Original Paper

Prolonged Hyperglycemia and Renal Failure after Primary Percutaneous Coronary Intervention

Elena Izkhakov^a Zach Rozenbaum^b Gilad Margolis^b Shafik Khoury^b
Gad Keren^b Yacov Shacham^b

^aInstitute of Endocrinology, Metabolism, and Hypertension, Tel Aviv Sourasky Medical Center affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel;

^bDepartment of Cardiology, Tel Aviv Sourasky Medical Center affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Keywords

HbA1c · Glycated hemoglobin · Acute kidney injury · Acute myocardial infarction

Abstract

Background: There are limited data regarding the effect of long-standing hyperglycemia on the occurrence of acute kidney injury (AKI) in ST segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI). **Methods:** We retrospectively studied 723 STEMI patients undergoing primary PCI. Patients were stratified into two groups according to glycated hemoglobin (HbA1c) levels as a marker of prolonged hyperglycemia: those with HbA1c <7% and those with HbA1c ≥7%. Medical records were reviewed for the occurrence of AKI. **Results:** HbA1c levels ≥7% were found in 225/723 (31%) of patients. The occurrence of AKI was significantly higher among patients with HbA1c levels ≥7% (32/225, 14%) compared to patients with HbA1c levels <7% (32/498, 6%; $p = 0.001$). Patients with chronic kidney disease (CKD) and HbA1c ≥7% had an eight-fold increase in the incidence of AKI compared to patients with HbA1c <7% and no CKD (32 vs. 4%). In a multivariable regression model, HbA1c ≥7% was independently associated with AKI (OR 1.92, 95% CI 1.09–3.36, $p = 0.02$). **Conclusion:** HbA1c ≥7% was associated with a higher likelihood of AKI in STEMI patients treated with primary PCI.

© 2019 S. Karger AG, Basel

Drs. E. Izkhakov and Z. Rozenbaum contributed equally to this work. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Yacov Shacham, MD
Department of Cardiology, Tel Aviv Sourasky Medical Center
6 Weizman Street
Tel Aviv 64239 (Israel)
E-Mail kobyshacham@gmail.com

Introduction

Acute kidney injury (AKI) frequently complicates the course of ST segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) and is associated with adverse short- and long-term outcomes [1–4]. The worsening renal function may be a result of various factors, including contrast-induced AKI (CI-AKI) [5–7], reduced renal perfusion, and other metabolic factors [8–10]. Previous studies have shown that elevated glucose levels upon hospital admission increase the risk of contrast-induced nephropathy in patients undergoing elective [11, 12] and primary PCI [10, 13]; however, only limited data are present regarding the effect of long-standing hyperglycemia on AKI in STEMI patients undergoing primary PCI. In the present study we evaluated the association of long-term glycemic control (using glycated hemoglobin [HbA1c] as a marker of glucose control in the last 2–3 months) on the occurrence of AKI in a large cohort of STEMI patients treated with primary PCI.

Methods

Study Design

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

Study Population (Fig. 1)

Included were all patients admitted between January 2014 and August 2017 to the cardiac intensive care unit with a diagnosis of acute STEMI and treated with primary PCI. Patients were recognized as having diabetes mellitus (DM) if they had previously been diagnosed by a physician or if they received medication to lower blood glucose levels (oral antihyperglycemic agents or any extended-release insulin) [10, 14, 15]. A total of 210 patients in whom information regarding HbA1c was lacking were excluded from the analysis. We also excluded patients who died within 24 h of admission since we presumed there was insufficient time for AKI to occur, as well as patients requiring chronic peritoneal dialysis or hemodialysis treatment. The final study population consisted of 723 patients whose baseline demographics, cardiovascular history, clinical risk factors, treatment characteristics, and laboratory results were all retrieved from the hospital electronic medical records.

Study Procedure

The diagnosis of STEMI was established in accordance with published guidelines including typical chest pain history, diagnostic electrocardiographic changes (ST segment elevation >1 mm in two contiguous peripheral leads or >2 mm in two or more contiguous precordial leads or new left bundle branch), and serial elevation of cardiac biomarkers [14]. Primary PCI was performed on patients with symptoms lasting ≤12 h as well as in patients with symptoms lasting 12–24 h if the symptoms persisted at the time of admission and the admission electrocardiogram demonstrated persistent ST segment elevation. Critical state patients were defined as those mechanically ventilated or those in whom intra-aortic balloon counterpulsation was inserted. During the study period, none of these patients were treated with an Impella device or with extracorporeal membrane oxygenation. The contrast medium used in the procedures was iodixanol (Visipaque, GE Healthcare, Ireland) or iohexol (Omnipaque, GE Healthcare). Following coronary interventional procedures, physiologic (0.9%) saline was given intravenously to all patients at a rate of 1 mL/kg/h for 12 h after contrast exposure. In patients with overt heart failure, the hydration rate was reduced at the discretion of the attending physician. All patients underwent a screening echocardiographic examination within 48 h of admission. Left ventricular ejection fraction was calculated by the biplane method of disks (modified Simpson's rule). A 17-segment model was used for scoring the severity of segmental wall motion abnormalities. A random blood glucose level was measured on admission and thus represented the nonfasting level.

HbA1c levels were determined for all patients and included from blood samples taken within 48 h of hospital admission. Patients were stratified into two groups according to HbA1c levels: patients with HbA1c <7% and patients with HbA1c ≥7%. A cutoff point of 7% was chosen because it is the recommended target of glycemic control for type 2 DM to reduce complications [16].

Fig. 1. Study flowchart. HbA1c, glycated hemoglobin; STEMI, ST segment elevation myocardial infarction.

The serum creatinine (sCr) level was determined upon hospital admission and at least once a day during the cardiac intensive care unit stay and was available for all analyzed patients. The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation [17]. Chronic kidney disease (CKD) was defined as an admission eGFR of ≤ 60 mL/min/1.73 m² [18]. AKI was determined using the Kidney Disease: Improving Global Outcomes criteria [19] and defined as a sCr rise >0.3 mg/dL within 48 h of contrast exposure compared with admission sCr.

Statistical Analysis

All data were summarized and displayed as mean $\pm$ standard deviation for continuous variables and as number (percentage) of patients in each group for categorical variables. The p values for the categorical variables were calculated with the χ^2 test. Continuous variables were compared using the independent sample t test or with ANOVA. Identification of the independent predictors of AKI was done using the logistic regression model at the enter mode. We adjusted for age, sex, hypertension, left ventricular ejection fraction, critical state, heart failure, time to reperfusion, contrast volume, contrast volume/eGFR ratio, and eGFR ≤ 60 mL/min/1.73 m. A two-tailed p value <0.05 was considered significant for all analyses. All analyses were performed with the SPSS software (SPSS Inc., Chicago, IL, USA).

Results

The study population included 723 patients (mean age 61 ± 12 years, 81% males), 225 of whom (31%) had an HbA1c level $\geq 7\%$. The baseline characteristics of the patients according to HbA1c level are presented in Table 1. Patients with HbA1c levels $\geq 7\%$ were older and had more comorbidities, with significantly higher admission glucose levels, longer time to reperfusion, and higher C-reactive protein levels. Table 2 compares the sCr changes, the intravenous contrast volume applied, and the occurrence of AKI according to HbA1c levels. Patients having HbA1c levels $\geq 7\%$ had lower admission eGFR, were more likely to have CKD, and had higher peak sCr levels. The total volume of contrast medium did not differ statistically between the two groups. The occurrence of AKI was significantly higher among patients with HbA1c levels $\geq 7\%$ (32/225, 14%) compared to patients with HbA1c levels $<7\%$ (32/498, 6%) ($p = 0.001$).

In univariable analysis, the incidence of AKI was found to be related to baseline CKD. Among patients without CKD, the incidence of AKI in patients with HbA1c $\geq 7\%$ was two-fold

Table 1. Baseline characteristics of the 723 diabetic STEMI patients

Variable	HbA1c level		p value
	<7% (n = 498)	≥7% (n = 225)	
Age, years	60±12	63±12	0.005
Men	412 (83%)	174 (77%)	0.107
Diabetes mellitus	103 (21%)	198 (88%)	<0.001
Dyslipidemia	265 (53%)	156 (69%)	<0.001
Hypertension	220 (44%)	145 (64%)	<0.001
Smoker	244 (49%)	103 (46%)	0.469
Family history of CAD	139 (28%)	44 (20%)	0.02
Prior myocardial infarction	83 (17%)	64 (28%)	<0.001
Number of narrowed coronary arteries			
1	368 (75%)	123 (56%)	<0.001
≥2	130 (25%)	102 (54%)	
Atrial fibrillation	18 (4%)	12 (5%)	0.315
Time to reperfusion, min	517±448	620±555	<0.001
Critically ill	24 (5%)	16 (7%)	0.532
Admission glucose, mg/dL	140±43	253±92	<0.001
HbA1c level, %	5.8±0.4	8.7±1.7	<0.001
C-reactive protein, mg/L	12.1±27.1	20.4±41.2	<0.001
Peak CPK, U/L	1,205±1,468	1,082±1,145	0.687
Left ventricular ejection fraction	46±8	45±8	0.980

Values are presented as mean ± standard deviation or n (%). CAD, coronary artery disease; CPK, creatine phosphokinase; HbA1c, glycated hemoglobin; STEMI, ST segment elevation myocardial infarction.

Table 2. AKI, sCr changes, and intravenous contrast volume applied according to HbA1c levels

Variable	HbA1c level		p value
	<7% (n = 498)	≥7% (n = 225)	
eGFR, mL/min/1.73 m ²	82±29	72±25	<0.001
eGFR ≤60 mL/min/1.73 m ²	89 (18%)	58 (26%)	0.02
Admission sCr, mg/dL	1.16±0.25	1.15±0.37	0.274
Peak sCr, mg/dL	1.13±0.54	1.34±0.87	0.002
sCr change in hospital, mg/dL	0.08±0.34	0.13±0.44	0.02
Amount of contrast material amount, mL	155±419	149±63	0.29
AKI	32 (6%)	32 (14%)	0.001

Values are presented as mean ± standard deviation or n (%). AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; sCr, serum creatinine.

higher than in patients having HbA1c <7% (8 vs. 4, $p = 0.02$; Fig. 2). Among patients with baseline CKD, there was a numerical difference in the incidence of AKI between patients with HbA1c ≥7% versus patients with HbA1c <7% that did not reach statistical significance (32 vs. 19%, $p = 0.09$). Importantly, patients with CKD and HbA1c ≥7% had an eight-fold increase in the incidence of AKI compared to patients with HbA1c <7% and no CKD (Fig. 2).

We created a multivariable regression model in order to elucidate the risk factors associated with the development of AKI. In the model for the entire cohort (Table 3, model 1), an HbA1c level ≥7% was independently associated with AKI (OR 1.92, 95% CI 1.09–3.36, $p = 0.02$). Other risk factors associated with CI-AKI included age and the presence of CKD. The

Fig. 2. Incidence of AKI in patients with HbA1c <7% and ≥7% according to the presence of chronic kidney disease. AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

Table 3. Logistic regression models for the prediction of AKI

Correlate	Model 1 for entire cohort			Model 2 for patients without CKD		
	OR	95% CI	p value	OR	95% CI	p value
HbA1c ≥7%	1.92	1.09–3.36	0.002	2.16	0.97–4.79	0.004
Age	1.03	1.01–1.06	0.008	0.107	1.02–1.11	0.0001
Male sex	0.66	0.032–1.38	0.029	0.343	0.011–1.12	0.007
Hypertension	1.52	0.78–2.93	0.021	1.46	0.59–3.58	0.42
CKD	2.95	1.51–5.78	0.002			
Dyslipidemia	0.88	0.47–1.64	0.069	1.11	0.46–2.77	0.079
Past MI	1.46	0.79–2.70	0.19	2.11	0.92–4.89	0.08

AKI, acute kidney injury; CKD, chronic kidney disease; HbA1c, glycated hemoglobin; MI, myocardial infarction.

association of HbA1c level ≥7% with AKI was also maintained in a separate model (Table 3, model 2) for patients without CKD (OR 2.16, 95% CI 0.97–4.79, $p = 0.04$). In an analysis performed in the 683 patients who were not critically ill, HbA1c level ≥7% was also independently associated with AKI (OR 2.07, 95% CI 1.08–3.98, $p = 0.03$).

Discussion

This is the largest trial to date examining the association between HbA1c level and the occurrence of AKI among STEMI patients undergoing primary PCI. Our findings suggest that poor glycemic control (HbA1c ≥7%) was common (about 31%) among these patients and significantly associated with AKI.

Previous reports suggested that acute hyperglycemia was associated with a significant increase in CI-AKI following primary PCI [10, 13]. Marenzi et al. [10] demonstrated similar

rates of AKI development following primary PCI in type 2 DM patients with and without admission hyperglycemia. However, development of AKI was more common in nondiabetic patients with admission hyperglycemia compared to those without admission hyperglycemia.

There are several explanations for the relationship between hyperglycemia and deterioration of renal function. The outer medullary region in the kidney is particularly susceptible to ischemic injury because of its high metabolic activity and low prevailing oxygen tension [20]. The partial oxygen pressure of the outer medulla in the kidney is very low during normal function. Contrast media aggravate hypoxic injury to this region by increasing renal vascular resistance [21]. Hyperglycemia may lead to increased production of oxygen free radicals with increased oxidative stress and suppressed flow-mediated vasodilation, inducing medullary hypoxia and ischemia, thus exacerbating the deleterious effect of contrast medium [22, 23]. Furthermore, hyperglycemia may induce osmotic diuresis, resulting in volume depletion and increasing the risk for prerenal azotemia and contrast toxicity.

To date, only a few studies have examined the possible relationship between long-standing poor glycemic control and AKI. Yoshikawa et al. [24] reported a 5% increase in sCr and a decrease of 4 mL/min/1.73 m² in eGFR in patients with an HbA1c level $\geq 6.5\%$ compared to those with an HbA1c level $< 6.5\%$ following coronary computed tomography angiography. However, such a small change in the values neither fits the definition of AKI nor does it have any known clinical implications. An elevated HbA1c level ($\geq 7\%$) was not associated with a higher incidence of CI-AKI compared to an optimal HbA1c level ($< 7\%$) in patients with known type 2 DM undergoing elective coronary angiography [25]. In contrast, elevated HbA1c levels ($\geq 7\%$) were associated with a higher incidence of CI-AKI compared with optimal HbA1c levels ($< 7\%$) in type 2 DM patients with STEMI treated with primary PCI. However, both of these trials included only a small number of patients with known DM. Moreover, patients having CKD (with an eGFR of ≤ 60 mL/min/1.73 m²) were excluded, thus the effect of prolonged poor glycemic control on CI-AKI in this population could have not been assessed. Indeed, in the present cohort, patients with CKD and HbA1c $\geq 7\%$ had a ten-fold increase in the incidence of AKI compared to patients with HbA1c $< 7\%$ and no CKD, while the detrimental effect of long-term hyperglycemia was maintained after adjustment for the presence of CKD.

The results of the present study might be explained with the long and more marked effect of long-standing hyperglycemia on intrarenal mechanisms. Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction [26]. Other changes in intraglomerular hemodynamics include local activation of the renin-angiotensin system, biochemical derangements, proteinuria, and hypoxia in addition to the direct effect of hyperglycemia [27].

Our findings bear some important clinical implications. Among patients undergoing PCI, especially if nonemergent, HbA1c levels $\geq 7\%$ may point out those at high risk for CI-AKI and warrant prophylactic renal protection [28–30]. In addition, as 12% of patients without known DM had HbA1c $\geq 7\%$, it appears that a significant proportion of patients with an acute coronary syndrome may have occult type 2 DM. It appears that measurement of HbA1c levels should be considered, regardless of history of type 2 DM.

We acknowledge several important limitations of our study. This was a single-center retrospective and nonrandomized observational study and may have been subject to bias, even though we included consecutive patients and attempted to adjust for confounding factors using the multivariable regression model. The diagnosis of DM was considered if it had been previously diagnosed by a physician or if patients received medication to lower blood glucose levels. However, as some patients without known DM had elevated HbA1c levels, some of these nondiabetic patients actually had undiagnosed DM. The definition of the

Acute Kidney Injury Network criteria refers to sCr change within a time frame of 48 h. As the change in sCr can lag beyond this period due to delayed effects of contrast medium and drug, worsening of renal function might have occurred following hospital discharge in some patients, thus the true incidence of CI-AKI described in our study may have been underestimated. No information was present regarding the amount of postprocedural intravenous fluid the patients received. In addition, information on left ventricular end-diastolic pressure during cardiac catheterization, which would also help determine the fluid status of patients at time of acute STEMI, was not available as this is not performed routinely in our catheterization laboratory during primary PCI. Finally, as data regarding concomitant renin/angiotensin blockers and diuretics throughout hospitalization was not present in many patients, their effect on AKI development could not be assessed.

No information was present regarding the distribution of contrast medium between patients, thus sensitivity analysis to see whether the type of contrast medium affected the result could not be performed. Patients without information regarding HbA1c levels (not included in the present analysis) had less comorbidities, a fact which could have affected the rate of AKI reported.

In conclusion, in the present analysis we found that a HbA1c level $\geq 7\%$ was associated with a higher likelihood for AKI in STEMI patients treated with primary PCI.

Statement of Ethics

This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study. The study protocol was approved by the local institutional ethics committee with a waiver from informed consent (Institutional Board Review num: TLV-16-0224).

Disclosure Statement

The authors declare that no conflict of interest exists. This work received no funding or other financial support.

References

- Shacham Y, Leshem-Rubinow E, Steinvil A, Assa EB, Keren G, Roth A, et al. Renal impairment according to Acute Kidney Injury Network criteria among ST elevation myocardial infarction patients undergoing primary percutaneous intervention: a retrospective observational study. *Clin Res Cardiol*. 2014 Jul;103(7):525–32.
- Goldberg A, Hammerman H, Petcherski S, Zdoroviyak A, Yalonetsky S, Kapeliovich M, et al. In-hospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. *Am Heart J*. 2005 Aug;150(2):330–7.
- Parikh CR, Coca SG, Wang Y, Masoudi FA, Krumholz HM. Long-term prognosis of acute kidney injury after acute myocardial infarction. *Arch Intern Med*. 2008 May;168(9):987–95.
- Amin AP, Spertus JA, Reid KJ, Lan X, Buchanan DM, Decker C, et al. The prognostic importance of worsening renal function during an acute myocardial infarction on long-term mortality. *Am Heart J*. 2010 Dec;160(6):1065–71.
- James MT, Samuel SM, Manning MA, Tonelli M, Ghali WA, Faris P, et al. Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. *Circ Cardiovasc Interv*. 2013 Feb;6(1):37–43.
- Gurm HS, Dixon SR, Smith DE, Share D, Lalonde T, Greenbaum A, et al.; BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium) Registry. Renal function-based contrast dosing to define safe limits of radiographic contrast media in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol*. 2011 Aug;58(9):907–14.
- Seeliger E, Sendeski M, Rihal CS, Persson PB. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. *Eur Heart J*. 2012 Aug;33(16):2007–15.

- 8 Koreny M, Karth GD, Geppert A, Neunteufl T, Priglinger U, Heinz G, et al. Prognosis of patients who develop acute renal failure during the first 24 hours of cardiogenic shock after myocardial infarction. *Am J Med*. 2002 Feb;112(2):115–9.
- 9 Marenzi G, Assanelli E, Campodonico J, Lauri G, Marana I, De Metrio M, et al. Contrast volume during primary percutaneous coronary intervention and subsequent contrast-induced nephropathy and mortality. *Ann Intern Med*. 2009 Feb;150(3):170–7.
- 10 Marenzi G, De Metrio M, Rubino M, Lauri G, Cavallero A, Assanelli E, et al. Acute hyperglycemia and contrast-induced nephropathy in primary percutaneous coronary intervention. *Am Heart J*. 2010 Dec;160(6):1170–7.
- 11 Turcot DB, Kiernan FJ, McKay RG, Grey NJ, Boden W, Perdrizet GA. Acute hyperglycemia: implications for contrast-induced nephropathy during cardiac catheterization. *Diabetes Care*. 2004 Feb;27(2):620–1.
- 12 McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, et al.; CIN Consensus Working Panel. Risk prediction of contrast-induced nephropathy. *Am J Cardiol*. 2006 Sep;98(6 6A):27K–36K.
- 13 Shacham Y, Gal-Oz A, Leshem-Rubinow E, Arbel Y, Keren G, Roth A, et al. Admission Glucose Levels and the Risk of Acute Kidney Injury in Nondiabetic ST Segment Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention. *Cardiorenal Med*. 2015 Jun;5(3):191–8.
- 14 O’Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al.; American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013 Jan;61(4):e78–140.
- 15 Goyal A, Mehta SR, Gerstein HC, Díaz R, Afzal R, Xavier D, et al. Glucose levels compared with diabetes history in the risk assessment of patients with acute myocardial infarction. *Am Heart J*. 2009 Apr;157(4):763–70.
- 16 American Diabetes Association. Standards of medical care in diabetes – 2010. *Diabetes Care*. 2010 Jan;33 Suppl 1:S11–61.
- 17 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999 Mar;130(6):461–70.
- 18 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002 Feb;39(2 Suppl 1):S1–266.
- 19 Levin A, Warnock DG, Mehta RL, Kellum JA, Shah SV, Molitoris BA, et al.; Acute Kidney Injury Network Working Group. Improving outcomes from acute kidney injury: report of an initiative. *Am J Kidney Dis*. 2007 Jul;50(1):1–4.
- 20 Persson PB, Patzak A. Renal haemodynamic alterations in contrast medium-induced nephropathy and the benefit of hydration. *Nephrol Dial Transplant*. 2005 Feb;20 Suppl 1:i2–5.
- 21 Kim SJ, Salem MR, Joseph NJ, Madayag MA, Cavallino RP, Crystal GJ. Contrast media adversely affect oxyhemoglobin dissociation. *Anesth Analg*. 1990 Jul;71(1):73–6.
- 22 Kawano H, Motoyama T, Hirashima O, Hirai N, Miyao Y, Sakamoto T, et al. Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. *J Am Coll Cardiol*. 1999 Jul;34(1):146–54.
- 23 Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. 2006 Apr;295(14):1681–7.
- 24 Yoshikawa D, Isobe S, Sato K, Ohashi T, Fujiwara Y, Ohshima H, et al. Importance of oral fluid intake after coronary computed tomography angiography: an observational study. *Eur J Radiol*. 2011 Jan;77(1):118–22.
- 25 Akyuz S, Kemaloglu Oz T, Altay S, Karaca M, Yaylak B, Gungor B, et al. Association between Glycosylated Haemoglobin Level and Contrast-Induced Acute Kidney Injury in Patients with Type 2 Diabetes Mellitus. *Cardiorenal Med*. 2014 Aug;4(2):95–102.
- 26 Piconi L, Quagliaro L, Assaloni R, Da Ros R, Maier A, Zuodar G, et al. Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction. *Diabetes Metab Res Rev*. 2006 May–Jun;22(3):198–203.
- 27 Kanwar YS, Sun L, Xie P, Liu FY, Chen S. A glimpse of various pathogenetic mechanisms of diabetic nephropathy. *Annu Rev Pathol*. 2011;6(1):395–423.
- 28 Jia X, Fu X, Zhang J, Gu X, Xue L, Fan W, et al. Comparison of usefulness of simvastatin 20 mg versus 80 mg in preventing contrast-induced nephropathy in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Am J Cardiol*. 2009 Aug;104(4):519–24.
- 29 Khanal S, Attallah N, Smith DE, Kline-Rogers E, Share D, O’Donnell MJ, et al. Statin therapy reduces contrast-induced nephropathy: an analysis of contemporary percutaneous interventions. *Am J Med*. 2005 Aug;118(8):843–9.
- 30 Zhao JL, Yang YJ, Zhang YH, You SJ, Wu YJ, Gao RL. Effect of statins on contrast-induced nephropathy in patients with acute myocardial infarction treated with primary angioplasty. *Int J Cardiol*. 2008 Jun;126(3):435–6.