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The effect of lycopene on contrast-induced nephrotoxicity in diabetic patients undergoing coronary angiography

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Abstract

Introduction: Radiocontrast nephrotoxicity refers to one of the most prevalent and key complications in diabetic patients.

Objectives: This study was aimed to investigate the therapeutic and protective effect of lycopene on contrast-induced nephrotoxicity (CIN) in diabetic patients undergoing coronary angiography.

Patients and Methods: In this study, 113 patients who took lycopene with prevention of contrast induced kidney injury regime (lycopene group) or prevention of kidney injury regimen alone (regimen group) were investigated through medical records. Oral lycopene was administered 24 hours before to 72 hours after the angiography. Blood urea nitrogen (BUN), creatinine (Cr), and glomerular filtration rate (GFR) were assessed and recorded in a checklist. SPSS software was conducted for data analysis.

Results: At the baseline, there was no significant difference between the mean of urea, Cr, and GFR ($P>0.05$). However, after administration of lycopene, a significant difference between the mean BUN was observed among groups ($P<0.001$), with lower rate in the patients taking oral lycopene. Although the mean Cr decreased after the administration of oral lycopene, no statistically significant difference was seen ($P = 0.08$). The mean GFR was not significant different between the two groups of regimen and lycopene ($P=0.44$).

Conclusion: In patients with diabetes, taking lycopene for CIN may help improve some biochemical factors; nevertheless, its positive effect on the improvement of nephrotoxicity indices cannot be certainly determined.

Keywords: Lycopene, Nephrotoxicity, Coronary angiography, Radiocontrast agents, Diabetes mellitus

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Introduction

In recent decades, significant progress has been achieved in diagnostic and therapeutic methods. In some of these methods, imaging of body's blood vessels and internal organs is conducted by radiocontrast agents, in some patients leading to acute renal failure. The prevalence of contrast media nephrotoxicity in the general population undergoing coronary angiography is less than 2% (1). The preventive drugs' effect may be influenced by several factors. Therefore, studies on each of these drugs have been frequently conducted by changing the conditions of the studied patients. A review study in 2008 investigated 41 valid international studies on the prophylactic effects of fenoldopam, furosemide, theophylline, and N-acetyl cysteine (NAC) during 1999-2008 (2). However, patients with a history of chronic renal failure (about 20%-80%) and diabetes (about 40%) are at higher risk (3-7). It is worth noting that in individuals with diabetes, modular hypoxia is more severe, with more serious complications (8). The prevalence of contrast nephropathy in diabetic patients has also been reported up to 40% (9). Given the wide prevalence of diabetes in Iranian society, estimated at least 24% in the population over the age of 40 based on a study in 2009 (10), and it leads to a wide range of cardiovascular diseases requiring coronary angiography (11). On the other hand, nephropathy is one of the key and dangerous complications of diabetes, intensifying the problems in diabetic patients with coronary heart disease (12). In recent years, lycopene has attracted attentions and various studies have assessed its protective role in various diseases (13-15). On the other hand, the absence of an effective therapy for nephrotoxicity caused by contrast media may lead to short-term and long-term problems for the patient (16). Nevertheless, there are limited studies on the contrast nephropathy and although positive in these few studies, the role of this drug still requires further investigation and data increase.

Objectives

There is no similar study in this field in Iran. Hence, the present study is aimed at examining the therapeutic effect of lycopene on contrast-induced nephrotoxicity (CIN) in diabetic patients undergoing coronary angiography in humans.

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Implication for health policy/practice/research/ medical education

Taking lycopene for contrast-induced nephrotoxicity (CIN) in patients with diabetes may contribute to improve some biochemical factors.

Patients and Methods

Study design

This descriptive-analytical study was conducted on 113 diabetic patients who took lycopene with prevention of contrast induced kidney injury regime (lycopene group) or prevention of kidney injury regimen alone (regimen group). The data were collected through medical records. All patients were done coronary angiography. The selected patients had 20-80-year-old, with diabetes, heart disease, and without chronic and acute kidney disease, with creatinine (Cr) <1.5 (mg/dL) and glomerular filtration rate (GFR) >60 (mL/min). Based on the literature review, receiving lycopene, a natural ingredient in tomatoes, does not lead to any side effects for patients. Furthermore, the standard diet (appropriate fluid therapy) was performed in both groups. The lycopene group received lycopene in coronary angiography with 20-50 mL of Dixopaque 320 vial radiocontrast agent along with standard renal protection treatment (hydration and magnesium sulfate). The regimen group received 20- 50 cc of Dixopaque 320 vial radiocontrast agent along with standard renal protection treatment (hydration and magnesium sulfate). In the lycopene group, 25 mg/kg lycopene tablets made by 21st Century American Company were orally taken for 12 hours, 24 hours before to 72 hours after angiography. The variables assessed in this research included blood urea, Cr, and GFR. GFR was calculated according to the Cockcroft-Gault formula and recorded in a checklist designed to record the data.

Statistical analysis

SPSS version 23 software was employed to analyze the collected data. Quantitative variables were presented as mean ± standard deviation (SD). The normal distribution of demographic variables in the two groups was assessed by independent *t* test and paired *t* test was used to test the variables and final data at baseline and 72-hour follow up. The chi-square test was also employed. Further, $P<0.05$ was considered as a significant difference.

Results

In total, 113 patients were categorized in lycopene and regimen groups of 53 and 60, respectively. Out of 113 patients, 71 were female (62.8%) and 42 were male (37.2%) and 60.4% of the lycopene group and 65% of the regimen group were female. According to chi-square test, the groups did not significantly differ regarding gender. The mean age of the lycopene group was 59.3 ± 9.05 in the range of 49-80 years. In the regimen group, the mean age was 61.8 ± 2.8 and ranged 49-80 years. Independent t-test revealed no significant difference between the two groups regarding age ($P=0.135$; Table 1). Comparing all patients' performance variables at the baseline showed no significant difference between the two groups before the use of lycopene. Comparing all patients' performance 72 hours after the administration of lycopene using paired t-test showed a significant difference in the mean Blood urea nitrogen (BUN) ($P<0.001$). However, there was no significant difference between the mean Cr and GFR ($P>0.05$).

Table 1. Comparison of age between lycopene and regimen groups

Variable		Mean	SD	*P* value
Age (y)	Lycopene	59.3	9.05	0.135
	Regimen	61.8	2.8	

Discussion

The current study was carried out to assess the effect of lycopene on CIN in patients with diabetes. In this study, it was revealed no significant difference between the means of the studied indicators at the onset of the study and before the intervention. However, after administration of lycopene, a significant difference was observed between the means of BUN in the intervention and the control groups. Although the mean Cr declined after the use of lycopene, no statistically significant difference was found. On the other hand, there no significant difference was observed between the two groups in respect of the mean GFR.

In a study by Buyuklu et al, four groups of seven rats were investigated, including control group, group receiving lycopene only (4 mg/kg/day for 16 days), group receiving radiocontrast with the protocol (10 mg/kg furosemide + 10 mg/kg indomethacin + 10 ml/kg iomeprol with 24-hour dehydration, and the group receiving radiocontrast and lycopene. In their study, it was revealed that renal impairment was significantly declined in the group receiving radiocontrast and lycopene compared to the one receiving radiocontrast only and histological factors were better in the lycopene groups than in the other two groups (17). Another study reported that lycopene reduced the formation rate of ribose induced advanced glycation end product besides preventing glycation-induced diabetic nephropathy, therefore it neutralizes oxidative stress and improves kidney function through inducing its anti-inflammatory properties. In general, lycopene prevents diabetic nephropathy and improves renal function (12).

Another study assessing the protective effects of lycopene against streptozotocin-induced nephrotoxicity in rats reported that lycopene led to increased weight, decreased blood sugar concentration, increased high-density lipoprotein cholesterol levels, declined low-density lipoprotein cholesterol level, and decreased urinary protein. On the other hand, it provided protection against oxidants, enhanced the bioactivities of superoxide

dismutase and glutathione peroxidase, and decreased malondialdehyde. Moreover, lycopene neutralized the precursors of cell necrosis in all diabetic rats (17). Another study by Li et al on the impact of lycopene on improving kidney function in rats with diabetic kidney disease indicated that treatment of diabetic rats with lycopene declined blood urea, urea protein, and 24-hour Cr. Oxidative stress of their kidneys reduced, too (18). Studies examining the effects of lycopene on nephrotoxicity caused by various toxins and drugs reached similar results. For example the previous study on the effect of lycopene on kidney toxicity caused by mercuric chloride, concluded that lycopene prevented the increased plasma Cr, it reduced necrosis and improved glutamine peroxidase and catalase, while declining superoxide dismutase activity.

Due to its antioxidant properties, lycopene prevents nephrotoxicity caused by mercuric chloride. In another study (18), it was reported that cisplatin injection into rats led to nephrotoxicity, declined GFR, and increased Cr and plasma urea. Besides, it resulted in renal dysfunction associated with increased concentrations of malondialdehyde in renal tissue. The findings of this study indicate that taking lycopene before or after cisplatin administration leads to significant protection of kidneys against nephrotoxicity after the administration of cisplatin, besides improving blood counts in rats (19). Furthermore, in the study by Dogukan et al, the Cr and plasma urea levels in the cisplatin group with lycopene were significantly lower than the cisplatin group alone after the development of nephrotoxicity. In addition, lycopene significantly inhibited the increase in malondialdehyde and declined lipid peroxidation in rats. Ultimately, they confirmed the protective role of lycopene against nephrotoxicity following the use of cisplatin (20). In a study by Erman et al on an animal model, rats were investigated in four groups of control, lycopene, cisplatin, and cisplatin with lycopene. Following nephrotoxicity, it was revealed that taking lycopene after cisplatin administration reduces the serum levels of BUN, Cr, and other studied biomarkers and significantly protects the kidneys against the consequences of cisplatin (19).

A study to determine the short-term protective effect of lycopene was conducted on ischemia-reperfusion injury in rat kidney. Following the induction of nephrectomy and perfusion ischemia in rats, their blood samples were taken and assessed for renal factors. At the stage after renal ischemia, a significant difference was found between the two groups in terms of sodium levels. Furthermore, the pathology score of malondialdehyde, glutathione, and catalase in the control group was higher than that in the lycopene group. Hence, lycopene has a protective effect on renal damage and its related surgeries (21). In general, antioxidant compounds may decline the cisplatin-induced nephrotoxicity risk. As this study and other studies revealed, as an antioxidant, lycopene is involved in declining oxidative stress and preventing cancer (22).

Contrast media nephrotoxicity has a complex pathophysiology. Intravascular injection of contrast media nephrotoxicity creates an immediate biphasic hemodynamic response in the kidney. Then, rapid and short-term dilation of renal arteries initially result in enhanced renal blood flow, followed by long-term vasoconstriction with increased renal artery resistance and declined renal blood flow. Extra-renal vessels under transient vasoconstriction are generally followed by a stable decrease in peripheral vascular resistance (23). These hemodynamic changes result in reduced GFR and renal ischemia rate, particularly in the renal medulla. Moreover, under normal conditions, the outer part of the medulla receives little oxygen. Prostaglandins, nitric oxide (NO), and adenosine continuously regulate medullary tubular transport activity and restrict oxygen supply through increasing peripheral blood flow and decreasing tubular transport (7). For instance, reduced NO production in the vasa recta provides the conditions for hypoxia (11). Moreover, radiocontrast media cause osmosis, in turn enhancing the water inflow and ultimately increasing renal reabsorption in the diuretic loop, again in turn increasing energy and oxygen consumption and finally exacerbating modular hypoxia (24,25). Modular hypoxia results in reactive oxygen species formation (18,26), directly damaging endothelial tubes and blood vessels, in addition to causing hypoxia of renal parenchymal cells (7,11,18). Furthermore, radiocontrast media themselves have cytotoxic properties and they may lead to endothelial cell and renal tubular necrosis (17). Thus, if case of any problem with any of these protective mechanisms, it will result in modular hypoxia (27).

Lycopene reduces the side effects of many chronic diseases such as diabetes (7), hence in diabetic patients, it may enhance insulin levels, decrease blood sugar, and improve blood lipids, thus playing a significant role in reducing the diabetes complications (26). Nevertheless, based on the present study, the questionable results may be justified by the association of diabetes with nephrotoxicity in this study, since nephropathy refers to one of the fundamental and dangerous complications of diabetes doubling the difficulties in diabetic patients with coronary heart disease (12).

Further biochemical factors are recommended to be investigated in future studies, besides considering the standards for hypersensitivity and accelerated nephrotoxicity. It is also suggested that longer-term studies be carried out to assess the impact of lycopene on patients' long-term prognosis in addition to determining the possible unknown interactions. Moreover, future studies are recommended compare different compounds as a useful measure for assessing the antioxidants' effectiveness on nephrotoxicity.

Conclusion

Taking oral lycopene for CIN in patients with diabetes

may contribute to improve some biochemical factors; however, the positive effect of lycopene on improving nephrotoxicity indices cannot be certainly explained. Hence, further research is required in this field and its effect should be studied in a longer period.

Limitations of the study

One of the limitations of this study was the need for almost long-term follow-up of the patients and cooperation of as many patients as possible to meet large sample size.

Authors' contribution

Conceptualization: LM.
Methodology: LM.
Validation: FG.
Formal analysis: FG.
Investigation: AB.
Resources: FG.
Data curation: FA.
Writing—Original Draft Preparation: MM.
Writing—Review and Editing: MM.
Visualization: FA.
Supervision: FA.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Shahrekord University of Medical Sciences approved this study (IR.SKUMU.MSP.REC.1395.226). Accordingly, written informed consent was taken from all participants before any intervention. This study was conducted as the M.D., thesis of Farzad Abkhou at the department of internal medicine of this university. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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