1   **Etiologic Classification Criteria of ARCO on Femoral Head Osteonecrosis, Part 1:**

2   **Glucocorticoid-Associated Osteonecrosis**

3   **Abstract**

4   **Objective:** Glucocorticoid usage, a leading cause of osteonecrosis of the femoral head (ONFH), and its

5   prevalence was reported in 25-50% of non-traumatic ONFH patients. Nevertheless, there have been no

6   unified criteria to classify glucocorticoid-associated ONFH (GA-ONFH). In 2015, the Association

7   Research Circulation Osseous (ARCO) addressed the issue of developing a classification scheme.

8   **Methods:** In June 2017, a task force was set up to conduct a Delphi survey concerning ONFH. The task

9   force invited twenty-eight experts in osteonecrosis/bone circulation from eight countries. Each round of

10   the Delphi survey consists of questionnaires, analysis of replies and feedback reports to the panel. After

11   three rounds of the survey, the panel reached a consensus on the classification criteria. The response rates

12   were 100% (round 1), 96% (rounds 2) and 100% (round 3), respectively.

13   **Results:** The consensus on the classification criteria of GA-ONFH included: 1) patients should have a

14   history of glucocorticoid use > 2g of prednisolone or its equivalent within a 3-month period; 2)

15   osteonecrosis should be diagnosed within two years after glucocorticoid usage, and 3) patients should not

16   have other risk factor(s) besides glucocorticoids.

17   **Conclusion:** ARCO established classification criteria to standardize clinical studies concerning GA-

18   ONFH.

19   **Key words:** osteonecrosis; avascular necrosis; hip; femoral head; glucocorticoid; corticosteroid; Delphi
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21 **Introduction**

22   Osteonecrosis of the femoral head (ONFH) is a potentially devastating disease frequently leading to

23 collapse of the femoral head and osteoarthritis of the hip.[1, 2] Specifically, non-traumatic ONFH usually

24 affects young and middle-aged adults and the prevalence has been reported to be increasing.[3, 4]

25 Although non-traumatic ONFH is the final common manifestation of various diseases or conditions

26 compromising the local circulation in the femoral head, the pathogenic mechanisms are multifactorial and

27 have yet to be fully elucidated.[5]

28   Among non-traumatic ONFH cases, glucocorticoids have been identified as the leading cause and

29 reportedly contributed to its development in 25-50% of patients.[3, 6-8] These agents have been used as a

30 first-line anti-inflammatory and immune-modulating drug for many immune-mediated conditions or as an

31 adjunctive therapy for some infectious or malignant diseases. Prospective studies using magnetic

32 resonance imaging (MRI) have reported that glucocorticoid-associated ONFH (GA-ONFH) was detected

33 in 15 to 35% of patients with systemic lupus erythematous.[9] The susceptibility to GA-ONFH has been

34 considered dependent on multiple factors including genetic background, the duration or amount of

35 glucocorticoids exposure, and underlying diseases.[10, 11] Thus, it is difficult to determine the risk dose

36 or duration of glucocorticoids to develop ONFH and previously, most researchers could not avoid using

37 their own definitions or criteria for corticosteroid-associated ONFH. As a result, because of

38 inhomogeneity within the GA-ONFH populations studied, it is difficult to compare the results across the

39 studies and to collect data enough to augment our understanding of patients with this association.

40   The Association Research Circulation Osseous (ARCO) founded in 1973 has been the only international

41 society promoting the study of bone circulation and its disorders in particular of osteonecrosis. In April

42 2015, ARCO addressed some of these issues on classification criteria of non-traumatic ONFH and formed

43 a task force to establishing the criteria for GA-ONFH and alcohol-associated osteonecrosis. Because of

44 the lack of sufficient scientific evidence in the literature, the task force decided to employ a modified,

45 consensus-building Delphi method, by gathering data from experts using rounds of questionnaires.

46 Since the present study aimed to develop the classification criteria for GA-ONFH to identify a well-

47 defined homogenous population for research, our criteria should not be misinterpreted as diagnostic

48 criteria for clinical practice.

49 **Methods**

50 *ARCO task force*

51 The ARCO task force was set up to prepare the Delphi survey and consisted of 7 members; 4 orthopaedic

52 surgeons, 1 expert researcher on bone circulation/osteonecrosis, 1 rheumatologist and 1

53 statistician/methodologist. The task force performed a search of PubMed, using the key search terms

54 "osteonecrosis", "avascular necrosis", "aseptic necrosis", "glucocorticoid", and "steroid" for entries from

55 January 1, 1960, to May 31, 2017. The search was restricted to human studies in the over 18 years' age

56 group. The task force reviewed 75 citations relevant to GA-ONFH and selected 23 key literatures

57 (Supplementary 1). Through the comprehensive literature review, the task force raised 4 issues to develop

58 novel etiologic classification criteria of GA-ONFH; 1) whether experts necessitate classification criteria

59 of GA-ONFH, 2) minimal dosage of glucocorticoids that need to have been administered to the patients;

60 3) the latent period after exposure to glucocorticoid, when a diagnosis of ONFH can be made; 4) how to

61 classify ONFH patients, who have other risk factor(s) besides glucocorticoid.

62 *Expert panel members*

63 In June of 2017, the task force initially invited 30 experts because the sample size of a panel has usually

64 been recommended to 15 to 30 participants in the Delphi study design and a larger sample size (beyond

65 30) has rarely found to improve the results.[12] ARCO made the panel qualifications for the Delphi study;

66 college faculty, more than 10 years of clinical and/or research experience, and 3 or more publications on

67 bone circulation/osteonecrosis, for a homogeneous panel based on the knowledge on ONFH and level of

68 clinical or research experience. Among the 30 experts, one declined the invitation and one did not reply to

69 the invitation. The remaining 28 experts on osteonecrosis/bone circulation participated in the Delphi

70 procedure (Table 1). The panel members had a mean of approximately 18 years of clinical and/or research

71 experience.

72 *The modified Delphi procedure*

73 The Delphi technique is a widely accepted method for achieving convergence of expert opinions. The

74 following features characterize the procedures: anonymity, iteration, and controlled feedback. Anonymity

75 allows participants to express their opinions freely without being pressured by other participants, and

76   permits them to change their opinion if necessary, thus helping participants consider the issues based on

77   merits alone. In this study, anonymity was achieved by an Internet survey. Iteration is achieved by

78   presenting questionnaires several times over a number of rounds, thereby allowing participants to change

79   their opinions. Controlled feedback takes place between rounds: each participant learns of the other

80   participants' opinions. Participants often receive this feedback as a simple statistical summary of

81   responses, although arguments may present. This ensures that all of the participants contribute to the

82   discussion.

83   **Construction of Delphi rounds**

84   A total three or four rounds was expected to reach consensus on the 4 issues, which were raised by the

85   ARCO task force. In the first survey, the panel members were asked to answer 4 open-ended questions on

86   the 4 issues; 1) whether etiologic classification criteria for glucocorticoid are necessary and their reasons

87   why; 2) their own criteria to classify osteonecrosis as GA-ONFH in terms of cumulative dose of

88   prednisolone or its equivalent; 3) the duration of the effects of lasting risk exposure (latent period – time

89   from the past exposure to diagnosis of ONFH); and 4) how to classify ONFH patients who have 2 or

90   more risk factors including glucocorticoid therapy.

91   Replies to the first survey were analyzed to determine whether consensus was reached or not.

92   In the second and further rounds, the panel members were asked to answer the revised questionnaires on

93   the issues, on which the panel members did not reach consensus in the previous round. The rounds were

94   continued until final consensus was obtained on the 4 issues.

95   *Cut-off point for consensus*

96   The content validity ratio (CVR) is a linear transformation of a proportional level of agreement.[13] The

97   main benefit of CVR is to readily indicate whether the level of agreement among panel members exceeds

98   50%. It represents the proportion of panel participants, who rate an item as essential, and is calculated as

99   follows:

100   $\dfrac{NE - (N/2)}{N/2}$ NE is the number of panel members rating the item as essential

101   N is the number of panel members.

102   We had 28 panel members; therefore, the cut off value of CVR was 0.357, which means 19 is a

103   minimum number of panels required to reach a consensus in each questionnaire.

104   **Data synthesis and analysis**

105   Data from all Delphi rounds were extracted from the online survey database to an Excel V.20.0

106   spreadsheet, and anonymously reported as feedback to each panelist. Qualitative data (i.e., expert answers

107   and justifications) were analyzed by content analysis and discussed by the task force.   In the first open-

108   ended round, the replies were integrated and classified according to the frequency analysis. In the second

109   and further rounds consisting of multiple choice questions, the percentage and CVR of answers in each

110   item were calculated.

111   **Source of Funding**

112   No external funding was received in support of this work and ARCO.

113   **Results**

114   Three consecutive Delphi rounds were performed between July 1, 2017 and October 31, 2017. Through

115   the three Delphi rounds, full consensus was reached on the classification criteria of GA-ONFH.

116   *Round 1: Open round*

117   Four questionnaires were sent to the panel members (Table 2) and the response rate was 100%.

118   From the replies to the first Delphi survey, consensus was reached on one issue (questionnaire 1) about

119   the necessity of the classification criteria. Twenty-three panel members (82.1%) agreed the necessity of

120   classification criteria, whereas, five members (17.9%) disagreed. The most common reason for the

121   agreement was that although glucocorticoid is the most common associated risk factor for ONFH, there

122   are no defined classification criteria.

123   Predictably, consensus was not reached on the remaining three issues of cumulative dose of

124   glucocorticoids, latent periods, as well as how to classify patients with multiple risk factors (Table 2).

125   Several panel members also suggested changing the term "glucocorticoid-induced" to "glucocorticoid-

126   associated" because the exact causal relationship between glucocorticoid and the development of ONFH

127   has not been determined yet.

128   *Round 2: Selecting and limiting round with multiple choice questions*

129   Questionnaires on the three issues, on which consensus was not reached in Round 1, were modified to

130   multiple-choice questions in order to promote convergence of the various replies. Four multiple-choice

131   questionnaires were compiled using lists of categories and panelists were asked to select the most

132   appropriate category. The issue of terminology change from "glucocorticoid-induced" to "glucocorticoid-

133   associated" was also included in Round 2.

134   The response rate was 96% in Round 2. Consensus was reached on two issues: the classification of

135   patients with multiple risk factors and the term issue. However, consensus was not reached on the two

136   issues of risk dose and latent period (Table 3).

137   *Round 3: Ranking round*

138   To promote convergence of replies on the two unresolved issues in Round 2, the panel members were

139   given the opportunity to state whether or not they agreed with the category showing the highest response

140   frequency in Round 2 and to re-enter their rationale or reason why they did not agree. This was to ensure

141   that the respondents had the opportunity to state whether or not they agreed with the category showing the

142   highest response frequency in round 2. The response rate was 100% in Round 3 and since consensus was

143   reached on the remaining two queries, the classification criteria for GA-ONFH were completed (Table 4).

144   *Final consensus*

145   To classify an ONFH patient as a GA-ONFH patient: 1) subjects should have a history of glucocorticoid

146   use > 2 grams of prednisolone or its equivalent within a 3 month duration; 2) ONFH should be diagnosed

147   within two years after this glucocorticoid dosage; and 3) patients should not have other risk factor(s) than

148   glucocorticoids (Table 5).

149   *Approval of the consensus*

150   The results of the Delphi study and the final consensus on the classification criteria of GA-ONFH were

151   presented (Table 5) and approved in the general meeting of ARCO, which was held in October 25, 2017

152   in Berlin.

153   **Discussion**

154   Glucocorticoid usage has been a leading cause of non-traumatic ONFH. In addition, this risk factor may

155   be a second insult added in patients with severe diseases requiring high dose long-term glucocorticoid

156 therapy.[14] GA-ONFH can develop within several weeks after starting high dose glucocorticoid

157 treatment in many patients.[15] Most patients that gave large-to-moderate asymptomatic ONFH lesions

158 frequently progress to need surgical treatment.[16] However, we cannot predict GA-ONFH development

159 in each patient with glucocorticoid therapy because GA-ONFH has a multifactorial etiology.

160   Some glucocorticoid users with genetic predispositions have a greater susceptibility for developing

161 ONFH, while other users without genetic predispositions may not develop the disease.[17-20] It is not

162 possible to define the risk dose of glucocorticoids to develop ONFH. Nevertheless, previous studies have

163 shown that there is a strong association between ONFH development and higher doses of glucocorticoid.

164 In a quantitative review of 22 studies with sufficient information, a strong correlation was found between

165 daily total dose and the rate of ONFH (r = 0.61-0.80). The rate of the disease increased by 4.6 % in

166 accordance with every 10 mg increase in daily dose of glucocorticoid.[21] In a prospective MRI study in

167 302 patients who required glucocorticoid therapy due to SLE or other rheumatological disorders, the

168 incidence of ONFH at 1 year was 37% in SLE patients and 21% in non-SLE patients. High daily dose of

169 glucocorticoid (>40 mg/day) entailed a higher risk of ONFH compared with a daily dose of

170 glucocorticoid <40 mg/day (OR = 4.2).[22] Another prospective MRI study of 286 patients undergoing

171 renal transplantation investigated the risk of ONFH at a very early stage after transplantation. According

172 to the total doses of glucocorticoid use in the first 2 weeks postoperatively, patients were classified as

173 lower ($\leq$ 520 mg), middle (520–600 mg), and higher (> 600 mg) tertiles. The incidence of ONFH was 6%

174 in the lower-dose group, 17% in the middle-dose group, and 28% in the higher-dose group.[23] Thus, we

175 included the dose of glucocorticoids as a criterion in the present classification criteria for GA-ONFH; the

176 experts reached a consensus that subjects should receive a cumulative dose of 2 g or more over less than 3

177 months. In fact, such criteria about the dose and administration duration were deduced from the previous

178 studies performed in adult patients with several diseases including SLE and renal transplantation. But,

179 glucocorticoids are introduced for the treatment of a variety of inflammatory, immunologic, or neoplastic

180 conditions. In a recent large population-based study, although underlying disease conditions were

181 statistically independently associated with ONFH, a similar dose relationship was found between

182 glucocorticoids and ONFH among adults with low-risk and high-risk diseases.[24] Therefore, we

183 recommend to apply the criteria regardless of underlying diseases.

184   A previous study suggested that there is a risk period for developing ONFH in glucocorticoid users.[25]

185 In two prospective studies, ONFH developed within 3 to 12 months after the initiation of glucocorticoid

186 treatment,[15, 23] by tracking serial MRIs in every patient regardless of symptoms. The natural history of

187 ONFH has been well- investigated. About one-third of patients with asymptomatic early GA-ONFH have

188 symptomatic or radiological progression over a period of several months to years.[26] Practically, there is

189 a time lag between the ONFH development and the diagnosis of the disease. The diagnosis is often

190 delayed because work-up is made when patients have pain and MRI are not always utilized. Zhao et al.

191 reported that the median period from glucocorticoid therapy to hip pain was 18 months in 269 patients

192 with GA-ONFH and that 67% complained of hip symptoms within 24 months after commencing

193 glucocorticoids.[27] Therefore, we discussed the issue of the time lag from the discontinuation of

194 glucocorticoids to ONFH diagnosis, and finally reached consensus that cases should be excluded if they

195 are diagnosed with non-traumatic ONFH after the discontinuation of glucocorticoids, in spite of past

196 exposure history to high dose glucocorticoid therapy.

197 In addition, to obtain as high a degree of homogeneity as possible, we assessed cases with 2 or more

198 associated risk factors. For example, in the study of Ikeuchi et al., the researchers classified patients with

199 non-traumatic ONFH according to risk factors and about 5% were both corticosteroid- and alcohol-

200 associated ONFH.[28] Our experts recommended not to classify the cases into GA-ONFH if they have

201 another possible cause other than high-dose glucocorticoids including trauma, alcohol overuse, hereditary

202 coagulopathies, Caisson disease, radiation therapy involving the femoral head, non-glucocorticoid

203 chemotherapeutics for cancer, or Gaucher's disease.

204 The current criteria should not be used as diagnostic criteria for GA-ONFH in clinical practice or are not

205 suitable for reference in a medicolegal issue. Classification criteria are standardized definitions to create

206 homogenous cohorts for clinical research, while diagnostic criteria are developed to reach an accurate

207 diagnosis.

208 The Delphi consensus method has low external validity in terms of scientific evidence. However, this

209 method is valuable in situations where imprecise or contradictory opinions exist.[29] Because of the

210 multifactorial nature, it is difficult to define this disease. Until now, we have no established classification

211 criteria for GA-ONFH and previous studies applied their own criteria or definitions, often without clear

212 underlying evidence. Many different definitions have hindered us from understanding of the disease as a

213 whole or acquiring new knowledge by collecting and analyzing the published data. In such a context,

214   ARCO believes that the present criteria for GA-ONFH can define a homogeneous group of subjects, and

215   facilitate performance of studies concerning various ethnic populations or by different researchers.

216   However, this study did not provide the validity and reliability of the criteria. Therefore, at the further

217   study, the classification criteria should be tested by comparison with clinical diagnosis made by

218   physicians and in multicenter or multiethnic large cohorts.

219   **Conclusion**

220   The current Delphi survey provides etiologic classification criteria of GA-ONFH. ARCO recommends

221   using the criteria for studies about ONFH.

222   **Disclosure statement**   The authors declare no conflict of interest.

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308   **Supplementary Information Legend**

309   Supplementary material 1. The 23 key studies were selected from 75 studies relevant to GA-ONFH by the

310   review of task force team.