The level of evidence in clinical studies of the use of rhBMP-2 in spinal interbody fusions

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To the Editor,

Miyazaki et al. [9] categorized each article included in their publication into one of the five levels on the basis of its study design. Well-designed randomized controlled trials and systematic reviews of such trials were classified as Level I studies; randomized controlled trials with less than 80% follow-up or unclear randomization and prospective cohort studies without control groups, as Level II; case-control studies and retrospective cohort studies, as Level III; case series, as Level IV; and expert opinions, as Level V studies [9]. However, as we came from different ethnic, demographic, and training backgrounds [11] we have to ask the authors for clarification related to classification of studies of osteoinductive growth factors which were our main topic of interest within the article.

Although the number of patients enrolled in the prospective, multicenter, nonblinded, randomized, and controlled human clinical pilot study of Boden et al. [2] was small, Miyazaki et al. [9] graded it as Level I. Conversely, three studies of Burkus et al. [4, 5, 7] were graded as Level II. One was a prospective, nonblinded, randomized, 2-year study, study investigating the radiographic progress of

fusion at 6, 12, and 24 months in 42 patients who underwent a single-level anterior lumbar interbody fusion (ALIF) using cylindrical interbody fusion cages [4]. The second was a prospective, multicenter, nonblinded, randomized study, consisting of 279 patients with degenerative lumbar disc disease randomly divided into two groups that underwent interbody fusion using two tapered threaded fusion cages [5]. The last of three mentioned studies of Burkus et al. [7] was prospective, multicenter, nonblinded, randomized human clinical pilot study which was conducted under an approved investigational device exemption (IDE). As some of the authors are leading experts in performing reviews of the literature, it is hard for us to question the grading system they used in the entire analysis of the literature presented in the article, but it is interesting that the pivot phase of that study in which the results of pilot phase were included [6, 7] was graded in JBJS Am as therapeutic Level I study [6]. We understand that there can be interobserver differences, but it was found that even non-epidemiology-trained reviewers can apply the levels-of-evidence guide to published studies with acceptable interobserver agreement [1]. Anyway, since the dose of the rhBMP-2 used in the pilot phase was higher (8–12 mL at concentration of 1.5 mg/mL, i.e. 12–18 mg) [3, 7] than the pivot phase (8.4–12 mg) [6], we accept possibility that those were two completely distinct studies, and that they could be graded differently. So, we are interested as to what were the exact reasons why the mentioned studies of Burkus et al. [4, 5, 7] were graded as Level II compared with the grading of Level I for the study of Boden et al. [2]? Was the level-of-evidence decreased based on the authors' expert opinion or because of serious shortcomings identified within the papers of Burkus et al. [10]? It should be emphasized that studies of Burkus et al. were completely excluded from similar literature analysis [8].

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