Protective effect of vitamin E against acute kidney injury

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Abstract. It has been well-known for many years now that vitamin E is an essential nutrient; however, some of the physiological functions of this vitamin are still far from being understood. In recent years, a series of preclinical and clinical studies proposed a protective role of vitamin E on acute kidney injury (AKI), which has a high morbidity rate and mortality rate in clinical investigations. Based on the benefits associated with vitamin E, such as strong antioxidant function, low toxicity, rare side-effects, and low cost, this therapy strategy has garnered an extensive amount of interest in the scientific community for the development of new therapy modes against AKI. In this review, a concise overview of the application of vitamin E in the treatment of AKI is provided as well as a summary of a series of published data regarding the combination therapy modes and detailed therapy mechanisms of vitamin E-based therapy against AKI. At present, there are critical points of this therapy mode that are still in need of further clarification, meaning the current understanding of the role of vitamin E in the treatment of AKI remains incomplete. However, the development of more reliable pharmacological or biotechnical strategies with vitamin E for the eventual treatment of patients with AKI may guide the next chapter of vitamin E research.

Keywords: Vitamin E, acute kidney injury, antioxidant, kidney repair

1. Introduction

Vitamin E consists of a group of eight fat-soluble compounds, including four tocopherols (α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol) and four tocotrienols (α-tocotrienol, β-tocotrienol, γ-tocotrienol, and δ-tocotrienol), of which α-tocopherol has the highest biological activity. This vitamin is exclusively obtained from the diet and has a variety of biological functions, such as enzymatic activity [1], gene regulation [2], and inhibition of platelet aggregation [3]. However,
the vitamin E function that is regarded as the most important is its antioxidant ability [4], and it is this ability that endows vitamin E with a significant role in the cell antioxidant defense system.

Appropriate vitamin E supplementation through a healthy diet is necessary for our daily life. For example, considering the numerous important functions of vitamin E in the body, a vitamin E deficiency can result in many different diseases, including spinocerebellar ataxia [5], ataxia [6], myoclonus-dystonia syndrome [7], and various other diseases [8-10]. Furthermore, vitamin E has also been shown to be effective against certain diseases, such as cardiovascular diseases [11], Alzheimer’s disease [12], and nephropathy [13]. As a type of nephropathy, acute kidney injury (AKI) has a high morbidity and mortality rates in clinical investigations. However, the treatment options for this intractable disease are still currently limited. AKI can be induced by numerous different insults, and reactive oxygen species (ROS) have been shown to play a key role in AKI, causing extensive damage to DNA, proteins, and carbohydrates [14]. Vitamin E, however, poses a potential means of mitigating AKI symptoms [15, 16]. As a small molecule antioxidant, vitamin E has the ability to bind to a variety of active oxidant species (e.g., superoxide free radicals) and defend against damage caused by ROS.

In recent years, based on vitamin E’s protective quality against AKI, scientists have focused their attention on developing new therapy modes and investigating accurate therapy mechanisms. Therefore, in the current literature review, a general overview of the protective effect of vitamin E against AKI is provided, and strategies for developing future vitamin E-based therapies for treating AKI are discussed.

2. Therapeutic action of vitamin E against AKI

Despite being a well-known essential nutrient since 1922, the mechanisms of vitamin E’s physiological functions are still far from understood [17]. From among those functions, vitamin E’s antioxidant activity, in particular, has motivated many scientists to study its ability to prevent diseases caused by oxidation, such as AKI [14].

As early as 1987, scientists were investigating the therapeutic action of vitamin E against AKI [18]. Ramsammy et al. first investigated whether administering vitamin E could inhibit lipid peroxidation and prevent or ameliorate gentamicin-induced AKI in rats [18]. In their results, although the concurrent treatment of rats with vitamin E and gentamicin for six days did not produce an evident effect on the gentamicin-induced alterations of superoxide dismutase, malondialdehyde, catalase, or the glutathione cascade, the shift from polyunsaturated to saturated fatty acids was significantly reversed. They concluded that lipid peroxidation may not have been the major cause of gentamicin-induced nephrotoxicity. Later, these results were confirmed by another research group using a different AKI model. The researchers applied ferric nitrilotriacetate to establish an AKI model in rats and further examined the effect of vitamin E on renal tissue damage as well as lipid peroxidation [19]. The authors observed that lipid peroxidation in kidney tissue increased after the injection of ferric nitrilotriacetate in normal rats. Essentially, there was nearly no injury observed in the proximal convoluted tubules, although some injury could be observed in the medullary outer stripe in the vitamin E-supplemented rats. Therefore, their study indicated that vitamin E can suppress lipid peroxidation and protect kidney tissue against ferric nitrilotriacetate-induced AKI.

Based upon the aforementioned early reports that detailed the therapeutic action of vitamin E against AKI, it can be concluded that vitamin E has the potential to protect kidney tissue from lipid peroxidation and free oxygen radicals, and this function regulates its therapeutic action against AKI in different animal models. In addition, oxidation has been linked to numerous diseases; therefore, due it
its strong antioxidant activity, vitamin E may also hold promise for protecting other tissues from oxidation-caused injury, not just AKI. However, it is important to note that the biological functions of vitamin E are not just limited to antioxidant capabilities [1-3, 20], and while current research is far from understanding whether vitamin E’s other biological functions, such as enzymatic activity and gene regulation, are relevant for the AKI therapy process, perhaps these other functions will be the focus of a new research direction in the future.

While the protective effect of vitamin E against AKI was first reported over 20 years ago, since then the therapeutic action of vitamin E has been demonstrated in many different animals (including mice [16, 21], rats [13, 22, 23], rabbits [14], dogs [24], and pigs [25]) by using a variety of modeling methods (including ischemia/reperfusion [14, 26, 27], cisplatin [25, 28], and other methods [13, 29, 30]), and has even been demonstrated in clinical studies [31, 32] (Supplementary Table 1. Detailed information on the AKI models applied in the investigation of the protective effect of vitamin E). For example, contrast-induced AKI (CI-AKI) is regarded as the most common iatrogenic cause of new AKI, occurring within three days following intravenous contrast media administration in the absence of an alternative etiology [32, 33]. Prophylaxis admin/g76/g86/g87/g85/g68/g87/g76/g82/g81/g3/g90/g76/g87/g75/g3/g82/g85/g68/g79/g3/g302-/g87/g82/g70/g82/g83/g75/g72/g85/g82/g79/g3/g82/g85/g3/g534-tocopherol in combination with saline has been shown to be effective against CI-AKI in patients. Moreover, tocopherol produces a more significant effect than tocopherol when compared with the placebo group [31]. Most significantly, although the results of these early human trials still need to be further confirmed through adequately powered randomized controlled studies, these clinical studies mark the beginning of an extraordinary period in vitamin E-based therapy against AKI.

In recent years, a series of new therapy modes with vitamin E have been gradually developed. For instance, the combination of vitamin E with other therapy factors has been tested, and those new combination methods are more effective against AKI as compared with earlier reports. In contrast, the mechanisms of vitamin E’s therapeutic action against AKI have been further clarified by scientists. Thus, the two major research areas will be further discussed: namely, new therapy modes and new mechanisms of vitamin E-based therapy against AKI.

3. Development of new therapy modes with vitamin E against AKI

In the early reports of vitamin E therapy against AKI, a single administration of vitamin E was used to treat the disease [34-36]. However, it was also reported by some scientists that a single vitamin E administration did not have a beneficial effect on the prevention and severity of AKI, as the oxidative stress in the kidney tissue could not be absolutely related to renal dysfunction in some AKI models [22, 37]. Therefore, developing new therapy modes with vitamin E is essential for improving its therapeutic action against AKI as well as against other kidney diseases. In recent years, the combination of vitamin E and other therapy factors (e.g., other vitamins, amino acids, drugs, and cells) is regarded as a common optimized method (Figure 1).

First, scientists investigated the combination of vitamin E with other vitamins against AKI. For example, the protective action of co-supplementation of single or multiple doses of vitamins C and E against cisplatin-induced AKI has been investigated in mice, and the results indicated that although single-dose and multidose co-supplementation of vitamins C and E rendered significant protection against cisplatin-induced AKI in mice, the multidose administration of vitamins provided a better protection [28]. This result was also confirmed last year by other research groups, in which scientists demonstrated that the combination was more effective than each individual agent in reducing...
oxalate-induced oxidative renal injury, as well as subsequent calcium oxalate crystal deposition in recurrent stone formers [38, 39]. Therefore, the multidose combination of vitamins C and other vitamins at their lower doses could be regarded as an effective therapy mode for protecting mice against cisplatin-induced AKI because of the rare side effect from high vitamin intakes. Perhaps then, the main issue has become determining which vitamins should be used the combination. Moreover, the possibility of the existence of some synergistic actions and antagonisms in the treatment still needs to be further investigated.

In addition, other combination therapy modes have been established over time. As a type of mucolytic drug, erdosteine is mainly used for treating chronic obstructive bronchitis. An antioxidant pretreatment with a combination of α-tocopherol and erdosteine could inhibit the lipid peroxidation of renal cellular membranes. Scientists have also indicated that this combination therapy is more effective than single therapy because the combination of erdosteine and α-tocopherol has a synergistic effect on the protection against oxidative processes in AKI [27]. Additionally, amino acids were also applied in the optimization. Treatment and post-treatment with vitamin E and N-acetylcysteine (NAC) can restore renal function and suppress lipid peroxidation significantly in the gentamicin-induced AKI model, and the combination of the two therapy factors proved to be more effective than either vitamin E or NAC alone [23]. Moreover, the therapeutic action of the combination of L-arginine and α-tocopherol has also been confirmed in ischemia/reperfusion injury in renal transplantation [26]. Similar to vitamin E, most amino acids rarely produce side effects in clinical application and are absorbed by our body every day. Therefore, the appropriate combination of amino acids and vitamin E is highly significant in the treatment of AKI. Perhaps, consuming an appropriate diet could realize this kind of combination and thereby treat AKI without any side effects.

Continuing with research developments, there have been other new factors that have been used to develop new combination therapy modes with vitamin E [40, 41]. For example, Selenium (Se) is a component of the antioxidant enzymes glutathione peroxidase and thioredoxin reductase [42]. Some researchers have reported that Se and vitamin E can ameliorate the toxic effects of pesticide in renal tissue. The potential benefit of combined dietary supplementation was more effective against toxicity than when either Se or vitamin E was administered alone [40]. Later, their study was confirmed by other researchers who determined that the combination of Se and vitamin E powerfully reduces sodium azide-induced toxicity in kidneys [43]. Furthermore in combination therapy research, our group recently also established a new therapy method against AKI with vitamin E, which was used to improve the therapeutic action of bone marrow-derived mesenchymal stem cells (BMSCs) in AKI rats [41]. Our results indicated that the combination of BMSCs and vitamin E was more effective than either stem cells or vitamin E alone. However, further investigation has indicated that the two treatments could have possibly acted independently of each other, as indicated by their differences and noncooperative mechanisms during the process of restoring renal tissue in AKI. Therefore, even though some combination therapies resulted in a better therapeutic effect than did single therapy, it could be possible that there were no synergistic actions between the combined factors.

In summary, it can be concluded that a series of new therapy factors, including other vitamins, amino acids, drugs, and even cells (Figure 1), can be applied in combination with vitamin E against AKI. Moreover, it is likely that even more therapy modes are currently being developed by scientists. However, it is not yet clear which combination mode produces the best protective effect against AKI, and the outcomes of various strategies against AKI should still be compared within a single animal model and should not be interchanged from one model to another model. In addition, further clarification is needed for determining which factor in a combination is responsible for the main therapeutic action. For example, our study indicated that the therapeutic effect of BMSCs was superior...
to that of vitamin E against AKI in the single therapy group. However, in the combined group, it is unclear whether the interaction of the two factors could change their primary and secondary positions during the therapy process. Therefore, it is necessary to further investigate the interactions between combined factors in order to clarify the exact advantages inherent to combination modes.

4. Mechanisms of vitamin E-based therapy against AKI

In the early studies conducted on the mechanisms of vitamin E-based therapies against AKI, the ability of vitamin E to protect kidney tissue from lipid peroxidation and free oxygen radicals was regarded as the main mechanisms underlyng the beneficial effect associated with therapy [19, 44]. In recent years, however, more detailed mechanisms of the protective effect against AKI have been elucidated by scientists.

4.1. The direct antioxidant function of Vitamin E though inhibiting ROS

Partly due to how long vitamin E has been regarded as a strong antioxidant, scientists have made significant progress in elucidating the direct antioxidation mechanism of vitamin E-based therapy against AKI. Moreover, scientists have also found that reactive oxygen substances (ROS) play a key role in AKI and cause extensive damage to DNA, proteins, and carbohydrates. During the process of AKI, ROS have the potential to activate signaling pathways, such as the nuclear factor kappa B (NFκB) pathway and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, in addition to having the ability to further activate some transcription factors (AP-1, Nrf2, and P50) as well as activate an antioxidant response and inflammation. This response elicits oxidative and nitrosative stress, which then leads to cellular damage [45]. Furthermore, ROS could induce lipid peroxidation (LPO) and result in a large production of secondary products, such as malondialdehyde and 4-hydroxynonenal [46]. Those lipid peroxides could sustain free radical cascades and eventually lead to increased membrane rigidity as well as abnormal endothelial function, which may be involved in the pathophysiology of AKI [47-49].

Vitamin E binds to a variety of active oxidant species and effectively defends against damage caused by ROS, though directly inhibiting ROS. For example, a kidney injury can increase sympathetic nervous system activity and blood pressure as mediated by increased ROS in brain nuclei, but a vitamin E-fortified diet is able to mitigate the formation of ROS in the brain, and then, the antioxidants seem to be beneficial for managing hypertension caused by renal injury and increased sympathetic nervous system activity [50]. In addition, vitamin E also has the ability to protect the renal proximal tubular cells against injury in vitro by decreasing ROS production and by further preventing
cell lysis, maintaining adenosine triphosphate levels, and improving mitochondrial respiration, coupling, and membrane potential [51]. Therefore, vitamin E is therapeutically valuable for preventing renal injuries associated with ROS.

4.2. The therapeutic action of vitamin E against AKI depends on NO function

Nitric oxide (NO) is a significant component in the process of antioxidation and antiapoptosis. Researchers have indicated that the administration of vitamin E can enhance the activity of the NO/iNOS system in vivo [41, 52]. In addition, chronic NO synthase inhibition can induce renal vascular injury, proteinuria, hypertension, and can increase superoxide activity. Therefore, investigating the effects of vitamin E treatment on renal injury in the NO deficiency model will lead to a better understanding of the relationship between vitamin E and NO during the therapy process.

The NO deficiency rat model was established though treating rats with N-nitro-L-arginine. The treated rats exhibited severe hypertension, marked proteinuria, decreased glomerular filtration rate, kidney tissue injury, and complete loss of NO-dependent relaxation [53]. Moreover, with a vitamin E treatment, glomerular ischemia, renal vascular injury, and proteinuria can be improved to some degree, but this treatment hardly ameliorates impaired renal endothelial function, hypertension, and tubulointerstitial injury. This phenomenon indicates that oxidants are indeed involved in the pathogenesis of kidney injury in this model. However, an NO deficiency can interfere with the protective effect of vitamin E and can lead to markedly impaired endothelial function and unabated hypertension; therefore, the protective effect of vitamin E against AKI depends on NO functioning normally.

Even though vitamin E may improve the NO level and activate some antioxidant systems (e.g., NO/iNOS bioactivity) in vivo in other AKI models and the indirect protective action may have an important role in the treatment of AKI [41, 52], this modest function cannot work in a completely NO-deficient model. The final reasons for this phenomenon still need to be further investigated.

4.3. Therapy mechanisms of vitamin E against AKI at the subcellular level

Early on, scientists explored the therapy mechanism of vitamin E against AKI at the cellular level; however, in recent years, scientists have gradually focused on the mechanisms at the subcellular level. For example, a possible mitochondrial mechanism of dimethoate-induced nephrotoxicity may be that membrane-bound ATPases and plasma biomarkers are disturbed, and then, the administration of vitamin E ameliorates the toxic effects of this pesticide in the renal tissue because of its antioxidation mechanism [40]. Furthermore, some scientists have used vancomycin chloride to induce a concentration- and time-dependent cell injury in renal tubular cell lines (LLC-PK1) and have observed that the increased intracellular ROS production as well as the mitochondrial membrane depolarization could both be reversed by vitamin E because vancomycin chloride primarily causes apoptotic cell death in LLC-PK1 cells by enhancing mitochondrial superoxide production, thereby leading to mitochondrial membrane depolarization, followed by caspase activities [54].

In addition to mitochondria, vitamin E also has a protective effect on other cell organs in AKI models, such as the lysosome. The accumulation of iron can induce renal tubular injury in mice, including lysosomal membrane lipid peroxidation and the loss of lysosomal membrane integrity. This phenomenon has an important role in the development of diabetic nephropathy [21]. However, administering vitamin E to mice with nephropathy can significantly decrease intralysosomal
iron-induced oxidation in addition to lysosomal destabilization. Therefore, vitamin E has a therapeutic action against AKI and protects the lysosome as well.

However, only a few reports exist about the mechanisms of vitamin E against AKI at the subcellular level. Moreover, the subcellular mechanism is sometimes different from that at the cellular level due to different internal environments and molecular regulation. Therefore, investigating the subcellular mechanism of vitamin E against AKI has the potential to lead to the development of new application models in clinical studies.

In summary, vitamin E-based therapy against AKI has both direct and indirect protective mechanisms (Figure 2). More specifically, vitamin E not only inhibits lipid peroxidation, free oxygen radical injury, and other oxidative damage at the cellular and subcellular levels, but it also activates some antioxidant systems to assist with antioxidation. Although the detailed therapy mechanisms of vitamin E may differ from each other in different AKI models because of various causative factors, the antioxidation of vitamin E always assumes the most significant role during the therapy process. However, more investigation is needed in order to determine if other vitamin E functions can influence the protective effect against AKI. In addition, with the development of combination therapies (vitamin E with other factors) the mechanisms may be far more complex than is realized.

5. Conclusion and prospects

Throughout the last twenty years, both basic and clinical studies on vitamin E against AKI and other kidney diseases have expanded from primarily focusing on the single administration of vitamin E and its antioxidant effects to increasing the scope of investigation to include combination therapies and their non-antioxidant activities as well as metabolism. However, despite its well-documented antioxidant properties and other benefits, supplementation with vitamin E has failed to offer consistent benefits in some AKI models [22, 37] as well as in some other diseases [55-58], as oxidative stress in tissues may not be absolutely related to the dysfunction. Therefore, a clear comprehension of the pathogenies of those diseases can reasonably guide the application of vitamin E in clinical research.

![Fig. 2. Mechanisms of vitamin E-based therapy against AKI.](image-url)
Due to significant interest in the strong antioxidant function, low toxicity, and rare side effects of vitamin E, investigations on the application of vitamin E against kidney diseases have primarily concentrated on clinical studies in recent years [31, 32, 59]. However, to establish vitamin E as an important ally for human health, particularly in AKI protection, it is necessary to empirically resolve an appropriate therapy mode as well as appropriate dosage. While most researchers understand that the rationale for using high-doses of vitamin E in clinical investigations is its inherent low toxicity and rare side effects, this does not negate the fact that an appropriate dosage should be determined in order to evade any unknown potential side effects associated with high doses. Moreover, a more clear understanding of the mechanism underlying vitamin E-based therapy against AKI can aid in the development of more effective therapy modes against this disease in preclinical and clinical studies. Currently, the therapy mechanisms mainly focus on the antioxidation of vitamin E; however, it is still unclear whether other non-antioxidant activities (e.g., gene regulation and enzymatic activity) will affect the therapy mechanism of vitamin E against AKI. Exploring the roles of these non-antioxidant activities may be regarded as a new research interest for scientists in the future.

Although many excellent reviews have evaluated the potential benefits of vitamin E against human diseases, this review summarizes the protective effect of vitamin E against AKI in recent studies. Although a final decision still cannot be made on the benefit versus risk of the potential application of vitamin E to the treatment of AKI in humans, researchers have focused their attentions on the special properties of vitamin E in addition to its therapeutic action against diseases, for its efficacy, safety, and economic effects. Lastly, as evident from the information provided in this review, scientists have made significant progress in this research area over the years; however, there is still much to be learned and discovered in this exciting area of research.

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Appendix

Supplementary Table 1

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<td>mouse</td>
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References


