Letter to the Editor

Changing Grains for the Prevention and Treatment of Kashin-Beck Disease in Children: a Meta-analysis*

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To evaluate the efficacy of changing grains on the prevention and treatment of Kashin-Beck Disease (KBD) in children, community-based trials were acquired from seven electronic databases (up to July 2014). As a result, the methodological quality of the six trials that have been included into our analysis was low. The pooled ORs favoring the prevention and treatment effects of changing grains were 0.15 (95% CI: 0.03-0.70) and 2.13 (95% CI: 1.44-3.16) respectively by meta-analysis. Subgroup analysis demonstrated the pooled OR favoring treatment effect of exchanging grains rather than drying grains both compared with endemic grains. The results showed that changing grains had obvious effects on the prevention and treatment of KBD in children. However, the evidences were limited by the potential biases and confounders. Large and well-designed trials are still needed.

KBD, a chronic and endemic osteoarthropathy, manifests cartilage specific pathological changes, and chondrocyte apoptosis. Affected individuals exhibit short stature, joint deformities, and other features caused by impaired epiphyseal growth and ossification. KBD usually starts in childhood and may result in dwarfism. KBD occurs mainly in regions from the Northeast China to Sichuan-Tibet Plateau, Russia, and North Korea. In China, approximately 0.7 million patients suffer from the disease, and the 105 million residents who are living in the endemic provinces are at risk in the year 2010[1]. Therefore, the treatment of KBD has attracted great attention by Chinese health authorities.

In China, the deficiency of selenium in grains from endemic regions is one of the causes for KBD, and the commercial sodium selenite product is used for prevention and treatment of KBD. Cereal contamination by mycotoxin has been suggested as another environmental factor for the occurrence and development of KBD[2]. *In vitro*, Fusarium toxins showed to inhibit the DNA synthesis and cell proliferation, damage cell membrane system, disrupt the intracellular redox balance regulation, and impair the metabolism of chondrocytes and synthesis of cartilage matrix. It has been reported that T-2 toxin detected with 2.0-1549.4 ng/g from grains, as one of mainly detected Fusarium toxins in endemic regions, could inhibit chondrocyte proliferation and induce chondrocyte apoptosis in experimental study.

In the early 1950s, changing grains for the prevention of KBD were proposed by the experts from Soviet Union, which had showed effective results and KBD had been controlled in Soviet Union until 1964. Thus, although the mechanism of changing grains for KBD prevention was unclear, experts in Soviet Union firmly believed that the 'elimination' of KBD in Soviet Union was contributed to the changing grains. Since the 1950s, changing grains for KBD prevention and treatment have been implemented in the endemic regions in China[3-7]. However, the efficacy of changing grains on the prevention and treatment of KBD in children is still uncertain.

The objective of this meta-analysis was to synthesize the results from community-based trials to assess the efficacy of changing grains on prevention and treatment of KBD in children from the endemic regions. The inclusion and exclusion criteria are as following: all included community-based trials that used changing grains [include exchanging grains and drying grains (exchanging grains: exchanging the locally produced grain resources and variety for grains produced in

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non-endemic areas; drying grains: drying locally produced grain to control the moisture content below 13%) *vs.* endemic grains (locally produced grains in endemic regions). Studies reporting participants included healthy children and KBD children in the endemic regions with 0-18 years of age and data could be identified separately for the prevention and treatment effects. Studies which were excluded consisted of: (1) no control group, and (2) use of changing grains in combination with other treatments (e.g., selenium supplementation, vitamin C supplementation or water improvement).

We searched for all publications from January 1944 to July 2014 using electronic databases, which included Cochrane Central Register of Controlled Trials, MEDLINE, Google Scholar, EMBASE, CNKI, VIP, Wan Fang data, without language restrictions. The search was performed by using 'Kashin-Beck disease', 'Kaschin-Beck disease', 'Urov', and 'Changing grains', combined with MeSH terms and text words. In the beginning, titles and abstracts were assessed; studies were excluded if they did not fulfill the inclusion criteria. Subsequently the full text was obtained and assessed to determine the inclusion of potentially eligible studies. Any disagreement was resolved by consensus.

The methodological quality of the included community based trial was accessed based on a checklist described by Higgins et al.[8]. Data analyses were conducted by Stata version 9. For dichotomous data (e.g., the positive rate by X-ray), OR and 95% confidence intervals (CI) were estimated. A 'fixed-effect' approach was used when no significant heterogeneity was identified; otherwise a 'random-effect' statistical model was used[9]. Test for heterogeneity was carried out by using the Chi-square test with $P<0.1$. In addition, value of I^2=25%, 50%, 75% was considered as low, moderate, high heterogeneity, respectively[8-9]. The subgroup analysis was carried out to control the confounding factor based on different ways of changing grains (exchanging grains and drying grains), then P value <0.05 was considered to be statistically significant.

Finally, six trials in five articles were included (supplement Figure 1, see the website www.besjournal.com). All trials were conducted in China from 1961 to 2010 and published in Chinese language. Total of 1609 participates with 0-18-year old were involved in the meta-analysis, with 970 pupils in the intervention group and 639 students in the control group (supplement Table 1, see the website www.besjournal.com). The duration of follow-up of included trails ranged from 12 to 72 months. The KBD was diagnosed by clinical and X-ray diagnosis criterion (criteria of Yongshou scientific survey group of KBD, national standard), and X-ray detection rate of KBD was used as the outcome of changing grains.

The methodological quality of the six trials was shown in Supplement Table 2 (see the website www.besjournal.com). In general, the overall methodological quality of the included studies was low. The process and method used to generate random sequence was not clear in all trials. And allocation concealment was not clear or mentioned by any of them. Blinding method was not thoroughly implemented. Selection bias and detection bias might be induced in these trails. Additionally, sample size calculation was not mentioned in any of them and the sample sizes of trials on changing grains were small. Duration of follow-up varied from 1 to 7 years, which was obviously insufficient for such a chronic disease, though the most favorable duration is still uncertain. The small sample size and insufficient duration of follow-up may attributed to the potential biases in these trials.

Meta-analysis showed that four trials explained the prevention effect of changing grains (Figure 1). The pooled OR favoring exchange grains was 0.15 (95% CI: 0.03-0.70) by 'random-effect' model, which indicated a significant difference in efficacy between changing grains and control (Z=2.41, P=0.016). The pooled OR was less than 1, which meant the incidence of KBD decreased when grains had been changed. Heterogeneity was identified among different trials (I^2=81.4%, P=0.001).

Meta-analysis also showed that five trails interpreted the results of treatment effect of changing grains. In Figure 2, the pooled OR favoring changing grains was 2.13 (95% CI: 1.44-3.16) by 'fixed-effect' model, indicating a significant difference in efficacy between change grain and control (Z=3.77, P<0.001). Low heterogeneity was identified among the different trials (I^2=39.7%, P=0.157).

Subgroup analysis of exchanging grains and drying grains was conducted by 'random-effect' model (Figure 3). The pooled OR favoring exchanging grains was 2.36 (95% CI: 1.40-3.98), indicating a significant difference in treatment effect between exchanging grains and endemic grains (Z=3.21, P=0.001). The pooled OR unfavoring drying grains was 1.61 (95% CI: 0.36-7.11), which indicated no significant difference in treatment effect between drying grains and endemic grains (Z=0.63, P=0.53).

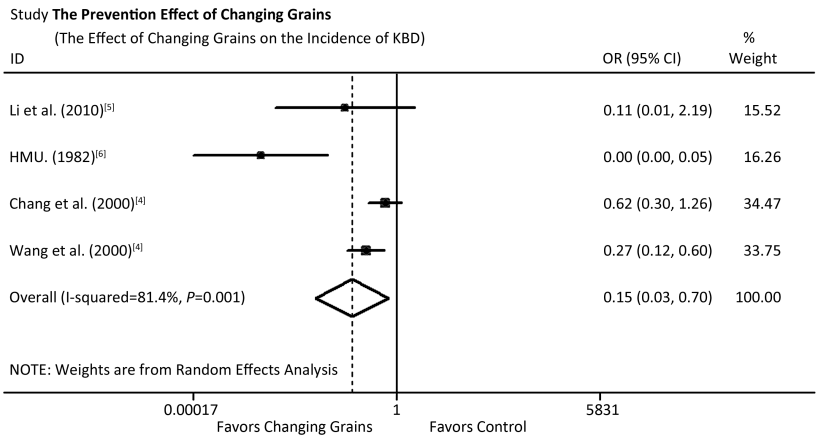

Figure 1. Meta-analysis of intervention (changing grains) *vs.* control (endemic grains) for prevention of KBD.

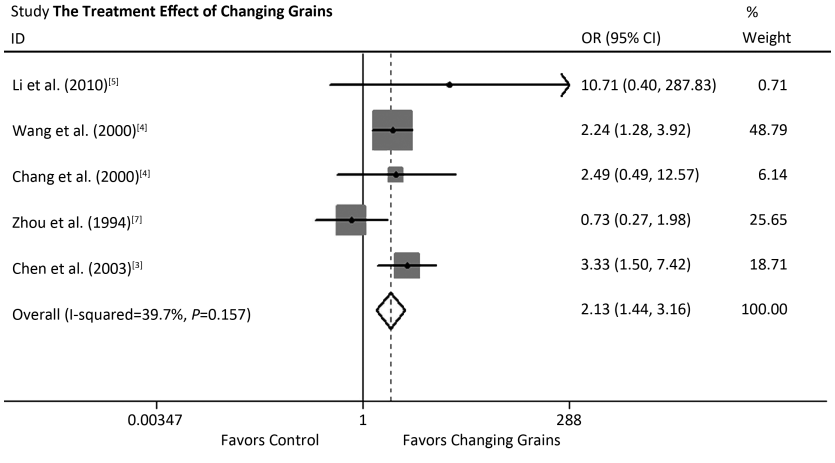

Figure 2. Meta-analysis of intervention (changing grains) *vs.* control (endemic grains) for treatment of KBD.

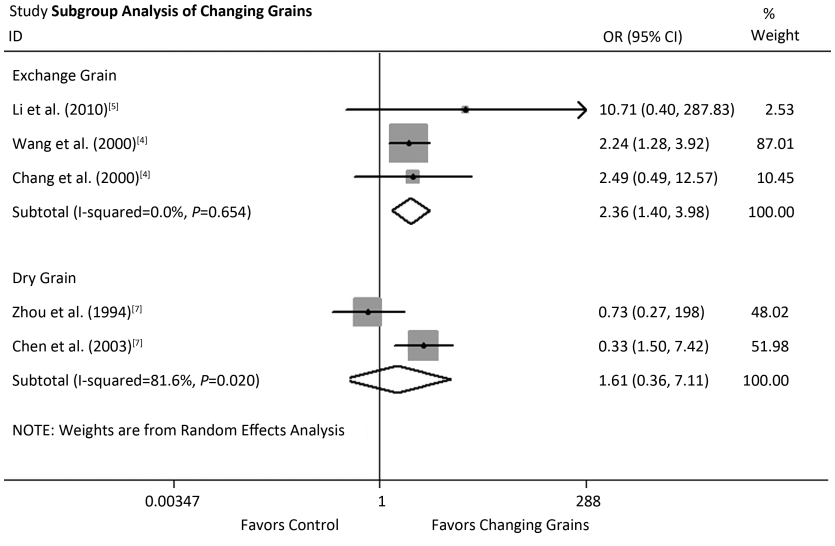

Figure 3. Subgroup analysis of intervention (exchanging grains/drying grains) *vs.* control (endemic grains) for treatment of KBD.

In summary, by meta-analysis, for KBD prevention, the pooled OR was 0.15 (95% CI: 0.03-0.70), which meant the incidence of KBD decreased with changing grains, and for KBD treatment, the pooled OR favoring changing grains was 2.13 (95% CI: 1.44-3.16). Current evidences from community-based trials suggested the benefits of changing grains for the prevention and treatment of KBD in children. By subgroup analysis, exchanging grains showed better treatment effect for KBD than drying grains. As we known, drying grains could control the moisture content of grains, protecting the grains from Fungi and toxin contamination. However, the pooled OR value suggested that drying grains were not as efficient for KBD treatment as expected, which supposed that the mildew could be controlled by drying grains before storage, however, the mildew did not seen to be controlled during the food storage. Moreover, there might be the other factors influenced the treatment effect of drying grains, one of the most important factors might be the nutrition deficiency of the grains, for example, low selenium, protein and so on, which still need our effort to explore the mysterious.

Unlike drugs, grains did not show definite indication, side and adverse effects. Although the source and quality of the exchanged grains could be controlled, the quality of the endemic grains was hard to define, and the dosage of the exchanging grains and endemic grains was difficult to determine for individuals. Methodological quality of the included trials was not accessed with blinding to the authors and institutions. Even though, for the poor living condition and nutrition status in that period of China, individuals might be more sensitive to the contamination of endemic grains by Fusarium. Thus, we should realize the function of exchanging grains for the overall control of KBD and pay more attention to the quality control of grains.

Nevertheless, the evidence may be limited by potential biases and confounders, and more evidence from high quality trials is needed. Large and well-designed trials are also required. It is suggested that healthy children (without KBD at the start of trials) be recruited in the studies should be followed for a sufficient period. Cluster-randomization should be implemented with at least 20 samples at different levels, such as village, school or classroom. Allocation concealment should be adequately implemented. Blinding should be used in at least participants and X-ray radiologists. Besides, the source and administration compliance of exchanging grains should be well-defined. Meanwhile, a better (bio-) chemical characterization of the exchanging grains used for intervention is needed, the amount of trace elements, especially selenium, which is known to strongly impact on KBD incidence, should be determined in the exchanging grains. And a standardized diagnostic criterion of KBD involving both clinical and X-ray manifestations (such as WS/T207-2010) should be applied. More details of joint pain and grade of motion restriction should be measured and presented.

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