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Antioxidant and Antithrombotic Therapies for Diabetic Kidney Disease

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With an increasing incidence, diabetic kidney disease (DKD) has been the leading cause of chronic kidney disease and end-stage renal disease, and conventional therapies did not change this situation. This study intended to review and analyze the antioxidant and antithrombotic treatments of DKD for seeking novel therapeutic strategies. Relevant articles involved with antioxidant and antithrombotic treatments in DKD were retrieved and analyzed via systematic assessment. Meta-analysis showed that pancreatic kallikrein definitely reduced glycated hemoglobin in DKD patients (mean difference, 0.36%; 95% confidence interval, 0.08% to 0.63%; P = .01). Apart from the classic agents such as aspirin, novel drugs such as pancreatic kallikrein, sulodexide, and especially the traditional Chinese medicine including Tripterygium wilfordii and lumbrukinase, exert beneficial effects in DKD patients. Antioxidant and antithrombotic treatments are beneficial for DKD patients and represent promising therapeutic strategies in the future.

INTRODUCTION

Diabetes mellitus (DM) is one of the most common metabolic diseases in adults and a serious global health burden.1 It is estimated that more than 382 million people suffer from DM worldwide and the number is expected to reach 592 million by 2035.2 The development of DM is closely associated with systemic damages to microvessels,3 resulting in a series of complications, which significantly affect the mortality and prognosis.4

Among diabetic complications, diabetic kidney disease (DKD) accounts for a significant proportion and has been the leading cause of chronic kidney disease and end-stage renal disease as well.5 With the increasing morbidity and extension of lifespan as a results of advancement in therapies in DM, the number of patients with DKD is rising rapidly.6 Approximately 20% to 30% of patients with type 1 DM and 40% of patients with type 2 DM will eventually develop DKD.7 In the United States, 44% of newly diagnosed end-stage renal disease patients are closely related to DKD.8

End-stage renal disease is not inevitable for DKD patients.9 With effective control of blood pressure and glycemia, mortality due to diabetic complications has decreased significantly among DKD patients and a better prognosis has been achieved. However, DKD still plays a major role in the causes of chronic kidney disease and end-stage renal disease. Thus, it is urgent to seek novel therapeutic strategies to maximally delay progression for DKD patients. The present study is intended to review and assess the efficacy of antioxidant and antithrombotic therapies in DKD treatment.

ANTIOXIDANT THERAPIES

Mechanism of Action

Oxidative stress caused by long-term hyperglycemia is closely related to the progression of DKD and risks of cardiovascular diseases.10-12 Advanced glycation end products, including
glycosylated lipids, proteins, and nucleic acids, can be peroxidized and accumulate in glomerulus, contributing to mesangial proliferation and glomerular sclerosis. Expression of antioxidant enzymes, including superoxide dismutase and glutathione peroxidase, can be inhibited by aldose reductase in hyperglycemia. Subsequent imbalance in oxidation-antioxidant system is responsible for the tissue damages. Simultaneously, activated cytokines, such as platelet-derived growth factor, intercellular adhesion molecule-1, and transforming growth factor-β1, promote the proliferation in basement membrane thickness and mesangial matrix. Systematic reviewing the literature, we concluded that Tripterygium wilfordii and pancreatic kallikrein are the most promising agents in antioxidant therapies for DKD.

**Tripterygium Wilfordii**

Tripterygium wilfordii is a traditional Chinese herbal medicine and is widely used in therapies of tumor and autoimmune diseases. Similar to glucocorticoids, Tripterygium wilfordii inhibits cellular and humoral immunity. However, Tripterygium wilfordii has much lower influence on blood pressure and glycaemia compared with glucocorticoids, which makes it its unique feature in treatment of DKD. Choi and colleagues showed that extracts from Tripterygium wilfordii significantly reduced cytoplasmic oxidation and inhibited damages in cellular morphology and DNA induced by hydrogen peroxide in human dopaminergic cells, suggesting that Tripterygium wilfordii is able to resist oxidative stress due to hydrogen peroxide. In addition, Tripterygium wilfordii therapies contribute to the upregulation of expression of superoxide dismutase and glutathione peroxidase, both being important factors in antioxidation. A clinical study from China showed that Tripterygium wilfordii inhibited the lesions in podocytes and significantly decreased albuminuria in DKD patients. Hepatotoxicity and sexual inhibition may occur among the patients with long-term use of Tripterygium wilfordii, which needs to be monitored periodically, and if necessary, its dose should be reduced or it should be stopped.

**Pancreatic Kallikrein**

Kallikrein is one of the vital factors in kallikrein-kinin system (KKS) which plays a critical role in renal hemodynamics. It is a serine endopeptidase consisting of 238 amino acids and pervasively distributed in tissues. Activated kallikrein facilitates the hydrolysis of kininogens into kinins which exert biological effects in KKS. It is promptly inactivated by several peptidases including angiotensin I-converting enzyme, endothelin converting enzyme, and neprilysin. Among these kinins, bradykinin exerts the major physiological effects via combination with bradykinin receptors. Though the renoprotective effects of KKS for DKD have been confirmed in series of animal models, clinic trials of multicenter and large sizes are needed for evaluating its efficacy in the human body.

**Effects on urinary albumin excretion.** Pancreatic kallikrein may significantly reduce urinary albumin excretion. Bodin and coworkers showed that in kallikrein-deficient mice, the urinary albumin excretion was more than 2-fold higher than in wild-type littermates 1 month after DM induction. In fact, stimulation of bradykinin receptors activates nitric oxide synthesis in endothelial cells, reducing DNA damages and senescence induced by reactive oxygen species. In addition, synthesis of prostaglandins, especially prostacyclin, induced by KKS, may decrease the production of reactive oxygen species and prevent apoptosis of tubular cells.

**Effects on glycosylated hemoglobin.** Kallikrein improves insulin sensitivity and promotes glucose intake, partially due to KKS-induced improvement in hemodynamics and substrates exchange across the cytomembrane. On the other hand, the effects of insulin on promoting glucose utilization can be partially reduced by kallikrein inhibitors. We performed a meta-analysis to assess the effects of pancreatic kallikrein on glycosylated hemoglobin in patients with DKD. To the best of our knowledge, this is the first meta-analysis of effects of pancreatic kallikrein on glycosylated hemoglobin. The screening process of articles is shown in Figure 1 and the characteristics of included articles are listed in Table 1. All of the participants included in the control groups were treated with valsartan at a dose of 80 mg/d to 160 mg/d on the basis of conventional therapies. While participants in experimental groups were additionally treated with pancreatic kallikrein, at an intramuscular dose of 40 U/d or an oral dose of 120 U/d to 240 U/d. The meta-analysis
showed a definite role of pancreatic kallikrein in the decreases of glycosylated hemoglobin (mean difference, 0.36%; 95% confidence interval, 0.08% to 0.63%; \( P = .01 \)), as shown in Figure 2.

**Synergistic effects with renin-angiotensin system antagonists.** It has been proved that angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers exert synergistic effects with KKS. The therapeutic efficacy of angiotensin-converting enzyme inhibitors is attributed partially to its ability in inhibiting kinin degradation.\(^{45}\) The plasma bradykinin levels can be increased by angiotensin II receptor blockers with an extent of 2-folds in DKD patients associated with hypertension,\(^{46}\) which is advantageous for KKS to exert renoprotective effects.

**ANTITHROMBOTIC THERAPIES**

With significant changes in hemodynamics, which is commonly called *prethrombotic state*, the thrombotic risk is much greater among DKD patients.\(^{47}\) In diabetic state, the increased production of cytokines, such as thromboxane A2, platelet activating factors, and thrombin, contributes to the activation of platelets and meanwhile the excessive expression of platelet surface adhesion molecules and receptors is directly associated with high platelet aggregation.\(^{48}\) In addition, hypercoagulation, endothelial lesions and depressed fibrinolysis are also involved with the thrombotic risks.\(^{49,50}\) The activated platelets and its procoagulant activity play important roles in the progression of DKD and incidence of complications.\(^{51}\) Clinical trials have shown the beneficial effects of antithrombotic therapies for DKD patients as it inhibits the formation of thrombus, reduces albuminuria, stabilizes kidney function, and finally, improves outcomes for DKD patients.\(^{52,53}\)

**Lumbrukinase**

Lumbrukinase is a group of fibrinolytic and thrombolytic enzymes extracted by Mihara and coworkers from the earthworm species, *Lumbricus rubellus*, in Japan in 1991.\(^{54}\) With a molecular weight

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>DKD Stage</th>
<th>Number of Participants</th>
<th>Mean Change in Hemoglobin A1c, %</th>
<th>Follow-up, mo</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cai(^{34})</td>
<td>2010</td>
<td>Early</td>
<td>Experimental 36, Control 35</td>
<td>0.80 ± 0.11, 0.80 ± 0.11</td>
<td>3</td>
<td>Pancreatic kallikrein and valsartan in the experimental groups and valsartan in the control groups.</td>
</tr>
<tr>
<td>Chen and Chen(^{35})</td>
<td>2007</td>
<td>Early</td>
<td>Experimental 26, Control 25</td>
<td>3.00 ± 0.27, 2.40 ± 0.28</td>
<td>3</td>
<td>Valsartan in the control groups.</td>
</tr>
<tr>
<td>Du et al(^{36})</td>
<td>2012</td>
<td>Early</td>
<td>Experimental 36, Control 32</td>
<td>0.07 ± 0.16, 0.02 ± 0.19</td>
<td>1</td>
<td>Valsartan in the control groups.</td>
</tr>
<tr>
<td>Fu and Wang(^{37})</td>
<td>2013</td>
<td>Early</td>
<td>Experimental 45, Control 45</td>
<td>-2.80 ± 0.4, -2.90 ± 0.22</td>
<td>6</td>
<td>Valsartan in the control groups.</td>
</tr>
<tr>
<td>Lu and Zhang(^{38})</td>
<td>2009</td>
<td>Early</td>
<td>Experimental 35, Control 35</td>
<td>1.60 ± 0.28, 1.00 ± 0.28</td>
<td>3</td>
<td>Valsartan in the control groups.</td>
</tr>
<tr>
<td>Ren et al(^{39})</td>
<td>2011</td>
<td>Advanced</td>
<td>Experimental 44, Control 44</td>
<td>2.02 ± 0.38, 1.86 ± 0.33</td>
<td>3</td>
<td>Valsartan in the control groups.</td>
</tr>
<tr>
<td>Shi et al(^{40})</td>
<td>2003</td>
<td>Advanced</td>
<td>Experimental 19, Control 17</td>
<td>0.95 ± 0.12, 0.35 ± 0.07</td>
<td>3</td>
<td>Valsartan in the control groups.</td>
</tr>
<tr>
<td>Sun et al(^{41})</td>
<td>2010</td>
<td>Early</td>
<td>Experimental 32, Control 30</td>
<td>0.70 ± 0.44, 0.30 ± 0.32</td>
<td>6</td>
<td>Valsartan in the control groups.</td>
</tr>
<tr>
<td>Wang et al(^{42})</td>
<td>2011</td>
<td>Early</td>
<td>Experimental 30, Control 30</td>
<td>0.20 ± 0.19, 0.10 ± 0.13</td>
<td>6</td>
<td>Valsartan in the control groups.</td>
</tr>
<tr>
<td>Wu(^{43})</td>
<td>2007</td>
<td>Advanced</td>
<td>Experimental 29, Control 29</td>
<td>1.30 ± 0.23, 1.30 ± 0.23</td>
<td>3</td>
<td>Valsartan in the control groups.</td>
</tr>
<tr>
<td>Yang(^{44})</td>
<td>2005</td>
<td>Early</td>
<td>Experimental 26, Control 24</td>
<td>2.18 ± 0.19, 1.87 ± 0.05</td>
<td>4</td>
<td>Valsartan in the control groups.</td>
</tr>
</tbody>
</table>

*DKD indicates diabetic kidney disease.
†Interventions were pancreatic kallikrein and valsartan in the experimental groups and valsartan in the control groups.
of 20,000 D, the enzyme is thermostable and displays in a broad optimal pH range. In recent years, lumbrukinase has been widely used in ischemic encephalopathy, coronary heart disease, DM, and deep vein thrombosis for its antithrombotic activity. The enzyme is able to directly dissolve fibrinogen and fibrin; moreover, it facilitates the conversion of plasminogen into plasmin by activation of endogenous tissue plasminogen activator and subsequently dissolving fibrin clots. The enzyme mechanism of action is shown in Figure 3.

Sun and colleagues showed that the downregulation of matrix metalloproteinase-2 and matrix metalloproteinase-9 and induction of collagen IV were significantly attenuated by lumbrukinase in streptozotocin-induced diabetic rats, suggesting the effect of lumbrukinase on alleviating glomerulosclerosis and tubulointerstitial fibrosis. Clinic trials showed that lumbrukinase significantly decreased urinary albumin excretion among DKD patients, as shown in Table 2. Compared with traditional anticlotting drugs (eg, urokinase, streptokinase, and tissue plasminogen activator), lumbrukinase is very specific to fibrin and it does not result in severe bleeding. As an agent that can be absorbed from intestinal mucosa and keep its fibrinolytic and proteolytic activities, it avoids administration via the intravenous route,

### Table 2. Studies of the Effect of Lumbrukinase on Urinary Albumin Excretion (UAE) in Patients With Diabetic Kidney Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Follow-up, wk</th>
<th>Number of Participants</th>
<th>Intervention</th>
<th>Mean Change in UAE, mg/24 h</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ge⁶⁰</td>
<td>2010</td>
<td>8</td>
<td>18</td>
<td>25</td>
<td>Lumbrukinase Placebo</td>
<td>38.00 ± 22.92 23.00 ± 13.06 &lt; .001</td>
</tr>
<tr>
<td>Sun and Han⁶¹</td>
<td>2003</td>
<td>2</td>
<td>11</td>
<td>11</td>
<td>Lumbrukinase Alprostadil</td>
<td>97.95 ± 10.76 61.97 ± 17.14 &lt; .001</td>
</tr>
</tbody>
</table>

*P values were calculated by the Welch 2-sample t test, for assessment of efficacy differences between the experimental and control groups.
which is used in traditional antithrombotic drugs.64

No adverse effects on the functions of cardiovascular vessels or the liver and kidney have been reported yet.65 More large-scale rigorous clinical trials are needed for more convincing evidence of its application in DKD patients.

**Aspirin**

Aspirin is one of antiplatelet agents with the longest histories, and it has been widely used in therapies of cardiac-cerebrovascular diseases, venous thrombosis, and inflammatory states. However, research of utilization of aspirin in DKD treatment is still relatively insufficient and its efficacy for DKD is not very clear. Yet it is certain that for patients with DKD, aspirin does not have significant benefits in reducing risks of cardiovascular death, stroke, and myocardial infarction.66,67

However, there are studies supporting its use in DKD treatment for its effects on renoprotection. Treatment with aspirin may stabilize kidney function via reducing platelet hypersensitivity and the production of thromboxanes, which in turn decreases the constrictor activity in the glomerular vessels and improves the renal microcirculation.53 For patients with DM, aspirin therapy is beneficial in reducing risk of DKD,68 while for DKD individuals, it significantly reduces urinary protein.69,70 Makino and colleagues showed that aspirin inhibited upregulation of connective tissue growth factor and transforming growth factor-β induced by hyperglycemia in streptozotocin-induced DKD rats, which affected mesangial expansion and kidney sclerosis.71 No adverse event reports of aspirin have been recorded in the DKD treatment yet, and its application in DKD patients needs further experimental and clinical evaluation.

**Sulodexide**

Sulodexide is a group of highly purified glycosaminoglycans extracted from porcine intestine mucosa, which consists of about 80% low-molecular-weight heparin, 20% dermatan sulfate, and less than 1% chondroitin sulfate. It has been the most extensively studied glycosaminoglycan for DKD patients with its antithrombotic activity. Though bearing similar biochemical characteristics to heparin, it does not have anticoagulation properties when given orally,72 and it does not cause severe bleeding.73 The exact mechanism of sulodexide in DKD therapies remains unclear, yet many potential therapeutic effects has been observed in animal models. It has been proved effective in suppression of mesangial matrix expansion and thickening of glomerular basement membrane mediated by transforming growth factor-β1.74,75 In addition, restorative effects of sulodexide on glomerular basement membrane anionic charge barrier were also observed.76,77 However, its efficacy in the treatment of DKD does not seem to be so optimistic. In a series of clinical trials, it was found that sulodexide only reduced the urinary albumin in early DKD, while for advanced DKD, it did not show significant kidney protective effects.78-80

**CONFLICT OF INTEREST**

None declared.

**REFERENCES**


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