IWJ International Wound Journal

International Wound Journal ISSN 1742-4801

ORIGINAL ARTICLE

Vitamin E and wound healing: an evidence-based review

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Key words
Antioxidant; Gene transcription; MRSA; Vitamin E; Wound healing

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doi: 10.1111/iwj.12295

Hobson R. Vitamin E and wound healing: an evidence-based review. Int Wound J 2016; 13:331–335

Abstract

Vitamin E has been demonstrated to modulate cellular signalling, gene expression and affect wounds infected with methicillin-resistant *Staphylococcus aureus* (MRSA), thus influencing wound healing. This evidence-based review aimed to identify and evaluate current research assessing the properties of vitamin E in relation to wound healing, through its role as an antioxidant and its influence on connective tissue growth factor (CTGF), MRSA and gene transcription. Literature dated from 1996 to 2012, published in English, involving either animals or adult humans with an acute or chronic wound were included. The databases that contained relevant articles were narrowed down to four, and a total of 33 identified studies were included. The literature review revealed that there is a significant dearth of robust studies establishing the effects of vitamin E on wound healing, and further research is clearly warranted.

Introduction

Wound healing

Wound healing is the interaction of a complex cascade of cellular events that comprise four intricate and overlapping phases such as haemostasis, inflammation, proliferation and tissue remodelling (1). During this process, reactive oxygen species (ROS), a natural derivative of oxygen metabolism produced by activated macrophages, was formed (2). Regulation of this oxidative stress and inflammatory response is important during tissue repair in order to minimise cell damage caused by ROS (3). Arguably, one of the most important considerations to improve wound healing while treating the patient holistically is to ensure adequate nutrition (4). Posthauer *et al.* (5) suggest that vitamin deficiency profoundly impacts cell migration and proliferation, and is thus an influential factor of prolonged wound healing. Indeed, Rojas and Phillips (6) observed that elderly patients with chronic wounds were found to have a diminished plasma level of various nutrients, such as vitamin E. Alvarado *et al.* (7) suggest that the elderly population are the group most at risk of nutrient insufficiency, as endogenous antioxidants decrease in an oxidative stress environment, such as that found in ageing tissue and cells. With an ageing population in the UK, Rippon *et al.* (8) postulate that the economic impact of wound care looks set to increase, particularly with patients who have comorbidities and multiple systemic pathologies. The human and economic costs of wound healing are of major concern within the National Health Service (9). Thomas (10) contends that the total annual cost of wound management in the UK amounts to £3 billion.

Key Messages

- recent advances in molecular biology and genomic techniques have led to research of the precise biological and molecular functions of vitamin E being carried out, and it has been suggested to be an influential factor during wound healing. This evidence-based review aimed to assess whether vitamin E has been overlooked as having beneficial tissue healing properties
- literature dated from 1996 to 2012, published in English, involving either animals or adults with an acute or chronic wound were included. The databases that contained relevant articles were narrowed down to four, and a total of 33 identified studies were included
- despite a large amount of research being carried out on vitamin E, comparisons and inference of the results were limited. The literature review revealed that there is a significant lack of robust studies investigating the effects of vitamin E on wound healing both on animals and on humans, and therefore will act as a basis on which to promote further research in order to study the effects of vitamin E on wound healing

Vitamin E

Vitamin E consists of eight fat-soluble compounds with physiochemical properties, which are then further categorised into two groups of four isomers, tocopherols and tocotrienols, which

Table 1 Search terms and number of articles retrieved

	Terms			
Database	Antioxidant/vitamin E/wound	CTGF/vitamin E/wound	MRSA/vitamin E/wound	Gene expression/vitamin E/wound
Ovid MEDLINE	9	12	2	38
CINAHL	0	0	0	26
Pubmed	5	9	1	20
Web of knowledge	43	18	1	42
Total	57	39	4	126

CTGF, connective tissue growth factor; MRSA, methicillin-resistant *Staphylococcus aureus*.

differ slightly in structure (11), with α-tocopherol being the most potent and abundant form in vivo (12). Through its scavenging activity, vitamin E defends cell membranes and polyunsaturated lipids from ROS attack by inducing the activation of various signal transduction pathways (13), and is thus recognised mostly for its role as an antioxidant. Indeed, studies have focused mainly on its antioxidant properties, although the role of the vitamin itself is broader and varied (14). For instance, Rimbach *et al.* (15) contend that the vitamin is important for maintaining the structural integrity of virtually all cells in a human body by influencing cell signalling, which was initially observed by Boscoboinik *et al.* (16). Vitamin E also modulates the expression of connective tissue growth factor (CTGF) (17), and regulates gene expression and transcription, thereby facilitating the protection of wounds against infections such as methicillin-resistant *Staphylococcus aureus* (MRSA) (18).

These issues prompted an evidence-based review (EBR) to consider the effects of systemic vitamin E on wound healing in order to assess whether the vitamin has been overlooked as having beneficial tissue healing properties.

Method

A logical method to frame the clinical question is the PICO method (19) as it provides a structured process for a search strategy (20). PICO is an abbreviation for patient/problem, intervention, comparison and outcome and forms the basis of proposing a question, searching the existing literature, assessing the data and evaluating the findings and to establish their relevance to clinical practice (21). For this review, the patient population included adults or animals with a wound or in vitro cell cultures from either group. The intervention was specifically administration of vitamin E, either through supplementation, exposure in the laboratory setting or in combination with other nutrients. This was often compared with control groups, although not all studies included one. The clinical outcomes was measured by the influence of the vitamin on localised factors such as cell proliferation and infection, to assess its overall influence on wound healing, whether demonstrated by the studies or hypothesised by the clinical findings.

Literature review

This review initially focused on three specific roles of vitamin E: as an antioxidant, its influence on CTGF and its effect on MRSA. However, a literature review of vitamin E as an antioxidant revealed studies assessing the role of the vitamin on gene expression, and therefore the review will include this additional role as a discussion in its own right. Through the literature review of vitamin E as an antioxidant, the impact of diabetes mellitus (DM) on the vitamin was revealed as a theme and was therefore included as a subsection of the review. Within the study on gene expression, two further areas of interest were identified, and therefore ageing (which encompasses the majority of studies in this area) was also examined. In addition, combined vitamins by amalgamating vitamin E with one or more other nutrients were explored. However, because of the lack of relevant research, the focus on the effects of vitamin E on CTGF was discounted, and therefore excluded from this EBR. The number of databases that contained relevant articles was narrowed down to four, and the time frame of published articles was limited to 1996–2012 to ensure that the evidence was recent. The search terms and results are summarised in Table 1.

The titles and abstracts, where available, were measured against the inclusion and exclusion criteria (discussed later) and then obtained in full text to ensure that they met the criteria if they were not excluded. The reference lists of each study were examined to identify additional research, and each of those articles was also scrutinised for citing articles in order to identify any subsequent studies that had not been identified in the existing literature review, to ensure that all the relevant evidence and key research were not omitted. Books such as *Annals of the New York Academy of Sciences* were hand searched, and archives of relevant journals, such as *Wounds UK* (www.wounds-uk.com) and the *Journal of Nutrition* (http://jn.nutrition.org/), were also explored for articles that did not show up on initial searches. In addition, individual article searches by particular authors who are specialised in research on the topic were undertaken in order to ensure that relevant studies were not erroneously missed and bias in the design of this review was prevented. Grey literature was also appraised.

Inclusion/exclusion criteria

Inclusion criteria consisted of either laboratory animals or human volunteers. Excisional, full or partial thickness wounds on any part of the body below the head, and those involving the dermis (rather than arterial operations) were included. Any subset or combination of vitamin E, and/or amalgamation with other nutrients and involvement of DM were also reviewed. Also, the articles must have been written in English, although it is acknowledged that this limits the external validity of the review due to the risk of language bias (22). Exclusion criteria included papers that researched angiogenesis/cardiovascular

ailments. Research on specific organs, for example the liver or epididymis, was rejected. Furthermore, paediatric patients were not included. Research that focused on any type of cancer, or therapy for it, was discounted. Priority on cosmetic appearances or treatment, including scars, was excluded in this review. Eye wounds, head trauma, bone/skeletal injuries, neurological disorders and interaction of vitamin E with drugs or their metabolism/side effects were also excluded. Articles assessing plant biopsies were omitted as they were not deemed relevant.

Scoring of evidence

Review tools such as the CONSORT statement (23) and PRISMA checklist (24) were used to assess each article. The Centre for Evidence-Based Medicine, Oxford [(25); http://www.essentialevidenceplus.com] 'Levels of Evidence' framework was also used to rate the studies. Of the total results, 33 articles were included.

Discussion

Three studies demonstrated that both naturally derived vitamin E and a synthetic analogue (raxofelast) had beneficial antioxidant functions for wound healing in rats and mice by inhibiting the detrimental effects of hyperglycaemia (26–28). Despite the lack of research in this particular area, these studies may be used as a basis for assessing whether either natural or synthetic vitamin E supplementation in humans with wounds may be beneficial as a contributor to extracellular matrix formation.

DM was induced by Streptozotocin injection in rats in two similar studies by Musalmah *et al.* (29,30) in 2002 and 2005, whereas Park and Lim (3) induced diabetes by alloxan monohydrate injection in mice. All three studies suggested that antioxidant supplementation reduced hyperglycaemia, and the research revealed that α-tocopherol enhanced the rate of wound closure, which may indicate the benefits of vitamin E supplementation during wound healing. Thus these findings may encourage research into the effects of vitamin E supplementation for people with poorly controlled hyperglycaemia to improve healing after tissue damage. However, the lack of a uniform approach to trial design, wound type, outcomes and follow-up periods limit accurate comparison of the data.

A high dose of 585 mg/day vitamin E supplementation in rats by Sakai and Moriguchi (31) was shown to increase macrophage function and prevent a decline in the plasma concentration of the vitamin, which is associated with ageing. However, Fischer *et al.* (32) found that deficiency of vitamin E alone in rats did not induce significant changes in gene expression, when compared with selenium deficiency, whereas combined deficiency of both elements revealed alterations in the level of protein expression involved in inflammation and cell adhesion. These apparent discrepancies may be explained by different ages of the animals, which are incidentally not clarified by Fischer *et al.* (32). Taken together, these findings do not strongly support recommendations for vitamin E supplementation, and dissimilar experimental designs may result in disparities between results.

In mice, supplementation of vitamin E stimulated phagocytosis (33) and improved all the immune functions, even at a lower daily dose of 134 mg (2,7). Supplementation of antioxidants in prematurely ageing mice by Alvarado *et al.* (34) resulted in an increased capacity for neutrophil chemotaxis, and similarly T-cell-mediated immune functions and age-associated defects of T-cell activation in mice was improved by vitamin E (35–38). Thus, mice overall demonstrated beneficial properties of vitamin E for the immune system, which was witnessed at various doses. These results may influence similar studies on aged and immunocompromised humans.

Overall, these findings have indicated that vitamin E supplementation is beneficial for wound repair and immune functions, particularly in elderly animals. However, caution must be applied when interpreting the data into clinical practice for humans due to discrepancies in the amount of supplementation used and the different type and breeds of animals involved, for example athymic mice. Thus this area of research would benefit from further studies involving humans to establish the influence of vitamin E on wounds.

In guinea pigs, De la Fuente *et al.* (39) demonstrated that a 1500-mg supplementation of vitamin E increased cell chemotaxis. Thus, these findings provide additional evidence that a large dose of vitamin E is beneficial for healing. However, this is a stand-alone study with no recent follow-up studies on the effects of vitamin E on guinea pigs with wounds, with which to compare the results.

Pierpaoli *et al.* (18) and Provinciali *et al.* (40) studied MRSA in mice, and both studies concluded that vitamin E in combination with daptomycin alone or both daptomycin and tigecycline was the most effective amalgamation to combat wound infections, such as MRSA. Therefore, these studies indicated that vitamin E had a potential antimicrobial benefit when used in combination with particular antibiotics. The methodologies of these studies, such as the use of control groups, support the rigour of the findings. Despite this, further studies to confirm these findings and contribute additional evidence are recommended.

In research on humans, there are conflicting results on the effects of vitamin E supplementation. Through the measurement of fasted blood samples, Belisle *et al.* (41) showed that vitamin E supplementation was mostly beneficial to the elderly with initial elevated cytokine concentrations, as the vitamin maintained these levels and thus increased the body's immunity against infections. More specifically, Pallast *et al.* (42) determined that 100 mg/day had a positive influence on cytokines, whereas Belisle *et al.* (43) recently observed no overall differences of a higher dose of 182 mg vitamin E on cytokines. The causes for these discrepancies are not clear, which limits conclusive recommendations of a beneficial vitamin E supplemental dose for cytokines. An extensive study in this area could provide more definitive evidence, and as such is a suggestion for future research.

Also administering a vitamin E dose of 100 mg/day, De Waart *et al.* (44) discovered that it did not significantly improve the proliferation of leucocytes and macrophages. However, these findings do not support the research by Meydani *et al.* (45), who found that 200 mg/day of vitamin E was the optimum level for elderly adults' immunity, and this was further demonstrated in studies assessing phagocytosis and chemotaxis of lymphocytes (46,47). No significant adverse effects of any dose

of supplementation, up to 727 mg, were witnessed by Meydani *et al.* (48). Thus, it appears from the data that a supplemental dose of 200 mg/day of vitamin E is an optimum amount for cellular functions.

All four of the tocopherols were identified by Wu *et al.* (49) to have the ability to modulate immune cell function, albeit with differing efficiency and outcomes. Moreover, not only did α-tocopherol stabilise cultured fibroblasts in vitro (50) but the tocopherols also had a direct influence on the activation of fibroblasts (51), and De Pascale *et al.* (52) demonstrated that vitamin E induced transcriptional activity in a keratinocyte cell line. However, a literature review of research assessing a combined supplementation of vitamin E and zinc by Lattanzio *et al.* (53) could not determine conclusive positive or negative influences of vitamin E on gene expression. It seems possible that these results are due to differences in the design of the studies included, which has resulted in a wide variability of the findings for the review by Lattanzio *et al.* (53).

Conclusion

By using the 'Levels of Evidence' framework, the research reviewed for this EBR was generally of Level 2b evidence, which is considered to be reasonable. Of the publications included, the majority were primary research studies ($n = 31$), strengthening the quality of the data. However, it is recognised that there are inherent limitations of an EBR on such a specialised subject such as the one chosen for this review. The time frame of research from 1996 to present may have inadvertently omitted relevant data preceding this date from seminal research. In addition, the nature of a sole and novice reviewer carrying out this EBR and the risk of selection bias is a possible threat to internal validity. Despite this, the use of the PICO method ensured a structured process during the literature review.

Through this EBR, it has been determined that research on vitamin E as an antioxidant and its influence on DM is inconsistent. The majority of the studies reviewed involved rodents, and thus the findings cannot be extrapolated to all patients. Moreover, comparison of the studies is restricted by differing endpoints, methodology and inclusion criteria limiting comparisons and inference of the results. In spite of this, it has been demonstrated that vitamin E limits ROS damage of healing tissue, and this is particularly exhibited in diabetic animals, which is an important issue for future research.

To date, there has been little discussion about the influence of vitamin E and its microbial effects on MRSA, and thus drawing conclusions is restricted as only two pieces of research by the same group of authors were available. Future studies on the current topic are therefore recommended. In spite of this, the findings have so far demonstrated that vitamin E has a potent antimicrobial effect, which is enhanced when in conjunction with particular antibiotics.

The data presented by clinical trials assessing the effects of vitamin E on gene expression have been varied, partly because of the diversity of the cells and participants involved. Furthermore, the various study designs lack consistency and limit comparisons. Crucial and significant details are often missing from the data, which can allow erroneous conclusions. The conflicting findings of the studies reviewed highlight that an effective and safe dose of vitamin E, as well as the minimum duration of treatment, is yet to be established. In spite of this, the basic functional importance of antioxidants in wound healing has been illustrated.

As no other review was found during this research that draws together current literature to assess the question of whether vitamin E has been overlooked as having beneficial tissue healing properties, this EBR has increased the knowledge base on this topic. Overall, the levels of evidence identified are insufficient at this time for issuing a public health recommendation to use vitamin E supplements to assist wound healing. It is important to note, however, that each species of tocopherol has its own mechanism of action that will individually influence wounds. Further research is clearly warranted in this area and should aim at defining specific reference guidelines for vitamin E supplementation.

Acknowledgements

The author thanks Samantha Holloway, Senior Lecturer, Cardiff University School of Medicine, and her colleagues Mrs Lorraine Stevenson and Mrs Pauline Smith.

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