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ORIGINAL ARTICLE

SPECIAL AT-RICH SEQUENCE-BINDING PROTEIN 2 AND ITS ROLE IN HEALING OF THE EXPERIMENTAL MANDIBLE BONE TISSUE DEFECT FILLING WITH A SYNTHETIC BONE GRAFT MATERIAL AND ELECTRICAL STIMULATION IMPACT

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ABSTRACT

Aim: The purpose of the study was to identify the role of SATB2 in healing of the experimental mandible bone tissue defect filling with a synthetic bone graft material and electrical stimulation impact.

Materials and Methods: An experiment was carried out on 48 mature male rats of the WAG population, which were divided into 4 groups. Each group included 12 experimental animals. Group 1 included rats that were modeled with a perforated defect of the lower jaw body. Group 2 included animals that were modeled with a perforated defect similar to group 1. In animals, a microdevice for electrical action was implanted subcutaneously in the neck area on the side of the simulated bone defect. The negative electrode connected to the negative pole of the battery was in contact with the bone defect. The battery and electrode were insulated with plastic heat shrink material. Group 3 included rats that were modeled with a perforated defect similar to previous groups, the cavity of which was filled with synthetic bone graft "Biomin GT" (RAPID, Ukraine). Group 4 included animals that were modeled with a perforated defect similar to groups 1-3, the cavity of which was filled with synthetic bone graft "Biomin GT" (RAPID, Ukraine). The simulation of electrical stimulation was the same as in group 2. The material for the morphological study was a fragment of the body of the lower jaw from the zone of the perforated defect. Immunohistochemical study was performed using rabbit anti-human SATB2 monoclonal antibody.

Results: In the regenerate filling the defect in the bone tissue of the lower jaw of rats, there was an increase in SATB2 expression under conditions of electrical stimulation; filling the defect with a synthetic bone graft material; simultaneous filling the defect with a synthetic bone graft material and electrical stimulation. The most pronounced expression of SATB2 was observed under conditions of simultaneous filling the defect with a synthetic bone graft material and electrical stimulation; minimally expressed – in conditions of filling the defect with a synthetic bone graft material; moderately expressed – under conditions of electrical stimulation. In the regenerate, in cases of all treatment methods, SATB2 was expressed by immune cells, fibroblastic differon cells, osteoblasts, and in case of electrical stimulation, also by adipocytes, vascular pericytes and endothelial cells, epidermis.

Conclusions: The activation of SATB2 expression identified by the authors is one of the mechanisms for stimulating reparative osteogenesis under the conditions of electrical stimulation; filling the defect with a synthetic bone graft material; simultaneous filling the defect with a synthetic bone graft material and electrical stimulation.

KEY WORDS: synthetic bone graft material, electrical stimulation, experimental mandible bone tissue defect, reparative osteogenesis, special AT-rich sequence-binding protein 2

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INTRODUCTION

Bone plays an important role in maintaining motor function, hematopoietic function, protecting the internal organs and nervous system [1]. Bone also can regulate the metabolic requirements through calciotropic hormones [2].

Fractures and bone defects are common and complicated clinical problems that pose a great challenge for the healthcare system and place a huge burden on the affected patients [1, 3]. Bone is a very dynamic tissue characterized by self-renewal ability [4]. The bone tissue defects of critical size prevent the bone from self-healing and require further clinical intervention [5].

Large mandibular defects are considered difficult reconstructive challenges for oral and maxillofacial surgeons [2, 6]. They do not occur only in orthopedics or neurosurgery, but they are also a frequent problem in dentistry. Loss of alveolar bone may occur in cases of congenital malformations, trauma, infection, tumors, osteonecrosis (drug-induced osteonecrosis, osteoradionecrosis, traumatic, non-traumatic, spontaneous osteonecrosis) [7-9]. It is important to study the

molecular and cellular mechanisms underlying reparative osteogenesis to improve known and search for new methods of treating patients with large mandibular defects [10].

SATB2 is a DNA binding protein that specifically binds nuclear matrix attachment regions involved in transcriptional regulation and chromatin remodeling [11]. SATB2 plays a critical role in craniofacial and skeleton development, neurogenesis, tumorigenesis, bone healing and remodeling. SATB2 also modulates immunoglobulin expression [3, 12].

Electrical stimulation is a promising tool for bone tissue healing and remodeling being known to promote vital cellular processes such as cell proliferation, migration, and differentiation [5]. Our previous researches have shown the positive effect of electrical stimulation on the processes of reparative osteogenesis when modeling a defect in the mandible bone tissue filled with a hydroxyapatite-containing osteotropic material [13, 14]. In the literature, we have not found the information about the role of SATB2 in healing of the mandible bone tissue defect filled with a synthetic bone graft material and electrical stimulation impact.

AIM

The purpose of the study was to identify the role of SATB2 in healing of the experimental mandible bone tissue defect filling with a synthetic bone graft material and electrical stimulation impact.

MATERIALS AND METHODS

An experiment was carried out on 48 mature male rats of the WAG population, which were divided into 4 groups. Each group included 12 experimental animals.

Group 1 included rats that were modeled with a perforated defect of the lower jaw body. Anesthetized rats underwent a 1.0-1.2 cm long incision of the skin, subcutaneous tissue, and superficial fascia in the left submandibular area. A fragment of the outer surface of the branch and body of the lower jaw was skeletonized. With a ball-shaped drill and a straight tip with a diameter of 3.0 mm, a transcortical perforated defect of the body of the lower jaw was formed in the form of a channel, departing from the lower edge of the jaw upwards by 2 mm. The wound was sutured in layers with vicryl.

Group 2 included animals that were modeled with a perforated defect similar to group 1. In animals, a microdevice for electrical action was implanted subcutaneously in the neck area on the side of the simulated bone defect (a temporary Videx AG 4 battery; a constant sinusoidal electric current of an unchanging nature 1 milliampere, frequency 30 W). The negative electrode connected to the negative pole of the battery was in contact with the bone defect. The battery and electrode were insulated with plastic heat shrink material.

Group 3 included rats that were modeled with a perforated defect similar to previous groups, the cavity of which was filled with synthetic bone graft "Biomin GT" (RAPID, Ukraine), which includes hydroxyapatite and β-tricalcium phosphate. After filling the bone defect with a bone graft, the wound was sutured in layers with vicryl.

Group 4 included animals that were modeled with a perforated defect similar to groups 1-3, the cavity of which was filled with synthetic bone graft "Biomin GT" (RAPID, Ukraine). The simulation of electrical stimulation was the same as in group 2.

Animals of groups 1-4 were removed from the experiment on 3, 7, 14 and 28 days (3 animals for each experimental period).

The material for the morphological study was a fragment of the body of the lower jaw from the zone of the perforated defect. The material was fixed in a 10% solution of neutral formalin (pH 7.4) for 24-48 hours, decalcified, carried out according to the generally accepted method and embedded in paraffin. From paraffin blocks, serial sections with a thickness of 4-5 μm were made, which were stained with hematoxylin and eosin.

Immunohistochemical study was carried out on Super Frost Plus adhesive slides (Menzel, Germany). The Master Polymer Plus Detection System (Peroxidase, DAB chromogen) (Master Diagnostica, Spain) was used. Citrate buffer (pH 6.0) and EDTA buffer (pH 8.0) were used for high-temperature processing of antigen epitopes. Immunohistochemical study was performed using rabbit anti-human SATB2 monoclonal antibody (Clone EP281) (Master Diagnostica, Spain). The immunohistochemical reaction was assessed in the regenerate area by counting the absolute number of SATB2-positive cells in microscope field of view × 100.

Indicators in groups were processed statistically using the PAST program (version 4.15, Natural History Museum, University of Oslo, Norway). Average values of indicators in groups were compared using the Mann-Whitney U-test. Differences in indicators were considered significant at $p<0.05$.

RESULTS

In all groups, positive immunostaining for SATB2 was indicated in regenerate filling the bone defect cavity of the mandible, which was represented by granulation tissue (on day 3) (Fig. 1); granulation, connective, osteogenic fibroreticular tissues (on day 7) (Fig. 1); granulation, connective, osteogenic fibroreticular, lamellar bone tissues (on day 14) (Fig. 2, 3); connective, osteogenic fibroreticular, lamellar bone tissues (on day 28). In the regenerate area in all groups, SATB2 was expressed by immune cells, fibroblastic differon cells and osteoblasts. In groups 2 and 4, this antibody was also expressed by adipocytes, vascular pericytes and endotheliocytes. On the 14th and especially on the 28th day of the experiment, in groups 2 and 4, the epidermis, which was located on the surface of the regenerate, was characterized by pronounced or moderately nuclear SATB2 expression (Fig. 3).

After survey microscopy, the absolute number of immunopositive cells was calculated, the results of which are presented in Figure 4. In all groups, from days 3 to 28 of the experiment, the absolute number of SATB2-positive cells increased ($p<0.05$). In groups 2-4, the number of SATB2-positive cells was greater ($p<0.05$) compared to group 1. A comparative analysis in groups 2-4 showed that

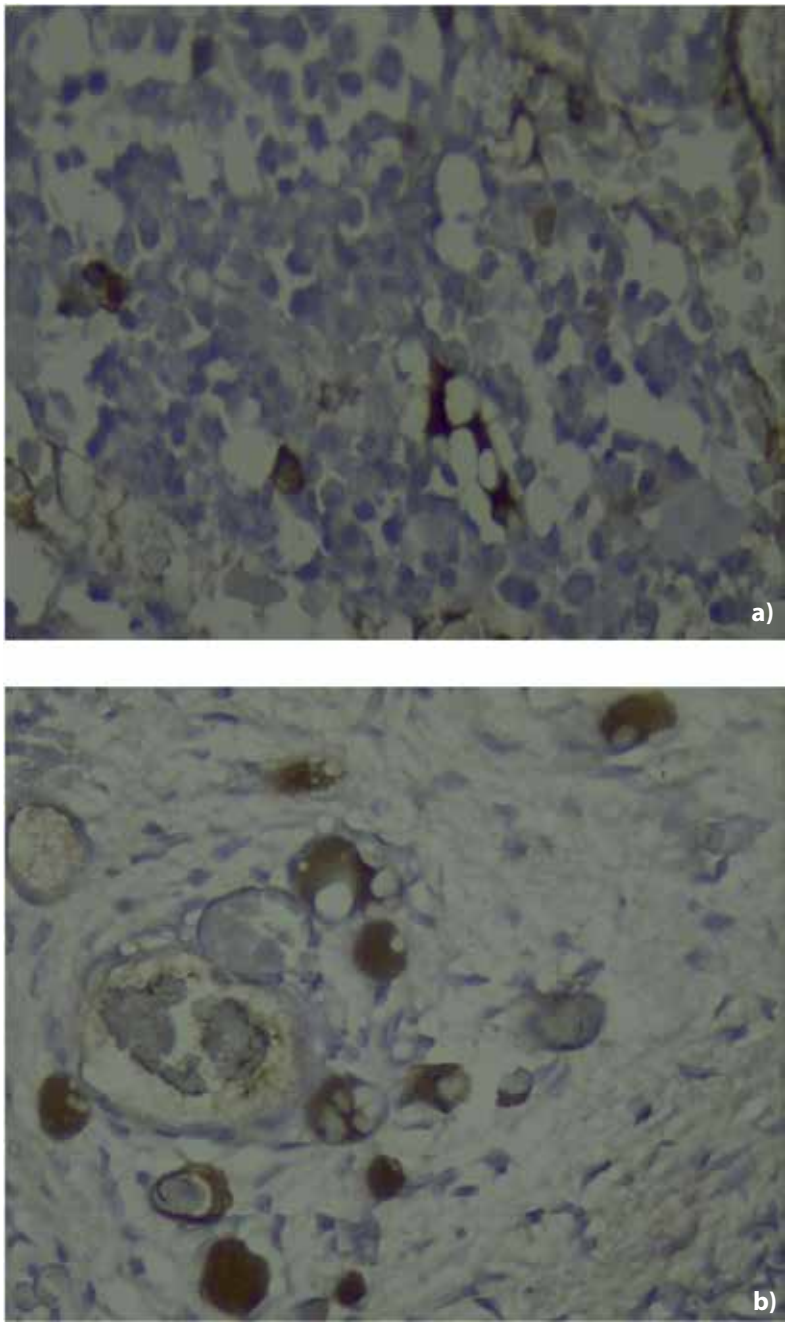

Fig. 1. Group 2. 3rd (a) and 7th (b) days of the experiment. SATB2 expression in granulation tissue in the regenerate area. Immunohistochemical reaction with monoclonal antibody to SATB2, a)×400, b)×400.

the increase in the number of immunopositive cells was maximally expressed in group 4, moderately expressed in group 2, minimally expressed in group 3.

DISCUSSION

In a comprehensive study of experimental material conducted by the authors, an increase in the number of SATB2-positive cells in the area of the regenerate filling the defect in the bone tissue of the lower jaw was revealed, in cases of filling it with a synthetic bone graft material, electrical stimulation and a simultaneous combination of these therapeutic measures. The maximum increase of such immunopositive cells was detected in cases of simultaneous filling of the bone tissue defect with a synthetic bone graft material and electrical stimulation; minimal increase – in cases of filling the defect with a synthetic bone graft material; moderate increase – in cases of electrical stimulation.

Numerous studies have shown that SATB2 acts as a potent transcription factor to enhance osteoblastogenesis and promotes bone regeneration. SATB2 increases expression levels of bone matrix proteins, osteogenic transcription factors, and a potent angiogenic factor, vascular endothelial growth factor [15]. SATB2 is a regulator of Osx which in turn, is responsible for the differentiation of mesenchymal cells into osteoblasts. SATB2 plays a role at 2 levels firstly by

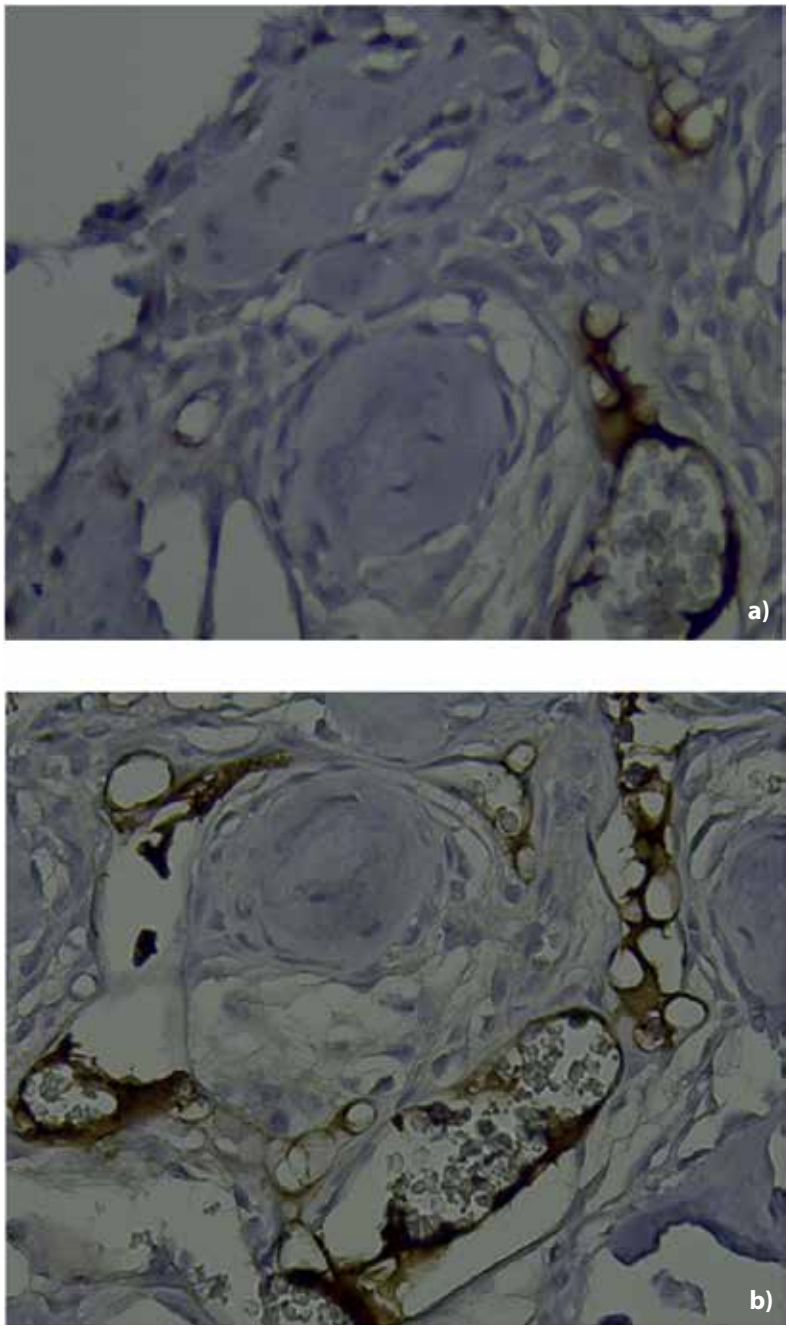

Fig. 2. Group 4. 14th day of the experiment. SATB2 expression in connective and osteogenic fibroreticular tissues in the regenerate area. Immunohistochemical reaction with monoclonal antibody to SATB2, a)×400, b)×400.

blocking Hoxa2, which controls negatively the differentiation of mesenchymal progenitor cells to pro-osteoblasts and secondly by stimulating the differentiation of osteoblasts [16]. SATB2 promotes the osteogenic differentiation of periodontal ligament stem cells, dental pulp stem cells, and stem cells from human exfoliated deciduous teeth [17]. SATB2 takes an active part in the processes of bone tissue mineralization [18, 19].

The increase in the number of SATB2-positive cells identified by the authors in this study indicates the positive effect of the taken treatment measures – stimulation of reparative osteogenesis in the lower jaw of experimental animals. An immunohistochemical study revealed that SATB2 in all groups was predominantly expressed by osteoblasts, which are known to be directly involved in bone formation processes [20]; fibroblastic differon cells that can transform into osteoblasts [21, 22].

It is interesting that in groups 2 and 4, i.e. under conditions of electrical stimulation, SATB2 was expressed by adipocytes from the regenerate area, which, according to literature data, can transform into osteoblasts [23]; vascular pericytes, i.e. process cells of connective tissue located along the periphery of the blood vessels walls, which play a crucial role in bone tissue regeneration through direct osteodifferentiation processes, paracrine actions, and vascularization [24]. In groups 2 and 4, this marker was also expressed by vascular endothelial cells, which, according to the literature, can also transform into osteoblasts. Recent research results

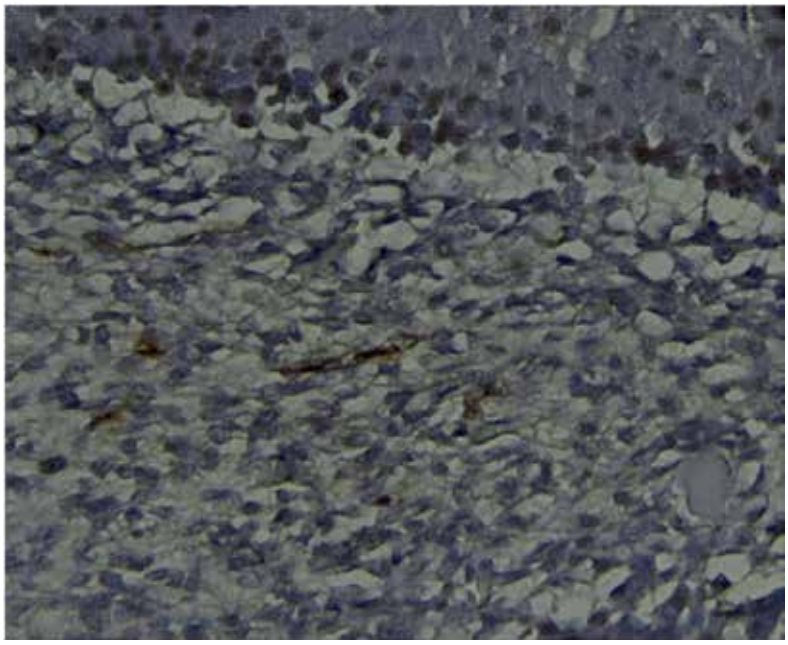

Fig. 3. Group 4. 14th day of the experiment. SATB2 expression in epidermis, which was located on the surface of the regenerate, and in underlying granulation tissue. Immunohistochemical reaction with monoclonal antibody to SATB2, ×400.

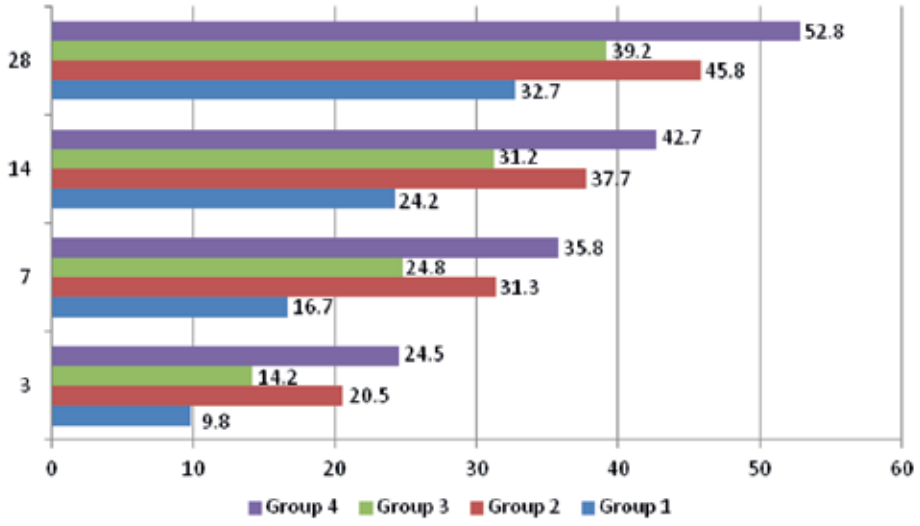

Fig. 4. Absolute number of SATB2--positive cells in groups 1-4 (X axis – absolute number of cells, Y axis – day of experiment).

have shown that endothelial cells-to-osteoblasts transition occurs during normal bone development and suggest a new paradigm regarding the endothelial origin of osteoblasts [25].

In groups 2 and 4, SATB2 expression was also detected in the epidermis, which covered the surface of the formed post-traumatic regenerate. There are a few controversial studies in the literature showing the possible transformation of skin epithelial cells into chondrocytes and osteoblasts [26].

The increase in the number of SATB2-positive cells and, accordingly, the activation of reparative osteogenesis of varying severity were due, from our point of view, to electrical stimulation in group 2; filling of the bone defect in the lower jaw with a synthetic bone graft material in group 3; electrical stimulation with simultaneous filling the bone defect with a synthetic bone graft material in group 4. Electrical stimulation, firstly, activated the morphofunctional state of osteoblasts, and secondly, increased the number of osteoblasts by reprogramming and transdifferentiation of cells of various histogenesis. The latter was manifested by mesenchymal-mesenchymal (transformation of fibroblastic differon cells, adipocytes, vascular pericytes into osteoblasts), endothelial-mesenchymal (transformation of vascular endothelial cells into osteoblasts), epithelial-mesenchymal (transformation of epithelial cells into osteoblasts) transformations.

According to literature data, electrical stimulation of the cells causes the cells to become more active, increases its metabolism, changes its gene expression and leads to its transformation [27].

Filling the bone defect of the lower jaw in groups 3 and 4 with a synthetic bone graft material containing hydroxyapatite and β-tricalcium phosphate stimulates reparative osteogenesis. The latter is due to the osteoconductive properties of the material, i.e. plays the role of a passive matrix (framework) for the formation of new bone.

CONCLUSIONS

In the regenerate filling the defect in the bone tissue of the lower jaw of rats, there is an increase in SATB2 expression under conditions of electrical stimulation; filling the defect with a synthetic bone graft material; simultaneous filling the defect with a synthetic bone graft material and electrical stimulation. The most pronounced expression of SATB2 is observed under conditions of simultaneous filling the defect with a synthetic bone graft material and electrical stimulation; minimally expressed – in conditions of filling the defect with a synthetic bone graft material; moderately expressed – under conditions of electrical stimulation. In the regenerate, in cases of all treatment methods, SATB2 is expressed by immune cells, fibroblastic differon cells, osteoblasts, and in case of electrical stimulation, also by adipocytes, vascular pericytes and endothelial cells, epidermis. The activation of SATB2 expression identified by the authors is one of the mechanisms for stimulating reparative osteogenesis under the conditions of the treatment measures.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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