

## **Antioxidants Reduce Oxidative Stress and Accelerate Tendon-to-Bone Healing after Rotator Cuff Repair**

Yoshiaki Itoigawa<sup>1</sup>, Hirohisa Uehara, HIRONORI TSURUKAMI, Akihisa Koga<sup>2</sup>, Daichi Morikawa<sup>3</sup>, Hatae Fumitoshi, Katsuhiko Maezawa<sup>1</sup>, Muneaki Ishijima<sup>4</sup>

<sup>1</sup>Juntendo University Urayasu Hospital, <sup>2</sup>Juntendo University Urayasu Hospital, <sup>3</sup>Department of Orthopaedics, <sup>4</sup>Juntendo University Faculty of Medicine

**INTRODUCTION:** Oxidative stress inhibits tendon-to-bone healing after rotator cuff repair. Regulation of oxidative stress can promote the healing, but the mechanism remains unclear. Therefore, we aimed to investigate the effects of reducing oxidative stress by applying antioxidants, such as N-acetylcysteine (NAC) and vitamin C (VC), on rotator cuff repair in a rat rotator cuff repair model.

### **METHODS:**

Forty-eight Sprague Dawley rats underwent bilateral surgery to repair the infraspinatus tendon to its insertion site 1 week after detachment. Rats were assigned to either the NAC group, VC group, or control group. Histological evaluation (number of chondrocytes and non-chondrocytes, percentage of aligned chondrocytes, area of fibrocartilage, and collagen fibers) was performed by hematoxylin-eosin HE/toluidine blue staining, and oxidative stress was assessed by dihydroethidium intensity and protein carbonyl concentration at 3 and 6 weeks. Superoxide dismutase (SOD) 1, SOD2, SOD3, peroxiredoxin 5, collagen type I (COL1), COL3, matrix metalloproteinases (MMP)-1, MMP-3, and MMP-13 expression and SOD activity were determined at 3 and 6 weeks. Biomechanical tests (stiffness and ultimate load) were performed at 6 and 12 weeks.

**RESULTS:** Histological evaluation showed that the number of chondrocytes in the NAC group at 6 weeks and in the VC group at 3 and 6 weeks, the area of fibrocartilage at 6 weeks in the VC group, and collagen fibers at 6 weeks in the NAC and VC groups were significantly increased compared with those in the control group. Dihydroethidium intensity at 3 and 6 weeks and protein carbonyls at 6 weeks in the NAC and VC groups were significantly decreased. SOD1 expression and SOD activity at 3 weeks in the VC group, and peroxiredoxin 5 expression at 6 weeks in the NAC group were significantly upregulated than in the control group. COL3 expression was significantly upregulated at 6 weeks in the VC group, and MMP-13 expression was significantly decreased at 3 and 6 weeks in the NAC and VC groups. The biomechanical strength showed no significant difference.

**DISCUSSION AND CONCLUSION:** Antioxidant treatment, through NAC or VC administration, in combination with rotator cuff repair reduced oxidative stress in the rotator cuff repair site and accelerated the healing.