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Relationship between serum TSH and urine albumin excretion in euthyroid subjects with diabetes

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Conflict of interest

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Abstract:

Objective: Thyroid status can profoundly influence kidney function and also impact vascular endothelial function. This can be of substantial importance for the general population, but particularly for patients with diabetes who are predisposed to develop generalized vascular impairment due to multi-factorial causes leading to microalbuminuria, chronic kidney disease and overt nephropathy. The purpose of this study was to determine the relationship between serum thyrotropin (TSH) and urine albumin excretion in patients with diabetes.

Methods: A total of 433 patients were included in this retrospective cross sectional study. Data included anthropometric measurements and estimation of HbA1c, lipid profile, renal function (creatinine and eGFR), free thyroxine (FT4), thyroid stimulating hormone (TSH) and a spot urine sample for urine albumin creatinine ratio (UACR). Males with UACR > 2.5 and females > 3.5 mg/mmol were considered to have microalbuminuria.

Results: 34.9% patients had microalbuminuria. The prevalence for microalbuminuria increased according to TSH quartiles [26.9, 34.6, 38.5 and 44.9%, P for trend =0.02]. In a fully adjusted logistic regression model higher TSH levels were associated with high prevalence of microalbuminuria [adjusted odds ratio 2.06 (95% CI 1.14-3.72); p=0.02] while comparing the highest with the lowest quartile of TSH. Multiple linear regression analysis showed that serum TSH level was independently associated with UACR ($\beta = 0.007$, $t = 2.03$ and $p = 0.04$). We also established that the risk for having microalbuminuria was higher with rise in TSH concentration in patients with younger age (<65 years), raised BMI ($\geq 25 \text{ kg/m}^2$), hypertension, type 2 diabetes and hyperlipidemia and age was the most important determinant (P for interaction = 0.02).

Conclusion: Serum TSH even in the euthyroid range was positively associated with microalbuminuria in euthyroid patients with diabetes independent of traditional risk factors. This suggests TSH may have a key role in the pathogenesis of microalbuminuria in high risk patients.

Introduction

Thyroid hormones are essential for the embryonic development of kidneys. Furthermore they regulate several physiological functions of the kidney in the adult life both directly and indirectly. The direct effects are usually on the glomerular function, the tubular absorptive and secretory capacities and the functioning of different electrolyte pumps whereas indirect actions are due to its influence on the cardiovascular system which eventually affects the renal blood flow (RBF).¹ On the other hand, the kidney also exhibits substantial influence on the synthesis, secretion, metabolism and elimination of thyroid hormones and is a target organ of some iodothyronines action.^{2,3} Such a dynamic interplay can alter significantly in a dysthyroid state (hypo or hyperthyroidism) leading to changes in clinical renal parameters like glomerular filtration rate (GFR), urine specific gravity (USG), urinary protein creatinine ratio (UPCR) and markers of tubular function.⁴ Likewise, moderate to advanced renal disease can lead to thyroid hormone dysfunction due to alteration in renal haemodynamics and manifest as subclinical or overt thyroid disease.⁵

Microalbuminuria is major marker of endothelial damage and an important determinant of vascular disease especially in diabetic patients. Moreover it increases the risk of diabetes, hypertension, decline in renal function and cardiovascular (CV) and all cause mortality in non diabetic subjects. Thyroid hormones have been also crucially linked to endothelial damage due to its influence on dilatation of blood vessels, production of vasodilator molecules, inhibition of angiotensin II receptor and effects on signal processes that regulate endothelial function and homeostasis.^{6,7} As thyroid function and microalbuminuria are both associated with endothelial damage and vascular disease, several authors have studied this inter-relationship intricately. Albuminuria has been identified to be an independent risk factor for elevated levels of thyroxine (T4) in patients with chronic kidney disease (CKD).⁸ Free triiodothyronine (FT3) concentrations were found to be independently associated with microalbuminuria in a euthyroid cohort⁹ and also in patients with diabetic nephropathy who were euthyroid as well.¹⁰ Others have also established that subclinical hypothyroid disease is independently associated with microalbuminuria in pre-diabetic adults¹¹ and in patients with type 2 diabetes.¹²

In diabetic patients, albuminuria remains a well established micro vascular complication and can lead to progressive renal impairment and atherosclerotic vascular disease. Serum

thyrotropin (TSH) has been established to be independently associated with renal function and CKD in normoglycaemic euthyroid adults¹³ which is expected to worsen in overt or subclinical thyroid disease. The evidence regarding the association of urine albumin excretion and serum TSH in euthyroid diabetic adults is scarce. In this study we aimed to investigate this relationship in a large Caucasian adult population.

Patients and Methods

Study population and Design

This is a retrospective cross sectional analysis of patients who attended the diabetes clinic at our hospital from October 2010 to May 2015. A total of 598 patients were included initially but upon exclusion only 433 were found to be eligible for the study. Patient's were included if they had anthropometric indices, bloods [renal function, HbA1c, lipid profile, thyroid function] and a spot urine sample for albumin creatinine ratio (UCAR) checked during their attendance. Patients were excluded if they had biochemical evidence of thyroid disease and/or receiving thyroxine, carbimazole, propylthiouracil, lithium, glucocorticoids, amiodarone, antipsychotic and antiepileptic drugs [n=36]. We also excluded patients who had established kidney disease [n=68] or were taking medications like Angiotensin converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARB) [n=61]. Anthropometric parameters like weight, height and blood pressure were measured by nurses in the outpatient department. Body mass index was calculated using the formula: weight in Kg/height in m². Patients were defined to have hypertension if their systolic blood pressure (SBP) was > 140 mmHg and/or diastolic blood pressure (DBP) was > 90 mmHg [average of three measurements] or when they had an established diagnosis of hypertension and were taking regular medications. Patients were defined to have hyperlipidemia according to National Cholesterol Education Program Adults Treatment Panel III (NCEP ATP III) criteria.¹⁴ A first voided early morning spot urine sample was collected for assessing UCAR as containers are sent routinely to patients prior to their visit to the clinic. Patients were defined to have microalbuminuria if their UACR was > 2.5 mg/mmol in males and > 3.5 mg/mmol in females. The study was registered and approved by the Research and Development department of Cwm Taf University Health Board with the project number CT/580/15. All data were handled according to Caldicott principles.

Biochemical measurements

(TBC)

Data Analysis

Continuous variables are presented as means \pm standard deviation (SD) where possible and as medians and interquartile range (IQR) if not approximating the normal distribution. We used paired “*t*” test to compare means between subgroups and Mann Whitney test to compare medians.

The study population were divided into four groups according to the quartiles of TSH. We described demographic and metabolic and demographic features in each quartile and a P for trend was calculated across TSH quartiles.

We investigated the association of TSH categories and microalbuminuria by using univariable and multivariable adjusted logistic regression models using UACR as the dependent variable and TSH categories as the independent variable. In multivariate logistic regression model we adjusted for potential confounding factors like age, sex, BMI, type of diabetes, SBP, FT4 and high lipids. We also confirmed the findings of logistic regression models by performing additional bootstrap analysis.

We also studied if the association of serum TSH and microalbuminuria was more prominent in certain subgroups by performing stratified analyses on the association between TSH and the risk of microalbuminuria by the prominent risk factors like gender, age, BMI, hypertension, eGFR and hyperlipidemia. Adjusted odds ratio was calculated for increase of each 1 SD in log TSH concentration in subgroups of different variables. A P value for interaction was calculated using likelihood ratio tests in each subgroup to evaluate their impact on the association of serum log TSH and microalbuminuria risk. For all statistical analysis a P value of < 0.05 was considered to be statistically significant. All statistical analysis was undertaken using STATA version 12 (STATA CORP, College Station, TX, USA).

Results

1. Characteristics of the study population

Table 1 shows the baseline characteristics of the study population which had a mean age of 60 ± 15.5 years and majority of them were males [273/433 (63.1%)]. Most of our patients had Type 2 diabetes [379/433 (87.5%)] and the overall glycaemic control for the whole group was sub-optimal [HbA1c – $8.8 \pm 1.9\%$]. In the total group the prevalence of microalbuminuria was 34.9% and majority of patients were males 69.5% (UACR > 2.5 mg/mmol) in comparison to females 30.5% (UACR > 3.5 mg/mmol).

Table 2 demonstrates the general characteristics and metabolic parameters of the study population when they were divided into four groups according to quartiles of TSH with the first quartile representing the lowest one and fourth quartile representing the highest one (Q1- 0.46 to <1.28; Q2-1.28 to < 1.81; Q3- 1.81 to < 2.58; Q4- > 2.58 mU/l). There was no major statistically significant difference in age, weight, BMI, DBP, HbA1c, creatinine, eGFR, FT4 and lipid profile with the increment in TSH but a difference in trend was noted with risk factors including sex, SBP and prevalence of Type 2 diabetes across different groups (all P for trend < 0.05). In comparison to the patients in the lowest quartile of TSH, those in the second, third and highest quartiles had higher levels of UACR [1.6 (0.9-3.2); 1.7 (1.0-4.3); 2.1 (0.8-4.4) and 2.4 (0.9-8.5) mg/mmol/ respectively], and this was statistically significant (P for trend= 0.02).

2. Prevalence of microalbuminuria in different TSH levels

The prevalence of microalbuminuria was different in the TSH quartiles. From the lowest quartile of TSH across to the highest one, the prevalence of microalbuminuria increased from 26.9 % to 34.6%, 38.5% and 44.9% respectively (P for trend = 0.02, Figure 1). In comparison to the highest TSH quartile, the third, second and lowest TSH quartiles showed a significant decrease in the prevalence of microalbuminuria (p=0.04, 0.005 and 0.01 respectively).

3. Association between TSH and Microalbuminuria

In the univariable logistic regression model, the risk of microalbuminuria increased across TSH quartiles. The odds ratio (OR) for the highest TSH quartile compared with the lowest quartile was 1.98 [95% CI (1.12-3.49); p=0.01] and those in the second and third quartile were also more likely to have microalbuminuria [OR-1.48, 95% CI (0.83-2.65); p=0.17] and

[OR-1.58, 95% CI (0.89-2.80); $p=0.11$] and the test for the trend was significant (P for trend = 0.02). We used two different models to adjust for potential confounding factors. In Model 2 (Table 3) we adjusted for age, sex, BMI and type of diabetes and a logistic regression analysis showed similar association that the patients in the second, third and highest quartiles were more likely to have microalbuminuria compared to those in the lowest quartile [adjusted OR 1.45, 95% CI (0.8-2.63); $p=0.21$], [adjusted OR 1.56, 95%CI (0.86-2.81); $p=0.13$] and [adjusted OR 1.95, 95% CI (1.09-3.48); $p=0.02$] respectively with a statistically significant p for trend = 0.03. In Model 3 we adjusted for age, sex, BMI, type of diabetes, SBP, FT4 and high lipids and the association remained fairly similar. In such a adjusted models patients again were more likely to develop microalbuminuria when their TSH was in the highest quartile in comparison to the lowest quartile [adjusted OR 2.06, 95% CI (1.14-3.72); $p=0.01$] and the trend was identical in the second [adjusted OR 1.67, 95% CI (0.91-3.07); $p=0.09$] and in the third quartile [adjusted OR 1.67, 95% CI (0.92-3.05); $p=0.09$] and the test for trend was statistically significant ($P_{\text{trend}} = 0.02$). We also performed a simple and multivariate adjusted linear regression analyses and we found TSH levels positively and significantly associated with UACR ($p < 0.05$) .

We also performed stratified analyses for multivariate adjusted odd's ratio of microalbuminuria with each 1 SD increment in log TSH concentration in different subgroups (Table 4) and we found that the associations between microalbuminuria and TSH were not consistent. We observed positive and significant association between TSH and microalbuminuria in the following subgroups of different strata: female population, age < 65 years, BMI ≥ 25 kg/m², patients with hypertension, type 2 diabetes and patients with hyperlipidemia. We didn't observe any significant association in the remaining subgroups of different strata. The interactions between TSH and the risk factors was only significant in the age category ($p=0.02$) (Table 4).

Discussion

In the present study we demonstrated a statistically significant association between serum TSH and urine albumin excretion in euthyroid patients with diabetes and our results indicated that the prevalence of microalbuminuria increased gradually as the quartiles of TSH levels increased. Our results also indicated that TSH levels significantly correlated with UACR after adjustment for a wide spectrum of demographic and biochemical risk factors. We also observed that in our diabetic cohort the risk of microalbuminuria was higher with incremental rise in TSH when patients are younger (<65 years) and have raised BMI, hypertension and dyslipidemia and have type 2 diabetes.

Microalbuminuria is a well recognised complication in patients with diabetes and serves as a marker of systemic endothelial dysfunction.^{15,16} In addition it is also a well known predictor of diabetic nephropathy and an independent risk factor for cardiovascular disease (CVD), morbidity and mortality.¹⁷ Thyroid hormones play an important role in the growth, development and physiology of the kidneys. Alteration in thyroid function causes remarkable changes in renal blood flow, glomerular filtration rate, tubular secretory and absorptive capacity, electrolyte pumps and structure of glomerular barrier¹³ which may significantly influence renal handling of albumin and other related proteins. Several authors have studied the intricate relationship between serum TSH levels and intrarenal haemodynamic parameters in normoglycaemic euthyroid subjects and have demonstrated that TSH is an independent factor for determining renal function and chronic kidney disease.^{5,13} Likewise, authors have also reported an independent association between FT3 concentration and microalbuminuria in large non diabetic population but no causal relationship was established.⁹

Our study provides a unique opportunity in studying the effects of serum TSH on urine albumin excretion in patients who had their thyroid function in the euthyroid range as previous studies examined a similar relationship in patients with diabetes but with established subclinical hypothyroidism (SCH).^{12,18,19} Thyroid hormones elicit crucial effects vascular and endothelial functions. Patients with SCH have endothelial dysfunction characterized by reduced endothelium dependent vasodilatation and impaired nitric oxide (NO) availability which is partially independent of dyslipidemia and can be reversed through levothyroxine replacement.²⁰ A similar impaired vascular function will be expected in patients with mild SCH or in patients with TSH in the higher end of the reference range like our patients due to underlying arterial stiffness and increased systemic vascular resistance. This has been

reported by Volzke et al ²¹ who found that serum TSH levels in the upper reference range are also associated with impaired endothelial function measured through flow mediated dilation. As endothelial dysfunction is associated with albuminuria in diabetes ²²; therefore it is entirely possible that such dysfunction is the possible link between higher level of TSH and albuminuria.

Thyroid function has a substantial impact on glucose and lipid metabolism and have been linked to components of insulin resistance (fasting insulin and HOMA-IR). ²³ On the other hand, insulin resistance has been described to be the principal pathophysiological process that underpins metabolic syndrome (Mets) ²⁴ which is a cluster of modifiable risk factors associated with increased risk developing CVD. The NHANES III data have shown strong positive association between microalbuminuria and Mets ²⁵ and other studies have also shown that the underlying insulin resistance would be a major determinant of microalbuminuria. ²⁶ Previous studies have identified links between components of Mets with low normal thyroid function (euthyroid state) ²³ and in patients with subclinical thyroid disease. ²⁷ Such findings are consistent with our observations that elevated TSH (in euthyroid range) can increase the risk of microalbuminuria in patients when patients have components of Mets like insulin resistance (manifested as type 2 diabetes), raised BMI, hypertension and dyslipidemia. We also showed that the risk is higher if patients younger (<65 years) and if are females.

Our study has limitations. First it has a cross sectional design which doesn't establish the casual relationship between TSH and microalbuminuria hence prospective, longitudinal studies are needed to clarify this intricate relationship. Second, we didn't have information about smoking status of individual patients which may impact thyroid function, kidney function and urine albumin excretion and may be a key confounder. Third, we didn't include thyroid auto-antibody status in our assessment as anti thyroperoxidase (TPO) antibody might be responsible for endothelial dysfunction and subsequent microalbuminuria in euthyroid patients with Hashimoto's disease as reported by other authors. ²⁸

Conclusion

In summary, our study shows a significant association and positive correlation between microalbuminuria, a surrogate marker of endothelial dysfunction and serum TSH in a euthyroid diabetic population. It helps us to understand the influence of thyroid function in the development of microalbuminuria and we suggest that gradually rising TSH, even though in the euthyroid range should be considered as an additional risk factor for microalbuminuria

beyond the traditional risk factors in diabetic subjects. Further studies are needed to explore this relationship and for development of intervention strategies.