Relation of Subclinical Hypothyroidism to Acute Kidney Injury Among ST-Segment Elevation Myocardial Infarction Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT: **Background:** Data suggest that subclinical hypothyroidism (SCH) is associated with progression of chronic renal disease; however, no study to date has assessed the possible relation between SCH and acute deterioration of renal function.

Objectives: To investigate the possible relation between SCH and acute kidney injury (AKI) in a large cohort of patients with ST-elevation myocardial infarction (STEMI) treated with primary coronary intervention (PCI).

Methods: We evaluated thyroid stimulating hormone (TSH) and free T4 levels of 1591 STEMI patients with no known history of hypothyroidism or thyroid replacement treatment who were admitted to the coronary care unit (October 2007–August 2017). The presence of SCH was defined as TSH levels ≥ 5 mU/ml in the presence of normal free T4 levels. Patients were assessed for development of AKI (0.3 mg/dl increase in serum creatinine, according to the KDIGO criteria).

Results: The presence of SCH was demonstrated in 68/1593 (4.2%) STEMI patients. Patients presenting with SCH had more AKI complications during the course of STEMI (20.6% vs. 9.6%, $P = 0.003$) and had significantly higher serum creatinine change throughout hospitalization (0.19 mg/dl vs. 0.08 mg/dl, $P = 0.04$). No significant difference was present in groups regarding baseline renal function and the amount of contrast volume delivered during coronary angiography. In multivariate logistic regression model, SCH was independently associated with AKI (odds ratio = 2.19, 95% confidence interval 1.05–4.54, $P = 0.04$).

Conclusions: Among STEMI patients treated with PCI, the presence of SCH is common and may serve as a significant marker for AKI.

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KEY WORDS: acute kidney injury (AKI), hypothyroidism, ST-elevation myocardial infarction (STEMI), subclinical hypothyroidism (SCH)

Subclinical hypothyroidism (SCH) is defined as a serum thyroid-stimulating hormone (TSH) level above the upper limit of normal despite normal levels of serum-free thyroxine [1]. The prevalence of SCH increases with age and is higher among woman and ranges from 3–8% in the total population [2]. Patients with overt hypothyroidism have an increased risk of functional cardiovascular abnormalities as well as accelerated atherosclerosis and an increased risk of coronary artery disease [3,4]. Overt hypothyroidism is associated with reduced renal plasma flow, low glomerular filtration rate, decreased sodium reabsorption, and the inability to dilute urine [5,6]. Moreover, thyroid hormone replacement therapy can reverse the deterioration of renal function in hypothyroid patients [6]. Recent reports demonstrated that SCH was associated with deterioration of renal function among patients with diabetes mellitus and chronic kidney disease [7,8]. To the best of our knowledge, no study has assessed the possible relation between SCH and acute deterioration of renal function.

In the present study we investigated the possible relation between SCH and deterioration of renal function resulting in acute kidney injury (AKI) in a large cohort of patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

PATIENTS AND METHODS

STUDY POPULATION

A retrospective, single-center observational study was performed at the Tel Aviv Sourasky Medical Center, a tertiary referral hospital with a 24/7 primary PCI service.

Included in this study were all 2234 patients admitted to the hospital between October 2007 and August 2017 with the diagnosis of acute STEMI subsequently treated with primary PCI. We excluded 591 patients in whom TSH level was not recorded. In the remaining patients, free T4 and TSH levels were evaluated at admission to the cardiac intensive care unit (CICU) following PCI. Subclinical hypothyroidism was defined as TSH levels ≥ 5 mU/ml in the presence of normal free T4 levels [1]. We

excluded patients with documented history of hypothyroidism and those receiving thyroid replacement therapy (n=45). We additionally excluded seven patients with TSH levels ≥ 5 mU/ml and clinical hypothyroidism (based on serum free T4 levels). The final study population included 1591 STEMI patients.

Diagnosis of STEMI was established in accordance with published guidelines, including a typical chest pain history, diagnostic electrocardiographic changes, and serial elevation of cardiac biomarkers [9]. Primary PCI was performed in patients with symptoms ≤ 12 hours in duration as well as in patients with symptoms lasting 12–24 hours, if pain was noted at the time of admission. Symptom duration was defined as the time from symptom onset (usually chest pain or discomfort) to emergency room/catheterization laboratory admission. Door-to-balloon time was defined as the time, in minutes, between a patient's arrival at the hospital (taken from the computerized patient file) and the first balloon inflation or device deployment in the culprit artery as documented in the patient's medical record. Baseline demographics, cardiovascular history, clinical risk factors, treatment characteristics and laboratory results were all retrieved from the hospital electronic medical records. The study protocol was approved by the local institutional ethics committee.

ASSESSMENT OF RENAL FUNCTION AND ACUTE KIDNEY INJURY

The serum creatinine level was determined at hospital admission (prior to primary PCI) and at least daily during the CICU and/or step-down unit stay until hospital discharge, and was available for all analyzed patients. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [10]. Chronic kidney disease (CKD) was defined as admission eGFR of ≤ 60 ml/min/1.73 m^2 [10]. AKI was determined using the KDIGO criteria [11]. and was defined as an increase in serum creatinine ≥ 0.3 mg/dl within 48 hours of admission or an increase in serum creatinine ≥ 1.5 times baseline, which was known or presumed to have occurred within the prior 7 days. Peak serum creatinine was defined as the highest level measured within 7 days of hospital admission.

STATISTICAL ANALYSIS

Continuous variables were presented as mean ± standard deviation and compared with the independent sample t test when normally distributed. Median and interquartile range was used in cases of non-normally distributed continuous variables. These variables were compared with Mann-Whitney U test. Categorical variables are presented as percentages; *P* values were calculated with the chi square test. Independent predictors of AKI were determined in a multivariate binary logistic regression model adjusted for all baseline variables found to be significant in the univariate analysis. A two-tailed *P* value of < 0.05 was considered significant for all analyses. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

A total of 1591 STEMI patients treated by primary PCI were included in the final analysis (age 61 ± 13 years, 82% male), 68 (4.2%) of whom demonstrated SCH at CICU admission. The baseline clinical characteristics of patients with versus those without SCH are listed in Table 1. Patients with SCH were more likely to be female and smokers. In addition, patients having SCH had lower left ventricular ejection fraction.

Table 2 compares the occurrence of AKI and serum creatinine changes in patients with and without SCH. Patients having SCH had more AKI complicating the course of STEMI (20.6% vs. 9.6 %; *P* = 0.003) and had significantly higher serum creatinine change throughout hospitalization (0.19 mg/dl vs.0.08 mg/dl; *P* = 0.04). No significant difference was observed in groups regarding baseline eGFR, CKD, and the amount of contrast volume delivered during PCI. Table 3 compares the baseline characteristics among patients with and without AKI. Accordingly, in a univariate logistic regression analysis, the odds ratio (OR) for AKI development was 2.44 (95% confidence interval [95%CI] 1.33–4.51, *P* = 0.004) when comparing patients with versus without SCH

Table 1. Baseline criteria of 1591 ST-elevation myocardial infarction patients undergoing primary coronary intervention stratified by presence or absence of subclinical hypothyroidism

	No SCH (n=1523)	SCH (n=68)	*P* value
Age, mean ± SD, years	61 ± 13	62 ± 14	0.44
Male gender, n (%)	1257 (83)	40 (59)	< 0.001
Diabetes mellitus, n (%)	367 (24)	20 (29)	0.32
Hyperlipidemia, n (%)	744 (49)	40 (59)	0.11
Family history of IHD disease, n (%)	325 (21)	16 (24)	0.67
Smoking, n (%)	746 (49)	44 (65)	0.01
Hypertension, n (%)	668 (44)	33 (49)	0.45
Past myocardial infarction, n (%)	193 (13)	12 (18)	0.23
CAD severity, n (%)			0.06
1 vessel	663 (43)	29 (43)	
2 vessel	457 (30)	13 (23)	
3 vessel	403 (27)	26 (38)	
Free T4(ng/dl), mean ± SD	1.10 ± 0.2	1.09 ± 0.2	0.88
C-Reactive protein(mg/dl), median (IQR)	4.4 (1.5–11)	6.5 (1.7–13)	0.34
Left ventricle ejection fraction, mean ± SD	47 ± 8	44 ± 9	0.008
Left ventricle ejection fraction < 45%, n (%)	451 (30)	29 (43)	0.03
Heart failure (Killip Class > II), n (%)	153 (10)	7 (10)	0.95

CAD = coronary artery disease, IHD = ischemic heart disease, IQR = interquartile range, SCH = subclinical hypothyroidism, SD = standard deviation

Table 2. Acute kidney injury, serum creatinine changes, and intravenous contrast volume applied according to presence of subclinical hypothyroidism

	No SCH (n=1523)	SCH (n=68)	*P* value
Acute kidney injury, n (%)	146 (9.6)	14 (20.6)	0.003
Baseline eGFR (ml/minute/1.73^2), mean ± SD	75 ± 24	73 ± 24	0.49
Baseline chronic kidney disease, n (%)	372 (24)	22 (32)	0.14
Admission sCr (mg/dl), mean SD	1.12 ± 0.3	1.21 ± 0.6	0.24
Peak sCr (mg/dl), mean ± SD	1.19 ± 0.58	1.39 ± 0.87	0.06
sCr change in hospital (mg/dl), mean ± SD	0.08 ± 0.43	0.19 ± 0.45	0.04
sCr at discharge (mg/dl), mean ± SD	1.07 ± 0.4	1.22 ± 0.75	0.11
Contrast material amount (ml), mean ± SD	147 ± 45	126 ± 29	0.16

eGFR = estimated glomerular filtration rate; sCr = serum creatinine, SD = standard deviation

Table 3. Baseline criteria of 1591 ST-elevation myocardial infarction patients undergoing primary primary coronary intervention stratified by presence or absence of acute kidney injury

	No AKI (n=1431)	AKI (n=160)	*P* value
Age, years, mean ± SD	60 ± 13	71 ± 13	‹ 0.001
Male, gender, n (%)	1179 (82)	118 (74)	0.008
Diabetes mellitus, n (%)	325 (23)	62 (39)	‹ 0.001
Hyperlipidemia, n (%)	697 (49)	87 (54)	0.17
Family history of IHD disease, n (%)	324 (23)	17 (11)	‹ 0.001
Smoking, n (%)	735 (51)	55 (34)	‹ 0.001
Hypertension, n (%)	587 (41)	114 (71)	‹ 0.001
Past myocardial infarction, n (%)	176 (12)	29 (18)	0.04
CAD, severity, n (%)			‹ 0.001
1 vessel	640 (45)	52 (33)	
2 vessel	426 (30)	44 (28)	
3 vessel	365 (26)	64 (40)	
TSH (mU/ml), mean ± SD	1.9 ± 1.6	2.4 ± 1.9	0.01
Free T4 (ng/dl), mean ± SD	1.09 ± 0.2	1.12 ± 0.2	0.25
C-Reactive protein(mg/dl), median (IQR)	4.3 (1.4–10.1)	8.6 (2.4–21.7)	‹ 0.001
Left ventricle ejection fraction, mean ± SD	47 ± 8	41 ± 9	‹ 0.001
Left ventricle ejection fraction ‹ 45%, n (%)	398 (30)	82 (52)	‹ 0.001
Heart failure (Killip Class ≥ II), n (%)	99 (7)	61 (38)	‹ 0.001

AKI = acute kidney injury, CAD = coronary artery disease, IHD = ischemic heart disease, IQR = interquartile range, SD = standard deviation, TSH = thyroid stimulating hormone

[Table 4]. In a multivariate logistic regression model SCH was independently associated with AKI (OR 2.41, 95%CI 1.17–4.94, *P* = 0.017). Other predictors for AKI included CKD, hypertension, left ventricular ejection fraction ≤ 45%, and heart failure at presentation [Table 4].

Table 4. Univariate and multivariate binary logistic regression for acute kidney injury

	Univariate analysis		Multivariate analysis	
Variable	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Subclinical hypothyroidism	2.44 (1.33–4.51)	0.004	2.41 (1.17–4.94)	0.017
Age › 60 years	4.26 (2.86–6.33)	‹ 0.001	1.57 (0.96–2.56)	0.07
Chronic kidney disease	5.06 (3.61–7.09)	‹ 0.001	2.33 (1.54–3.52)	‹ 0.001
Female gender	1.66 (1.14–2.42)	0.008	0.89 (0.58–1.39)	0.63
Diabetes mellitus	2.15 (1.53–3.03)	‹ 0.001	1.40 (0.95–2.06)	0.09
Family history for IHD disease	0.41 (0.24–0.68)	0.001	0.85 (0.48–1.51)	0.58
Smoking history	0.49 (0.35–0.69)	‹ 0.001	0.77 (0.52–1.14)	0.19
Past myocardial infarction	1.57 (1.02–2.43)	0.04	0.92 (0.56–1.51)	0.75
Hypertension	3.56 (2.49–5.09)	‹ 0.001	2.25 (1.49–3.39)	‹ 0.001
Ejection fraction ‹ 45%	2.72 (1.95–3.79)	‹ 0.001	1.72 (1.18–2.51)	0.005
Heart failure (Killip Class ≥ II)	8.29 (5.67–12.1)	‹ 0.001	4.82 (3.14–7.39)	‹ 0.001

IHD = ischemic heart disease, OR = odds ratio, 95%CI = 95% confidence interval

DISCUSSION

The main finding of our study is that among STEMI patients undergoing primary PCI, SCH was common and independently associated with AKI.

The interactions between the kidney and thyroid functions are bilateral. Thyroid hormones are essential for growth and development of the kidney as well as for the maintenance of water and electrolyte homeostasis [12]. However, the kidney is involved in the metabolism and elimination of thyroid hormones [13,14]. Patients with hypothyroidism demonstrate a reduction in renal function related to various factors. Reduction in cardiac systolic and diastolic function results in reduced renal perfusion [15]. In addition, hypothyroidism affects renal hemodynamics and excretion function directly as total blood volume is reduced, peripheral vessel resistance is increased, and intrarenal vessels are contracted, which leads to reduced renal blood flow [16]. Changes in tubular reabsorption and secretion function, as well as a decline in eGFR were also reported, with eGFR in patients with hypothyroidism is only two-thirds that found in individuals with normal thyroid function [17].

Hypothyroidism might also affect oxidative and enzyme metabolism in each segment of the renal tubule, thereby causing renal tubular injury [17]. These alterations among patients with clinical hypothyroidism improved after thyroid hormone treatment was introduced [18]. Recent data also suggested that SCH may be associated with renal dysfunction. The prevalence of chronic renal disease was reported to be higher in patients with SCH compared with those having normal thyroid function [19,20]. A recent report by Zhang et al. [8] demonstrated a correlation between SCH and renal injury among patients with

diabetes. Similarly unresolved SCH was an independent factor contributing to the rate of eGFR decline, and that individuals had a higher risk of progression to end stage renal disease [7].

To the best of our knowledge, no report to date has examined the possible relation between SCH and AKI. In our report, patients with SCH were two times more likely to develop AKI compared to patients without SCH. The fact that no significant difference was present between the groups with regard to baseline serum creatinine and CKD rate further points to the possible relation to acute hemodynamic effect. Indeed, patients with SCH had lower left ventricular ejection fraction, which was previously shown to result in decreased renal perfusion and AKI among STEMI patients [21]. In addition, impaired left ventricular diastolic function, which is characterized by slowed myocardial relaxation and increased ventricular filling pressures was the most consistent cardiac abnormality in patients with mild thyroid hormone deficiency [22]. This abnormality was also recently shown to be associated with AKI in STEMI patients [23].

In SCH, inflammation is known to be more prevalent than in euthyroidism [20]. In addition, elevated C-reactive protein was recently demonstrated to be associated with AKI among STEMI patients [24,25]. In our cohort, patients with SCH demonstrated higher C-reactive protein levels; however, it did not reach statistical significance. To explore the possible mechanism of renal function decline in SCH patients, further investigations are needed related to particularly in cardiac and inflammatory dysfunction.

LIMITATIONS

We acknowledge several important limitations of our study. Our single center retrospective and non-randomized observational study may have been subject to bias even though we included consecutive patients and attempted to adjust for confounding factors using the multivariate regression model. Sample size was small for patients with SCH, which may undermine our results. No information was present on T3 and serum albumin levels, thus their relation to SCH and AKI could have not been assessed. Due to delayed effects of contrast material and drugs, worsening of renal function might have occurred following hospital discharge in some patients, thus the true incidence of AKI described in our study may have been an underestimated. In addition, as data regarding concomitant of statins, renin/angiotensin blockers and diuretics throughout hospitalization was not present in many patients, their effect on renal function could not be assessed.

CONCLUSION

Among STEMI patients undergoing primary PCI, SCH was independently associated with AKI. Large-scale prospective studies are needed to further explore this relationship.

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