

Hypothyroidism is Associated with Reduced Estimated Glomerular Filtration Rate in Saudi Patients. A Retrospective Single Centre Study

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Abstract

Background and Objective: The prevalence of hypothyroidism increases as estimated glomerular filtration rate (eGFR) decreases. Thus, the present study was conducted to find out the relationship between hypothyroidism and reduced eGFR in a cohort of Saudi population.

Design: We analyzed retrospectively 1560 participants whom are between the age 20 to 94 years. All patients were from the population of the Primary health centre at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. All data were collected on the basis of a review of electronic medical data. Patients with thyrotropin level (TSH) above the normal range of TSH for our laboratory reference, history of hypothyroidism and taking thyroid replacement therapy were included. Patients whom are T2DM or pregnant were excluded. The reference range values of TSH 0.22 - 4.2 mIU/L, Free T4 12.0 - 22.0 pmol/L. All patients in the present study fulfilled the revised National Kidney Foundation criteria for the diagnosis of CKD. eGFR was calculated using a modified MDRD equation as follows: $eGFR = 186 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female})$. The total number of cohort were separated on basis of age values into five groups: < 40 years, 40 - 49 years, 50 - 59 years and ≥ 60 years.

Results: Out of 1560 subjects included, there were 340 cases (21.8%) males and 1120 cases (78.2) were females with mean age 37.9 ± 13.1 . There were 151 cases (9.7%) and 112 cases (7.2%) with hypertension (HTN) and hypothyroidism respectively. The mean TSH and free thyroxine (FT4) and eGFR values were 2.6 ± 4.3 mIU/l, 15.2 ± 3.2 pmol/l and 115.3 ± 28.2 ml/min per 1.73 m^2 respectively. In the univariate analysis, hypothyroidism was associated with impaired renal function defined by $eGFR < 60 \text{ mL/min/1.73 m}^2$ (19.2% vs. 7.0%, $p = 0.03$) and the crude ORs (95% CI) were 3.2 (1.2 - 8.6), $p = 0.03$. After controlling for the potential risk factors, participants with hypothyroidism still had a significant 850% increase in the risk of $eGFR < 60 \text{ mL/min/1.73 m}^2$ (the adjusted OR = 9.50; 95% CI: 2.48 - 36.38), $p = 0.001$, after adjustment of potential risk factors (age, gender, HbA1c and hypertension (HTN)). Mean TSH was significantly higher in patients with than without impaired renal function patients (7.1 ± 19.2 vs. 2.6 ± 3.5 , $p < 0.0001$). Moreover, Mean FT4 was significantly lower in patients with than without impaired renal function patients (12.7 ± 5.1 vs. 15.2 ± 3.2 , $p = 0.02$). The prevalence of hypothyroidism in patients with glomerular filtration rate $< 60 \text{ mL/min per } 1.73 \text{ m}^2$ was non-significantly higher in ages < 40 years and 40 - 50 years and significantly higher in patients more than 60 years (2.7% vs. 1.0% respectively, $p = 0.009$).

Conclusion: We concluded that despite the limitations of this hospital-based retrospective study, hypothyroidism is highly prevalent in cohort of Saudis with reduced eGFR as defined by $< 60 \text{ mL/min/1.73 m}^2$. The majority of our patients with hypothyroidism in our finding were predominantly females. These two observations remain to be validated by population-based studies. In the absence of registry data, larger cooperative studies involving diverse population samples from multiple centers could help to provide further information on the true frequency nationally.

Keywords: Hypothyroidism; Estimated Glomerular Filtration Rate; Saudi Arabia

Introduction

Hypothyroidism has been increased recently and considered the commonest endocrine diseases [1]. Estimated glomerular filtration rate (eGFR) is a definition which is given to this biochemical function of kidney and any alteration from its normal value is an indicative of kidney diseases [2]. Serum creatinine concentration and its clearance from blood circulation by kidney is applied to assess the eGFR which correspond to the amount of blood filtered by kidney [3,4].

Thyroid hormone suppression negatively affect the eGFR, but the effect on tubular mechanism is not as hard as on glomerular function [5]. Chronic kidney disease (CKD) is associated with a higher prevalence of hypothyroidism [6,7]. In fact, the prevalence of hypothyroidism increases as GFR decreases [5]. A recent study has shown a prevalence of hypothyroidism of 7% in patients with estimated eGFR \geq 90 ml/min per 1.73 m² that increased to 17.9% in subjects with eGFR < 60 ml/min per 1.73 m² [8]. Many case reports and small case series documented increased levels of serum creatinine with hypothyroidism in humans [5,9-12]. The importance of understanding the impact of thyroid dysfunction on renal function is highlighted by recent studies indicating subclinical and clinical hypothyroidism is common in patients with estimated eGFR, 60 ml/min per 1.73 m², begging the question of whether hypothyroidism might be contributing to the low GFR in some of these individuals [7,8]. Thus, the present study was conducted to find out the relationship between hypothyroidism and reduced eGFR in a cohort of Saudi population.

Methods

We analyzed retrospectively 1560 participants whom are between the age 20 to 94 years. All patients were from the population of the Primary health centre at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. All data were collected on the basis of a review of electronic medical data. Patients with thyrotropin level (TSH) above the normal range of TSH for our laboratory reference, history of hypothyroidism and taking thyroid replacement therapy were included. Patients whom are T2DM or pregnant were excluded. The reference range values of TSH 0.22 - 4.2 MIU/L, Free thyroxine (FT4) 12.0 - 22.0 pmol/L. All patients in the present study fulfilled the revised National Kidney Foundation criteria for the diagnosis of CKD [13]. Estimated eGFR was calculated using a modified Modification of Diet in Renal Disease (MDRD) equation as follows: $eGFR = 186 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female})$ where S_{cr} is serum creatinine [14]. The total number of cohort were separated on basis of age values into five groups: < 40 years, 40 - 49 years, 50 - 59 years and \geq 60 years.

Statistical analysis

Continuous variables were described using means and Standard Deviations. Univariate analysis of baseline demography both between groups, were accomplished using unpaired t-test and Chi square test were used for categorical data comparison. Regression analysis was performed to assess for odd ratio (OR). P value < 0.05 indicates significance. The statistical analysis was conducted with SPSS version 23.0 for Windows.

Results

Out of 1560 subjects included, there were 340 cases (21.8%) males and 1120 cases (78.2) were females with mean age 37.9 ± 13.1 (Table 1). There were 151 cases (9.7%) and 112 cases (7.2%) with HTN and hypothyroidism respectively. The mean TSH and FT4 and eGFR values were 2.6 ± 4.3 mIU/l, 15.2 ± 3.2 pmol/l and 115.3 ± 28.2 ml/min per 1.73 m² "respectively".

In table 1 and 2, we summarized the characteristics of participants with different eGFR status. In the univariate analysis, hypothyroidism was associated with impaired renal function defined by eGFR < 60 mL/min/1.73 m² (19.2% vs. 7.0%, p = 0.03) and the crude ORs (95% CI) were 3.2 (1.2 - 8.6), p = 0.03. After controlling for the potential risk factors, participants with hypothyroidism still had a significant 850% increase in the risk of eGFR < 60 mL/ min/1.73 m² (the adjusted OR = 9.50; 95% CI: 2.48 - 36.38), p = 0.001, after adjustment of potential risk factors (age, gender, HbA1c and hypertension (HTN)). Mean TSH was significantly higher in patients with than without impaired renal function patients (7.1 ± 19.2 vs. 2.6 ± 3.5 , p < 0.0001). Moreover, Mean FT4 was significantly lower in patients with than without impaired renal function patients (12.7 ± 5.1 vs. 15.2 ± 3.2 , p = 0.02).

Parameters	Total > 60	Estimated glomerular filtration rate (ml/min per 1.73 m ²)		P value
		< 60		
Numbers	1560	1534 (98.3)	26 (1.7)	
Age (years)	37.9 ± 13.1	37.4 ± 12.6	65.1 ± 16.3	< 0.0001
Gender	Male	340 (21.8)	328 (21.4)	0.006
	Female	1120 (78.2)	1206 (78.6)	
Hypertension	151 (9.7)	135 (8.8)	16 (61.5)	< 0.0001
Hypothyroidism	112 (7.2)	107 (7.0)	5 (19.2)	0.03
TSH (mIU/l)	2.6 ± 4.3	2.6 ± 3.5	7.1 ± 19.2	< 0.0001
FT4 (pmol/l)	15.2 ± 3.2	15.2 ± 3.2	12.7 ± 5.1	0.02
Glomerular filtration rate (ml/min per 1.73 m ²)	115.3 ± 28.2	116.5 ± 26.9	46.4 ± 13.0	< 0.0001
Serum creatinine (µmol/L)	61.8 ± 18.5	60.6 ± 13.9	137.3 ± 57.5	< 0.0001

Table 1: Base line characteristics and comparison between renal function impairment groups (estimated glomerular filtration rate < 60 mL/ min/1.73 m²) [mean ± standard deviation or number (%)].

Parameters	Odd Ratio	P value
Male gender	1.39 (0.55 - 3.53)	0.5
Age (years)	1.11 (1.08 - 1.15)	< 0.0001
Hypertension	5.82 (2.22 - 15.23)	< 0.0001
Hypothyroidism	9.50 (2.48 - 36.38)	0.001

Table 2: Regression analysis for odd ratio of association between hypothyroidism and renal function impairment (estimated glomerular filtration rate < 60 mL/ min/1.73 m²).

The prevalence of hypothyroidism in patients with eGFR < 60 ml/min per 1.73 m² was non-significantly higher in ages < 40 years and 40 - 50 years and significantly higher in patients more than 60 years (2.7% vs. 1.0% respectively, p = 0.009) (Figure 1).

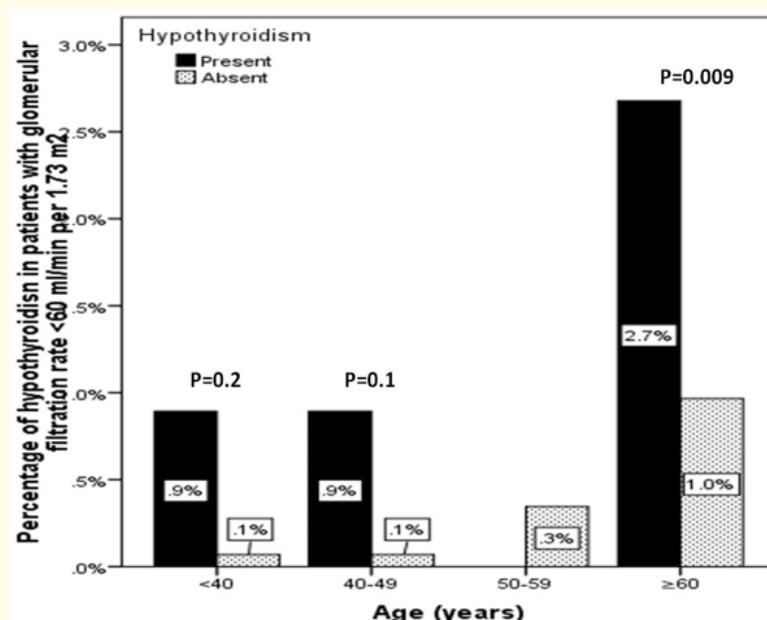


Figure 1: Hypothyroidism prevalence in patients with glomerular filtration rate < 60 ml/min per 1.73 m² in correlation to age category groups.

Discussion and Conclusion

In this retrospective study involving general population Saudi participants from a primary care centre, we found a clear association between hypothyroid status and low eGFR. The risk of impaired renal function, defined as eGFR less than 60 mL/min/1.73 m², increased by 2-fold in patients with hypothyroidism as compared to euthyroidism, which remained significantly increased (850%) after adjustment for other potential risk factors.

Our results are consistent with previous studies showing that the prevalence of hypothyroidism increased as eGFR decreased [7,8,15]. In the National Center for Health Statistics third national survey, the prevalence of hypothyroidism are 66.5% in subjects with eGFR < 60 mL/min/1.73 cm² [8]. In the Nord-Tronderlag Health Study, the mean eGFR decreased to 79.3 and 76.5 mL/min/1.73 cm² in subjects with hypothyroidism [15]. In another Italian study, the prevalence of hypothyroidism increased from 7% in participants with eGFR > 90 mL/min/1.73 cm² to 17.9% in participants with eGFR < 60 mL/min/1.73 cm². Many case reports and small case series document increased levels of serum creatinine with hypothyroidism in humans [5,9-12]. The importance of understanding the impact of thyroid dysfunction on renal function is highlighted by studies indicating hypothyroidism is common in patients with estimated eGFR < 60 ml/min per 1.73 cm² [7,8]. These data, together with our present study, support the association of hypothyroidism with reduced eGFR. Collectively, these data suggest hypothyroidism as a novel risk factor of reduced renal function. Several mechanisms by which hypothyroidism dampens eGFR were proposed. Mice deficient for thyroid hormone receptor developed hypotension and bradycardia, thereby reducing cardiac output and renal perfusion [16]. Hypothyroid rats also have a higher renal excretion of sodium [17,18]. Administration of thyroid hormone to hypothyroid rats restored proximal tubule sodium reabsorption due to an increase in Na⁺/H⁺ antiporter activity, which lead to volume expansion [19,20]. In addition, thyroid hormone has been shown to relax arteries and reduce arterial resistance [21]. These actions of thyroid hormone results in increased eGFR [20].

In the present study, patients with impaired renal functions as reflected by the reduced eGFR < 60 ml/min per 1.73 cm² had a higher prevalence of hypothyroidism than that previously reported; however, the demographic and clinical characteristics in the present study are different from those of patients in previous studies. For example, males are known to have a higher risk of nephropathy, while hypothyroidism is more common in females. In our study, females with or without hypothyroidism were more prevalent in patients with impaired renal functions than males.

In the same study conducted in Korea, the mean age (66.3 ± 10.7 years, euthyroid group; 67.2 ± 10.8 years, hypothyroidism group), older than our population, of the patients in a previous study conducted in China was older than other previous studies [7].

Due to the retrospective nature of this study, the observed population reflects a selected yet comprehensive group of patients rather than the general population. Our study could be limited by the question of clustering of cases within the study region and the effect that might have on our estimates, in addition, the current study population may appear limited in size and therefore may underestimate the true frequency of hypothyroidism in patients with reduced eGFR. In addition, the study shares the limitations of all retrospective studies.

We concluded that despite the limitations of this hospital-based retrospective study, hypothyroidism is highly prevalent in cohort of Saudis with reduced eGFR as defined by < 60 mL/min/1.73 m². The majority of our patients with hypothyroidism in our finding were predominantly females. These two observations remain to be validated by population-based studies. In the absence of registry data, larger cooperative studies involving diverse population samples from multiple centers could help to provide further information on the true frequency nationally.

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Conflict of Interests

The authors declare no conflict of interests.

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