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Commentary

Simvastatin and Ezetimibe-Loaded Nanofibers Administered Locally to Augment Bone Healing

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Background

Various methods have been introduced for the production of nanofibers. Electrospinning is one of the most common methods for synthesis of nanofibers, because of specific characteristics such as simple setup and mass-production ability (1). During the last decade, nanofibers have gained popularity as a drug delivery system, because of structural properties such as sustained drug release, high porosity, high surface-volume ratio, and cost-effectiveness. For these reasons, a great deal of investigations has focused on the efficacy of drug-loaded nanofibers in the treatment of different disorders (2). To date, many therapeutic agents have been loaded on nanofibers (e.g. anti-inflammatory drugs, antimicrobial drugs, anticancer drugs, cardiovascular drugs, palliative drugs, etc.), and their effectiveness has been evaluated in the treatment of different disorders (3).

Bone fracture healing is a complex physiological process that involves several immune and molecular cascades, requiring delicate crosstalk between immune and bone cells. Impairment of such processes could result in fracture nonunion or delayed union, which are seen in a considerable number of cases. To improve bone healing following the fracture, many strategies have been developed, including bone grafts, growth factors, and osteoconductive scaffolds (4).

Even so, the rate of fracture nonunion remains high; the overall risk of nonunion per fracture is reported to be 1.9%, which increases to 9% in specific age groups (5). On a “best-case scenario”, cost-identification query reveals costs of £17,200 for femoral bone non-unions (6). Fracture nonunion also significantly impairs the physical and mental health and quality of life (QOL) of the affected patients (7). Considering the significant economic and health burden of nonunion on the patient and society, the development of more effective strategies for the prevention of union problems seems necessary (5).

Lipid-lowering agents such as simvastatin have shown osteoconductive effects through inhibition of the mevalonate pathway (8). In this regard, oral statin consumption has been associated with increased bone mineralization, decreased risk of hip fracture, and promoted fracture healing (8). In a meta-analysis of randomized clinical trials, Wang et al. assessed the effects of statins on the bone mineral density of adults. Seven trials and 27,900 participants were included in this meta-analysis. According to this study, statin administration led to a significant increase in bone mineral density of participants when compared to the control group (9). The study by Lin et al. revealed the significant impact of simvastatin on reducing the risk of osteoporosis (10). These characteristics have made statin a good candidate for loading on nanofibers to be used as a bone healing substance. Subsequent investigations have shown the positive effects of local statin-loaded nanofibers in the acceleration of bone healing (11).

Ezetimibe is a non-statin lipid-lowering drug with pleiotropic effects, including immunomodulation and inhibition of inflammatory responses (12). The study of Berthold et al. suggested that a combination of simvastatin and ezetimibe inhibits the mevalonate pathway more than simvastatin alone (13). Based on this evidence, Hajializade et al. proposed that simvastatin and ezetimibe combination might also have a higher ability to induce bone regeneration. To evaluate this hypothesis, they compared the cumulative effect of simvastatin and ezetimibe-loaded nanofibers with their individual local administration on the treatment of rat femoral defect. 32 Wistar rats were randomly allocated into four study groups, including simvastatin-ezetimibe-loaded nanofibers, simvastatin-loaded nanofibers, ezetimibe-loaded nanofibers, and non-loaded nanofibers. The drugs were loaded on polyurethane nanofibers that were produced by the electrospinning method. The nanofibers were directly administered into a defect created by a high-speed drill. Four weeks after the intervention, all outcome measures (including the local and circulating expression of osteoprotegerin, Allen's fracture healing scores, and Hounsfield scale of bone density) were significantly superior in the simvastatin and ezetimibe combination therapy group when compared to the monotherapy groups or non-loaded nanofibers. They concluded that the positive effect of simvastatin-loaded nanofibers on bone healing could be even reinforced if combined with ezetimibe. Accordingly, they suggested that simvastatin-ezetimibe nanofibers, if locally administered, could be regarded a promising osteoinductive compound for the augmentation of bone healing (14).

The encouraging results of the study by Hajializade et al. demonstrated the remarkable potential of drug-loaded nanofibers for bone healing purposes. However, the optimization of these results and examination of the findings in the human model are necessary before their routine clinical applications. In this regard, the correct dosage of the therapeutic agents is a critical point that should be considered in future investigations. In addition, a preliminary drug release assessment test was not performed in the study by Hajializade et al. (14). Therefore, it cannot be determined if the drugs were released consecutively or suddenly. Another matter of debate is the optimal polymer for preparing nanofibers that should be addressed in the future.

Conflict of Interest

The authors declare no conflict of interest in this study.

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