and hypothyroidism	15/11/2023	121
Pubmed	Uric acid and subclinical hypothyroidism	15/11/2023	33
Google scholar	Uric acid and hypothyroidism	15/11/2023	18
Google scholar	Uric acid and subclinical hypothyroidism	15/11/2023	9

Inclusion criteria:

We included full text articles published in English language from all geographical locations between 2013 and 2023, which were related to the topic. Articles had at least one measurement of TSH and Uric acid by any method; however, this rule was not applied for the review articles.

Exclusion criteria:

Incomplete data and /or not meeting the inclusion criteria, and animal studies were the main reasons for exclusion.

Results

We identified 121 articles which were related to the topic by database searches, out of which 99 articles were excluded based on title and/or abstract not relevant to our study. Out of the remaining 22 full-text articles, we excluded four articles after further reading. Finally, we approved eighteen articles for the study. Figure 1 shows how the research articles were finalized.

Discussion

The articles reviewed are depicted in Table 2. Table 2 shows the various study articles reviewed and their results. Table 3 demonstrates typical laboratory data of some studies.

Figure 1: Process of article selection.

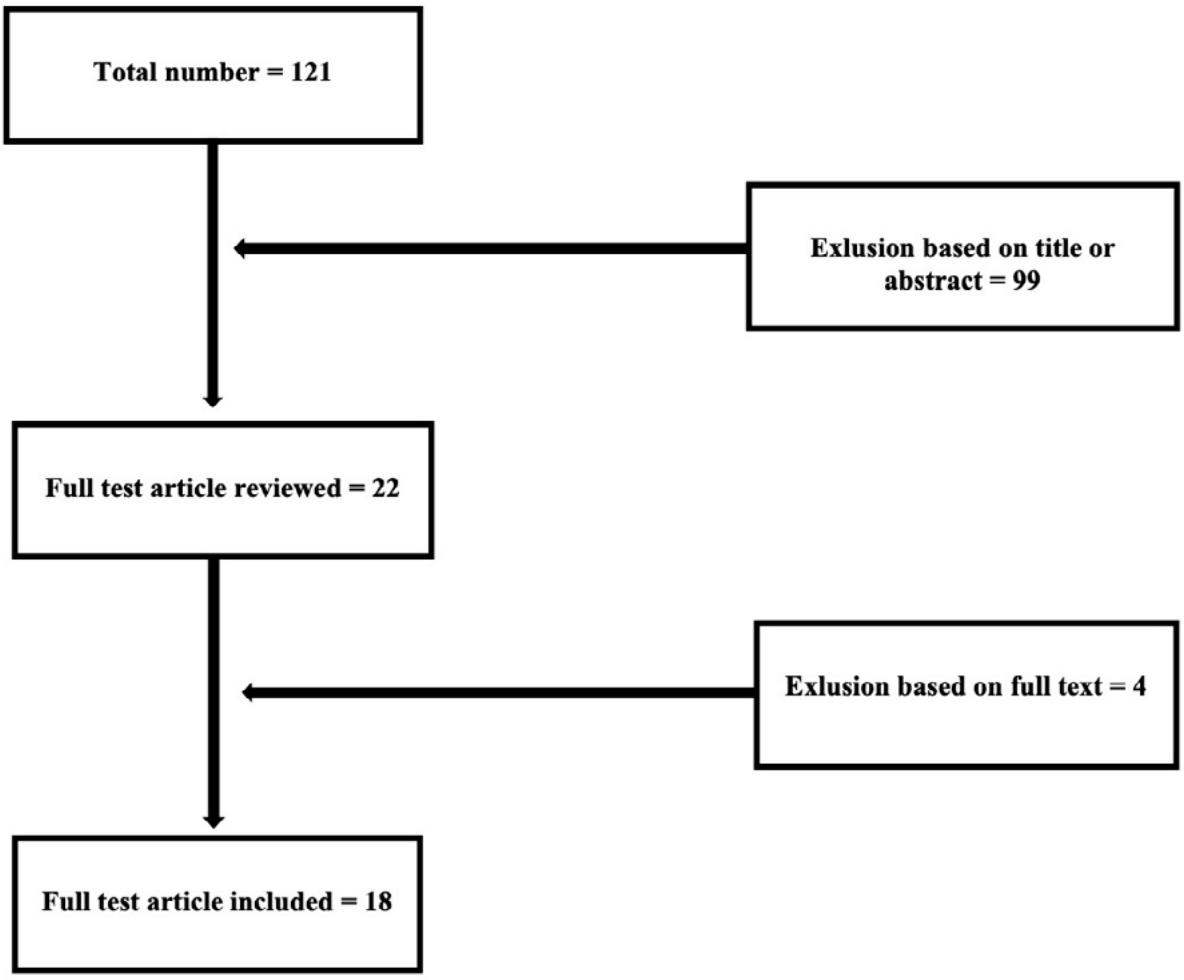

Table 2: shows the various study articles reviewed and their results

Source	Sample Size	Age Group	Study Type	Result	Conclusion
Lu et al [3]	15,955 euthyroid	≥ 18 years	Cross-sectional study	Subjects with reduced sensitivity to thyroid hormones had increased levels of UA in both genders ($p<0.001$).	Association between increased UA levels and impaired sensitivity to thyroid hormones.
Xie et al [4]	4,460 euthyroid	Adults	Cross-sectional study	A significant rise in serum UA with an increase in FT3/ FT4, TFQ/FT4, TFQ/FT3, TSHI, TT4R1 and TT3RI.	Association of Higher levels of serum UA with decreased sensitivity to Thyroid hormones.
Ittermann et al [5]	7,933 pooled data	20 – 93 years	Cross-sectional study	UA levels were 294 µmol/L in Hypothyroidism and 292 µmol/L in euthyroids.	Hypothyroidism might be associated with a reduced kidney function. Thyroid function might be more tightly related to the eGFR (OR: -3.35 (95%CI: -5.19 - -1.51) $p<0.05$) than to albuminuria (OR: 1.35 (95%CI: 0.93 - 1.97)) in the general population
Song et al [6]	26,342 hypothyroid patients	Adults	Observational study	Autoimmune hypothyroidism has a causal effect on gout, IVW results show (OR= 1.13, 95%CI: 1.03–1.21, PFDR= 0.0336); Autoimmune hyperthyroidism has a causal effect on gout, IVW results show (OR= 1.07, 95%CI: 1.01–1.12, PFDR= 0.0314).	Hypothyroidism and hyperthyroidism of autoimmune origin have increased risk of gout.
Huang et al [7]	6,587	Adults	Retrospective cohort study	Mean of UA 350 µmol/L, range of UA 274- 425 µmol/L had a significant ($p=0.028$) , non-linear ($p=0.516$) association with the development of thyroid nodules.	Uric acid is an independent non-linear risk factor for the formation of thyroid nodules.
Yang et al [8]	19,013	Adults (47.5 ± 14.5 years)	Cross-sectional study	The risk of developing Hyperuricemia in mild hypothyroidism (adjusted ORs (95%CI) of 1.370 (1.006-1.866) in males and 1.256 (0.858-1.838) in females).	Males with high TSH levels had significant risk of hyperuricemia.

Zhou et al [9]	443	Adults	Cross-sectional study	A positive correlation (p=0.005) between the severity of disease and UA in active patients is seen.	UA can be a Laboratory indicator for thyroid-Associated Ophthalmopathy (TAO)
Yang et al [10]	2831 euthyroid	Adults	Retrospective study	eGFR CKD-EPI was positively associated with FT3/FT4 (β = 23.31), and inversely correlated to PTFQI FT4 (β= -2.69) (both p <0.001). Thyroid hormone sensitivity index was negatively correlated to renal function.	Decreased sensitivity to thyroid hormone is associated with reduced renal function.
Xing et al [11]	4 databases	Adults	Systematic search	Significantly high UA levels in SCH as compared to controls. Prevalence of hyperuricemia in patients with subclinical thyroid dysfunction was higher than that of subjects with normal thyroid function, and the difference was statistically significant (I2 = 0%, p = 0.50, Z = 2.09, p = 0.04, OR : 1.16, 95% CI: 1.01–1.34.	SCH was significantly associated with hyperuricemia.
Torkian et al [1]	118	Adults (49.8 ±16.0 years)	Case-control study	UA (p<0.001) and TSH (p=0.006) are significantly high in SCH as compared to euthyroid controls. In SCH, TSH level correlated to creatinine levels but not with uric acid (r=0.302,p=0.001) and (r=0.033,p=0.772), respectively.	High UA and TSH in the SCH (P<0.05) as compared to controls. In SCH, significant correlation was found with creatinine but not with uric acid.
Jialin Li et al [13]	3,563 CKD patients	Adults	Retrospective study	Per 0.5 μIU/mL increment in TSH increased the risk of CKD stage 5 by 8% (1.08, 1.02-1.14). Per 0.3 ng/dL increase in FT4 was significantly associated with 21% reduced risk of CKD at stage5 (OR, 95%CI: 0.79, 0.69–0.89)	FT4 and TSH can be used as advanced-stage biomarkers among Chinese adults.

Sayari et al [14]	107	2–14 years	Case- control study	TSH (<0.001) but not UA (0.200) were significantly high in SCH as compared to controls. Non-significant correlation was found between TSH= 8.94±4.80 (mIU/L) and UA = 374.8 ±106.0 umol/L (r=0.043, p=0.759) in SCH.	UA in SCH children was not significantly different from control (p=0.200) and a non-significant correlation between TSH and UA was found in SCH.
See et al [15]	87,813	Adults	Retrospective, cross-sectional study	No significant correlation between TSH and serum UA (r=-0.005, p=0.164).	Both hyperthyroid and hypothyroid status were weakly associated with hyperuricemia.

UA: Uric acid, TSH:Thyroid stimulating hormone, eGFR: estimated glomerular filtration rate , FT3: free triiodothyronine, FT4 : free thyroxine, TFQ: thyroid feedback quantile-based index TSHI: thyroid stimulating hormone index, TT4R1: total thyroxine (T4) resistance index and TT3RI: total triiodothyronine (T3) resistance index. IVW: inverse variance weighting method, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation PTFQI: Parametric Thyroid Feedback Quantile-based Index.

Table 3: Demonstration of typical laboratory data of some studies.

	UA	**TSH**	**eGFR**	**r/p**	**OR (95%CI)**
Torkin et al [1]	450.8 ± 123.7 µmol/L	5.4 (2.3-9.7) mIU/L	-	r = 0.033 p = 0.72	
Yang et al [8]	Males: 372.81±76.93 µmol/L Females: 272.2±61.25 µmol/L	Males- 2.18±2.48 mIU/L Females 2.52±2.25 mIU/L			Males: 1.370(1.006-1.866) Females: 1.25(0.858-1.838)
Yang et al [10]	362.05±91.74 µmol/L	1.68 (1.21) mIU/L	eGFR (CKD-EPI) <90 mL/ min/1.73m^2		Correlation of eGFR with TSH 1.29 (1.13~1.47) p= <.001
Zhang et al [17]	-	-	Estimated glomerular filtration rate was significantly depressed in both genders with mild hypothyroidism		The significantly elevated risk for hyperuricemia was observed in mild hypothyroidism male participants with an odd ratio of 1.49 (1.10–2.02), whereas no statistical risk was found in female.

Kuzell et al in 1955 first proposed the association between hypothyroidism and hyperuricemia. High levels of serum UA were associated with reduced glomerular filtration rate (GFR) and renal plasma flow in hypothyroidism patients [15,16].

Thyroid hormones can affect purine metabolism involving the de novo purines synthesis, salvage pathway and degradation. Alteration in these pathways can culminate in UA production and impair its degradation. SCH could decrease cardiac contractility, as a result the GFR can decrease by 20–30% to below normal levels, hence, changing reabsorption and secretion in the tubules, which increase the levels of UA and decrease in UA excretion, respectively [17]. Another study found an inverse association between serum TSH levels and eGFR, suggested hypothyroidism might be associated with a reduced kidney function [5]. Some studies demonstrated that hyperuricemia is associated not only with gout but also with numerous cardiometabolic diseases, such as hypertension, metabolic syndrome, diabetes, and obesity [3].

The difference, due to gender, regarding the association between SCH and hyperuricemia could be caused by the protective effect of estrogen in females [18]. A study suggested that the effect of the UA metabolism in patients with recent-onset SCH was mediated by insulin sensitivity [18]. Huang et al suggested

UA as an independent risk factor for the formation of thyroid nodules [7]. The cause-effect still cannot be determined. See et al, on the other hand, found no significant correlation between TSH and serum UA levels, with a correlation coefficient of r=-0.005 (p=0.164) [15]. Deng et al found individuals in the SCH group (337.95 ± 105.28 µmol/L) presented with lower UA ($p<0.05$) as compared to euthyroid (UA levels 352.11 ± 106.07 µmol/L) subjects [12]. Thyroid hormones play important roles in renal development and function of many transport systems along the nephron. Thus, hypothyroidism may contribute to the exacerbation of pre-existing chronic kidney disease or the occurrence of acute kidney injury in the presence of other renal insults [19].

Study limitations

We could not do the systematic review and meta-analysis of all the articles which would have strengthened our paper. Secondly, the data cannot be generalized to Indian population. Thirdly, valuable findings in the articles published in the local languages might have been missed since we included the articles published only in the English language. Furthermore, we reviewed articles published since 2013 only, this could have excluded important conclusions from articles published earlier.

Conclusion

This study indicates the profound influence of thyroid hormone on renal function. The levels of serum UA significantly increased in SCH compared to normal controls. High levels of serum UA were associated with reduced glomerular filtration rate (GFR) and renal plasma flow in hypothyroidism patients. The thyroid function should, therefore, be routinely assessed for evaluation of patients presenting with impaired renal function and vice versa. This demonstrated the negative impact of hypothyroidism on renal function. As a result, it is advised to examine the renal state both at the time of hypothyroidism diagnosis and during the follow-up period.

Conflict of interest

None

Ethical clearance

The approval from the institutional ethical committee was not required.

Source of funding

None

Data Availability

Data included within this article.

Authors' Contributions

Dr Premjeet Kaur: Designed the study, Retrieved literature, extracted data and wrote article.

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