Dear Editor,

We read with interest the article by Tabatabaei and colleagues in the past issue of the Iranian Journal of Kidney Diseases. Thalassemia is one of the most common hemoglobinopathies in the world, and cardiovascular complication is a major cause of mortality and morbidity in this disease. In hemolytic diseases, such as sickle cell trait and thalassemia, there is systemic vasculopathy. Many investigations have revealed change of elastic properties of great arteries in patients with \( \beta \)-thalassemia major. Gedikli and colleagues, in a case-control study, showed that \( \beta \)-thalassemia major patients compared with healthy control subjects had significantly increased aortic diameters, lower mean aortic strain and distensibility that is associated with ferritin level. They also had higher mean aortic stiffness index related to platelet count. Abdominal aorta stiffness is also detected in \( \beta \)-thalassemia major and it is correlated with left ventricular mass indexes.

The pseudoxanthoma elasticum-like syndrome is reported in \( \beta \)-thalassemia major patients with higher prevalence than in general population. This finding is evidence of elastic tissue injury in these subjects. In \( \beta \)-thalassemia major, endothelial dysfunction is one of the fundamental pathophysiologic mechanisms that play a role in progression of cardiovascular involvements. Many studies showed there is an endothelial dysfunction in different vascular beds in these patients. Gullu found that diastolic peak flow velocity of the left anterior descending coronary artery was significantly higher in the \( \beta \)-thalassemia major group at baseline, however, coronary flow reserve, (reflecting of microvascular function, is impaired and is significantly lower than control group. He reported that carotid intima media thickness, evidence of early stage of atherosclerosis, is higher in \( \beta \)-thalassemia major group than controls.

Patients with \( \beta \)-thalassemia major showed an impairment of hyperemic response of brachioradial artery whereas glyceryl trinitrate–mediated dilation was preserved. They had greater carotid artery stiffness and brachioradial artery pulse wave velocity. These changes may reduce mechanical efficiency of the heart.

Molecular mechanisms of endothelial dysfunction recently are investigated. Alteration of nitric oxide synthesis and consumption is one of the most important hypotheses. During hemolysis packaged hemoglobin released from red blood cell into plasma and it rapidly reacts with nitric oxide. This provoke consumption of nitric oxide and reduction of concentration of this important vasoactive component. Inflammation is another cause of endothelial dysfunction, levels of serum interleukin-6, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1 can be increased in patients with \( \beta \)-thalassemia major.

Oxidant biomarkers are increased in patients with hemolytic anemia. Upregulation of antioxidant gene in response to oxidative stress even in young patients is reported. The hypercoagulable state is beside play roles in endothelial dysfunction and others vasculopathy phenomena in hemolytic conditions. The microparticles originating mainly from activated platelets and erythrocytes may provoke this condition. The platelet and erythrocyte-derived microparticles are increased in sickle cell disease patients. Their levels are significantly associated with sickling crisis, pulmonary hypertension, as well as severity of hemolysis, fibrinolysis, and iron overload. Moreover, D-dimer and von Willebrand factor antigen levels are elevated in sickle cell disease compared with controls. Likewise in people with essential hypertension, high levels of microparticles are detected that may contribute to the generation and perpetuation of a thrombotic stats.
Autonomic dysfunction and subclinical type of this abnormality are reported in β-thalassemia major patients. Heart rate variability, a marker of cardiac autonomic balance, is depressed in β-thalassemia major patients and it is significantly correlated with hemoglobin level.

Conventional atherosclerosis risk factors are changed, but extent and aspect of changes are anomalous. Some studies showed that β-thalassemia major patients have lower total cholesterol and high-density lipoprotein cholesterol and higher fraction of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol in compared with normal population. These alternations may be due to hepatic damage and anemia or change of lipid oxidation. Noteworthy in beta-thalassemia intermediate patients, total cholesterol, high-density and low-density lipoprotein cholesterol are lower compared with β-thalassemia major patients and normal population.

Blood pressure alteration is another interesting issue that is recently attracting attention. Some researchers showed that mean blood pressure, diastolic blood pressure and systolic blood pressure are lower in compared with normal population. Hypertensive individuals with beta thalassemia trait have better ambulatory blood pressure profile compared to nonanemic and anemic hypertensives patients.

In the study by Tabatabaie and coworkers, a relatively high prevalence of elevated blood pressure (16.7%) and no dipper statuses (56.7%) were reported in β-thalassemia major patients. These findings may be consequent to arterial stiffness, endothelial dysfunction, and autonomic neural dysfunction. Further case-control studies with long-term follow-up are required for evaluation of frequency and importance of blood pressure in β-thalassemia major individuals.

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REFERENCES

Dear Editor,

The recently published article by Sheela and colleagues in the *Iranian Journal of Kidney Diseases*, entitled “Effect of silymarin on streptozotocin-nicotinamide-induced type 2 diabetic nephropathy in rats,” had some interesting points that need to be explained more. In an experimental investigation, they found silymarin-treated groups showed significantly lower levels of blood glucose, glycosylated hemoglobin, urine volume, serum creatinine, serum uric acid, and urine albumin, when compared to the diabetic control group. In histopathological examination, they found a protective effect of silymarin, too. The authors concluded that silymarin had protective effects for kidneys affected by type 2 diabetes mellitus. They suggested that if the safety and efficacy of this herb is confirmed in human studies, silymarin would be a good medication to prevent nephropathy-induced premature death in diabetic patients.

The first question is what the clinical significance of this experimental study is. To answer, I refer to our recently published study on silymarin in rats. We aimed to study the protective properties of silymarin and deferoxamine against iron dextran-induced renal iron deposition in male rats. We studied rats, which were allocated to 6 groups and received iron dextran (200 mg/kg) for a period of 4 weeks every other day, but at the beginning of week 3, they also were subjected to a 2-week (every other day) treatment with vehicle (group 2, positive control), silymarin (200 mg/kg; group 3), deferoxamine (50 mg/kg; group 4), silymarin (400 mg/kg; group 5), and a combination of silymarin and deferoxamine (200 and 50 mg/kg, respectively; group 6). The results of this study showed that silymarin and deferoxamine treatments reduced the intensity of the kidney iron deposition, but only in the silymarin group, a significant reduction in kidney iron deposition was observed. We concluded that silymarin was a nephroprotective agent against injurious insult of iron deposition in the kidneys of animal models.

While, nephropathy is one of the most important complications of diabetes mellitus, I would like to mention a few points about the study conducted by Sheela and colleagues. In type 2 diabetes, metformin has been widely used for the treatment blood glucose elevation. Recently, attention has been made toward the possible kidney protective properties of metformin. Morales and coworkers observed that gentamicin-induced renal tubular injury was attenuated by metformin. To find the potential efficiency of metformin to renal protection against gentamicin-induced acute renal injury and also to examine whether postpone treatment with metformin in acute kidney injury, exerts similar benefits on gentamicin-renal toxicity in rats, we conducted a study on Wistar rats. We found that metformin was able to prevent and attenuate gentamicin-induced acute kidney injury. Hence, it might be beneficial in patients under treatment with this drug. More recently, to test the efficacy of co-administration of garlic extract and metformin for prevention of gentamicin-induced renal toxicity in Wistar rats, we conducted another study on 70 male Wistar rats, while we also showed the renoprotective efficiency of garlic juice alone in another study, too. The result of this study demonstrates that metformin and garlic juice or their combination has both curative and protective effects against gentamicin nephrotoxicity. Likewise to these studies, silymarin extract could safely be used together with metformin to increase the antioxidant potency and better renoprotection beyond, the control of diabetes, while most of