

# Subclinical Hypothyroidism Increases the Requirement of Renal Replacement Therapy After Cardiac Surgery

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## ABSTRACT

**Background:** Subclinical or biochemically diagnosed hypothyroidism (SCH) is defined as an elevated serum thyroid-stimulating hormone (TSH) with normal free thyroxine (FT4) levels. Thyroid hormones play a major role in the normal function of the heart and vascular physiology. Atherosclerosis, increased systemic vascular resistance, and decreased arterial compliance are common pathophysiological changes that may occur in hypothyroidism. Acute kidney injury (AKI) is one of the devastating complications after cardiac surgery. Age, diabetes mellitus (DM), preexisting renal dysfunction, hypertension, impaired left ventricular function, and severe arteriosclerosis are the major risk factors for the development of AKI. The purpose of the current study was to analyze the influence of SCH on AKI and the requirement of renal replacement therapy (RRT) after isolated coronary artery bypass graft surgery (CABG).

**Methods:** We retrospectively reviewed the prospectively collected data of 336 adult patients who underwent isolated CABG surgery with normal renal function (baseline serum creatinine value <1.4 mg/dL) from January 2017 to January 2019. The patients were divided into two groups either having the diagnosis of SCH (Group I, N = 47) or not (Group II, N = 289). SCH was diagnosed based on preoperative serum TSH and FT4 levels. Kidney injury was interpreted, according to RIFLE classification. The effect of SCH on AKI and the need for RRT after CABG was determined using logistic regression analysis and the results were expressed as odds ratio (OR) with a 95% confidence interval (CI). A *P* value < .05 was considered statistically significant.

**Results:** Subclinical hypothyroidism was diagnosed in 14% of all patients. Postoperative AKI occurred in 15 patients (31.9%) in Group I, whereas there were 42 patients (14.5%) in Group II. On logistic regression analysis, the presence of SCH was shown to be associated with an increased incidence of postoperative AKI (OR, 0.363; 95% CI, 0.181-0.727; *P* = .004). RRT was used in 2.97% of patients (seven patients

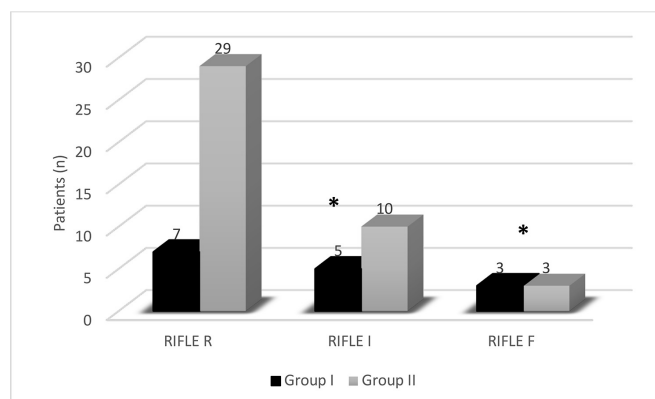
in Group I and three patients in Group II, *P* < .001). The 30-day mortality was 2.1%.

**Conclusion:** The presence of SCH seems to be associated with an increased incidence of AKI and increased requirement for RRT after cardiac surgery.

## INTRODUCTION

Subclinical or biochemically diagnosed hypothyroidism (SCH) is defined as elevated serum thyroid-stimulating hormone (TSH) with normal free thyroxine (FT4) levels [Kim 2014].

The prevalence of SCH ranges from 4% to 15% in the general population, being higher in women and older adults [Garber 2012]. It is suggested in the literature that both overt and subclinical hypothyroidism increase the risk of atherosclerosis and coronary artery disease [Saif 2018; Mousa 2020]. It also is reported that both overt and subclinical hypothyroidism are associated with hypotension, increased vascular resistance, and decreased sodium reabsorption, which leads to volume contraction and reduced renal blood flow and low glomerular filtration rate [Wikström 1998; Liu 2014; Michael 1972; Chang 2018]. Recent reports suggested that SCH was associated with acute kidney injury (AKI) in patients with



Comparison of Group I and Group II, according to RIFLE classification.\*statistically significant, *P* = .044 and *P* = .038, respectively. Group I: Subclinical hypothyroid patients, Group II: Patients with normal thyroid functions.

Received May 12, 2020; accepted June 24, 2020.

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Table 1. RIFLE Classification

GFR Criteria	Urine Output Criteria
Risk Increased plasma creatinine $\times 1.5$	$<0.5 \text{ mL/kg}^1/\text{h}^1 \times 6 \text{ hours}$
Injury Increased plasma creatinine $\times 2$	$<0.5 \text{ mL/kg}^1/\text{h}^1 \times 12 \text{ hours}$
Failure Increased plasma creatinine $\times 3$ or acute plasma creatinine $\geq 350 \mu\text{mol/L}$ or acute rise $\geq 44 \mu\text{mol/L}$	$<0.3 \text{ mL/kg}^1/\text{h}^1 \times 24 \text{ hours}$

Loss Persistent acute renal failure = complete loss of kidney function  $> 4$  weeks  
 ESKD End-stage kidney disease ( $>3$  months)  
 ESKD indicates end-stage kidney disease; GFR, glomerular filtration rate.

diabetes, coronary artery disease, and chronic kidney disease [Kim 2014; Zhang 2017; Zahler 2019].

Acute kidney injury is one of the devastating complications after cardiac surgery. Age, diabetes mellitus (DM), preexisting renal dysfunction, hypertension, impaired left ventricular function, and severe arteriosclerosis of the aorta are the major risk factors for the development of AKI [Doddakula 2007; Weerasinghe 2001; Chertow 1997]. Intraoperatively, inflammatory response syndrome due to cardiopulmonary bypass (CPB), nonpulsatile flow, and renal hypoperfusion also are important causes of AKI [Suen 1998; Hall 1997]. The purpose of the current study was to analyze the influence of SCH on AKI and the requirement of renal replacement therapy (RRT) after isolated coronary artery bypass graft surgery (CABG).

## MATERIALS AND METHODS

After we received institutional review board approval, we retrospectively reviewed the prospectively collected data of 378 adult patients, who underwent isolated CABG surgery with normal renal function (baseline serum creatinine value  $<1.4 \text{ mg/dl}$ ) from January 2017 to January 2019. All patients previously granted permission for the use of their medical records for research purposes. The clinical data of the patients included demographic data, laboratory data, length of stay, in-hospital complications, and mortality. Subclinical hypothyroidism was defined as TSH levels  $\geq 4.1 \text{ mIU/L}$  in the presence of normal FT4 levels ( $0.7\text{--}1.8 \text{ ng/dl}$ ), and the euthyroid state was defined as normal level of TSH ( $0.4\text{--}4.1 \text{ mIU/L}$ ) and normal FT4 levels ( $0.7\text{--}1.8 \text{ ng/dl}$ ). Preoperative measurement of thyroid functions routinely were performed for all patients undergoing cardiac surgery in our clinic. Patients with overt hypothyroidism, overt hyperthyroidism, and subclinical hyperthyroidism and patients receiving thyroid replacement therapy were excluded from the study ( $N = 42$ ). The patients ( $N = 336$ ) were then divided into two groups either having the diagnosis of SCH (Group I,  $N = 47$ ) or not (Group II,  $N = 289$ ). The primary outcome was the development of AKI. Kidney injury was interpreted according to RIFLE classification [Bellomo 2004], explained as RIFLE R: risk; RIFLE I: injury; RIFLE F: failure; RIFLE L: loss; and RIFLE E: end-stage kidney disease. (Table 1) Patients who were on either hemodialysis or peritoneal dialysis, patients

with emergent surgery, recent myocardial infarction, peripheral vascular disease, and patients undergoing operations other than or in conjunction with CABG were excluded from the study.

**CABG procedure:** All operations were performed in a standardized approach by a Terumo roller pump (Terumo Advanced Perfusion System 1, USA), membrane oxygenators (Inspire 8, LivaNova Sorin Group, Italy). Mild to moderate ( $28\text{--}32^\circ\text{C}$ ) hypothermia and pulsatile flow of  $2.2\text{--}2.4 \text{ L/m}^2$  were used. Myocardial protection was achieved with tepid antegrade blood cardioplegia, and a "hot shot" ( $250\text{--}500 \text{ ml}$ ) was delivered just before the removal of the aortic cross-clamp. The perfusion pressure was kept over  $70 \text{ mmHg}$  at all times. Induction and maintenance of general anesthesia with endotracheal intubation were standardized in all the patients (fentanyl, midazolam, and isoflurane in oxygen with air). The same surgical team performed all of the operations.

**Postoperative management:** Postoperatively, patients were followed in the intensive care unit (ICU) according to protocols of our institution. Electrocardiography, systemic mean arterial pressure, central venous pressure, pulmonary artery and wedge pressures, cardiac output and index, arterial blood gases, chest tube output, and hourly urine output were monitored. Serum electrolytes were measured in conjunction with arterial blood gas measurement. Fluid and electrolyte imbalances were immediately corrected with appropriate management. Hematocrit values  $<25\%$  were corrected with erythrocyte suspension administration postoperatively. Daily blood urea nitrogen, serum, and urea creatinine and serum electrolytes uniformly were measured in all patients until discharge from the hospital. Preoperative and postoperative creatinine clearances and peak creatinine clearance were calculated, according to the formulations reported in the literature [Lassnigg 2000; Cockcroft 1976]. The indication criteria for RRT, hyperkalemia ( $>6 \text{ mmol/l}$ ), oliguria  $<0.5 \text{ mL/kg/h}$  for 12 hours or anuria, and metabolic acidosis, were determined by our nephrologist. Vascular access for RRT was with a dual lumen catheter via a central venous vein. Patients were heparinized to achieve activated clotting time of 200 seconds. Fresenius polysulfone filter (Fresenius Medical care AG, Bad Homburg, Germany) was used for filtration.

**Statistical analysis:** All statistics were performed using SPSS version 18.0 for Windows (IBM Corporation, New York, USA). Continuous variables were expressed as mean  $\pm$

Table 2. Baseline and perioperative characteristics of patients.

Clinical characteristics	Subclinical hypothyroid patients (N = 47)	Euthyroid patients (N = 289)	P*
Age, years	64.9±12.1	60.9±10.1	.015
Female, %	44.7	21.8	.002
Body mass index, >30 kg/m <sup>2</sup> , %	51.1	30.1	.007
Hypertension, %	61.7	63.7	.871
Dyslipidemia, %	59.6	59.5	1.000
Diabetes, %	46.8	33.2	.098
Metabolic syndrome, %	36.2	16.6	.004
LV function, %	56.4±9.2	54.7±8.9	.239
CPB time, min	105.7±27.5	113.0±35.5	.178
Cross-clamp time, min	59.8±19.7	64.3±22.9	.207
Serum creatinine, mg/dl	0.93 ± 0.18	0.91±0.21	.603
Creatinine clearance, ml/min	85.3±30.5	91.9±38.9	.341
TSH, mIU/L	5.1±1.2	1.7±1.0	<.001
Free T4, ng/dl	1.0±0.3	0.9±0.2	.063

Data are presented as mean ± SD where indicated. CPB: cardiopulmonary bypass; LV: left ventricle, TSH: thyroid stimulating hormone. \*Chi-square and unpaired Student t tests. Statistically significant values are  $P < .05$ ).

SD and were compared by unpaired Student's t-test or the chi-squared test. The effect of preoperative SCH on AKI after CABG was determined using logistic regression analysis and the results were expressed as odds ratio (OR) with a 95% confidence interval (CI). A  $P$ -value  $< .05$  was considered statistically significant.

## RESULTS

Patient demographics and perioperative data are shown in Table 2. (Table 2) Among the patient characteristics and perioperative data, female sex, age, body mass index, metabolic syndrome (MetS), and TSH levels significantly were higher in Group I. Other data did not show statistically significant differences between the groups. Subclinical hypothyroidism was diagnosed in 14% of all patients. Postoperative AKI occurred in 15 patients (31.9%) in Group I, whereas there were 42 patients (14.5%) in Group II with postoperative AKI. On logistic regression analysis, the presence of SCH was shown to be associated with an increased incidence of postoperative AKI (OR, 0.363; 95% CI, 0.181-0.727;  $P = .004$ ). Multivariate logistic regression analysis revealed that DM (OR, 4.975; 95% CI, 2.707-9.145;  $P < .001$ ), obesity (BMI  $>30\text{kg/m}^2$ ) (OR, 3.878; 95% CI, 2.148-7.001;  $P < .001$ ), and MetS (OR, 3.817; 95% CI, 2.048-7.115;  $P < .001$ ) were other independent risk factors for AKI after isolated CABG.

The preoperative mean serum creatinine was  $0.93 \pm 0.18$  mg/dL in Group I and  $0.91 \pm 0.21$  mg/dL in Group II ( $P = .603$ ). Postoperative peak serum creatinine levels were higher in Group I patients than Group II ( $1.54 \pm 1.09$  mg/dL

and  $1.18 \pm 0.70$  mg/dL, respectively;  $P = .003$ ). When results were compared according to the RIFLE stage, the 15 patients in Group I included seven patients (46.7%) in RIFLE R, five patients (33.3%) in RIFLE I, and three patients (20%) in RIFLE F stage. Whereas 42 patients in Group II included 29 patients (69.1%) in RIFLE R, 10 patients (23.8%) in RIFLE I, and three patients (7.1%) in RIFLE F stage (RIFLE R,  $P = .222$ ; RIFLE I,  $P = .044$ ; RIFLE F,  $P = .038$ , respectively) (Figure).

Renal replacement therapy was used in 2.97% (N = 10) of patients (seven patients were in Group I, and three patients were in Group II,  $P < .001$ ). The creatinine value before the commencement of RRT was  $3.98 \pm 0.54$  mg/dL. RRT was started 33-52 hours after surgery and used for a maximum of five days. The mean creatinine level was  $1.37 \pm 0.78$  mg/dL before hospital discharge and none of the patients became hemodialysis dependent.

The mean ICU time was  $61.96 \pm 37.06$  hours in Group I and  $51.63 \pm 25.93$  hours in Group II ( $P = .018$ ); in-hospital stay time was  $7.94 \pm 2.88$  days in Group I and  $7.03 \pm 1.53$  days in Group II ( $P = .001$ ). The intraaortic balloon pump (IABP) support was required in 3.9% of patients (five patients in Group I and eight patients in Group II,  $P = .023$ ). Prolonged ventilatory support was necessary for 3.6% of patients and the mean ventilatory support time was  $9.06 \pm 6.79$  in Group I and  $7.40 \pm 3.67$  in Group II,  $P = .013$ ) and one of these patients required a tracheotomy. The 30-day mortality was 2.1% (N = 7, four patients in Group I and three patients in Group II,  $P = .009$ ). All patients died due to low cardiac output and multiorgan failure, and these patients required RRT.

## DISCUSSION

In the present study, we analyzed the effect of preoperative SCH on AKI and RRT requirement after CABG. Acute kidney injury was observed in 16.9% of the patients in our study. Postoperative AKI occurred in 15 patients in Group I (SCH) and 42 patients in Group II (euthyroid). Logistic regression analysis revealing the presence of SCH preoperatively was shown to be associated with an increased incidence of postoperative AKI (OR, 0.363; 95% CI, 0.181–0.727;  $P = .004$ ). Renal dysfunction after cardiac surgery is a common complication; however, the exact mechanism still is unclear. Hypertension, DM, age, severe arteriosclerosis, and impaired left ventricular function are the known major preoperative risk factors for postoperative AKI [Doddakula 2007; Weerasinghe 2001; Chertow 1997]. SCH is suggested to affect vascular systems, such as decreased arterial compliance, increased systemic vascular resistance, endothelial dysfunction, coagulation, and atherosclerosis [Kahaly 2005; Cooper 2012; Cikim 2004]. The intraoperative causative mechanisms of AKI, during cardiac surgery, are CPB induced SIRS that results in the production of excessive ROS, ischemia-reperfusion that also leads to the generation of free oxygen radicals and hypoperfusion of the organs, mainly the kidneys [Haase 2007]. Hypothyroidism also is reported to prompt oxidative stress, inflammation, and result in enzymatic metabolism changes in renal tubules, thereby causing renal tubular injury [Suher 2005; Marfella 2011]. Thus, we hypothesized that through these effects of SCH, it should further increase the risk of AKI after CABG. In our study, SCH was diagnosed in 14% of all patients; additionally, SCH was more common among females and older patients and these results were compatible with the literature [Garber 2012]. Our results showed that metabolic syndrome (MetS) was more common in SCH patients than in the euthyroid group.

Metabolic syndrome, like SCH, is a common problem in the general population and also in patients with cardiovascular disease. There is an ongoing debate about the link between SCH and MetS. It is reported that SCH was associated with MetS, especially among Asian populations [Yang 2016]. Obesity (BMI >30kg/m<sup>2</sup>), also a component of MetS, was reported to be more common in SCH patients in our study. It is known that obesity is associated with changes in thyroid hormones, and it also is known that hypothyroidism may induce obesity, thus it is stated that there is a bidirectional relationship between obesity and thyroid disease [Song 2019]. SCH is found to be also associated with hypertension, dyslipidemia, and Type 2 diabetes, in addition to obesity. However, our results did not show a significant difference between the groups regarding diabetes, dyslipidemia, and hypertension preoperatively.

In the literature, it is suggested that MetS and obesity (BMI >30kg/m<sup>2</sup>) is associated with postoperative AKI after CABG [Tekeli 2016]. In the present study, MetS and obesity were shown to be independent risk factors for AKI after CABG (OR, 3.817; 95% CI, 2.048–7.115;  $P < .001$  and OR, 3.878; 95% CI, 2.148–7.001;  $P < .001$ , respectively). Multivariate logistic regression analysis revealed that DM (OR, 4.975;

95% CI, 2.707–9.145;  $P < .001$ ) also was another independent risk factor of AKI in the present study.

We compared the patients according to the severity of AKI and reported that the SCH group had a higher number of patients in RIFLE I and RIFLE F stages. Renal hemodynamics are demonstrated to be affected by thyroid hormones. Pre-renal effects of thyroid hormones are mediated by their influence on the renin-angiotensin system, cardiovascular system, and the renal blood flow. It is suggested that the intrarenal vasoconstriction may decrease renal blood flow and may lead to prerenal kidney injury [Klein 2001]. It is well known that CPB leads to low T3 syndrome. Iglesias et al. reported an association between AKI and low T3 syndrome, and they showed an improvement of renal function by an increase in serum T3 levels [Iglesias 2013]. These could explain the association of SCH and AKI in the present study. It is suggested that postoperative AKI requiring RRT has an overall mortality of 40–80% [Lassnigg 2000]. It has an independent effect on early mortality and morbidity and also the quality of life in the short- and long-term. There are studies concerning treatment modalities for lowering the need for RRT [Iglesias 2013]. Continuous RRT aims to treat AKI by maintaining hemodynamic stability, acid-base, and electrolyte balances in critically ill patients with a very high risk of mortality. The present study demonstrates that RRT was required in 2.97% of patients. Seven patients were in Group I, and three patients were in Group II; this result was statistically significant. None of the patients became hemodialysis dependent. There is not a consensus regarding the timing and type of RRT to apply. The decisions regarding these factors were made together with our nephrologists in this study [Kunt 2009; Bouman 2002].

The mean ICU time, length of hospital stay, and mean ventilatory support times were statistically longer in Group I. This could be due to the increased use of RRT in SCH patients. Postoperative renal dysfunction affects not only mortality, but also the quality of life. AKI plays a vital role in postoperative mortality and morbidity in cardiac surgery patients. The rate of RRT is suggested to be 6% in patients with a high prevalence of AKI [Uchino 2005]. Among the patients who developed AKI, RRT was applied to 46.7% of the patients in our study group with SCH and 7.1% in the euthyroid group, where the difference was statistically significant. The overall 30-day mortality was 2.1% ( $N = 7$ ) four patients in Group I and three patients in Group II, where the difference was statistically significant. All of the patients died due to low cardiac output and required RRT. Hemodynamic instability in SCH patients, due to hypotension, increased vascular resistance, and decreased sodium reabsorption might explain this result.

The main strength of the study was that we could achieve statistically significant differences with this small number of SCH patients compared with euthyroid patients. There are some limitations of the study. First, the study design is retrospective. Second, in the present study, we don't know the postoperative levels of FT4 and FT3, so it was not possible to compare the prognosis of SCH and patients converted to the euthyroid state.



## CONCLUSION

AKI after CABG results in various postoperative complications and leads to prolonged hospitalization, and eventually increased costs as well as the increased rate of mortality. SCH is a common risk factor that showed a significant predictive effect on morbidity and mortality after CABG. Therefore, preoperative evaluation of thyroid function may be important to predict AKI a requirement for RRT after CABG. SCH is a modifiable issue; if it is converted to euthyroid state and well-controlled, its dreadful effects after cardiac surgery might be controlled as well. Further, prospectively designed studies of thyroid hormone replacement in patients with SCH before cardiac surgery are warranted.

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