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Genetic risk factors for glucocorticoid-induced osteonecrosis: A meta-analysis

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ABSTRACT

Glucocorticoid-induced osteonecrosis is a common and severe adverse event. We conducted a meta-analysis to investigate whether polymorphisms in target genes were associated with the risk of corticosteroid-induced osteonecrosis. Published literature from PubMed and EMBASE were searched for eligible publications. Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using a fixed- or random-effects model. There were 23 articles with 35 genes described the relationship between polymorphisms and glucocorticoid-induced osteonecrosis. Meta-analyses were carried out for those SNPs with three or more eligible studies, which included four SNPs located in three genes (PAI-1, MTHFR, ABCB1). The meta-analysis revealed that the PAI-1 4G allele was associated with an increased risk of osteonecrosis compared with the 5G allele (combined studies: OR = 1.932, 95% CI = 1.145–3.261). The OR for the 4G/4G vs. 5G/5G genotype of PAI-1 was 3.217 (95% CI 1.667–6.209 with combined studies), The relative risk of osteonecrosis was increased in the 4G allele vs. 5G/5G and 4G/4G genotype vs. 5G allele, with odds ratios of 2.304 (95% CI = 1.235–4.299) and 2.307 (95% CI = 1.527–3.485) in combined studies, respectively. The ABCB1 C3435T genotype distributions available confirmed that the C allele increased osteonecrosis risk compared with the T allele (OR 1.668, 95% CI = 1.214–2.293) and TT genotype (OR 2.946, 95% CI = 1.422–6.101). There was no evidence for significant association between MTHFR C677T and ABCB1 G2677T/A polymorphisms and risk of osteonecrosis. Results of this meta-analysis indicate that the PAI-1 4G/5G and ABCB1 C3435T polymorphisms may be risk factors for osteonecrosis.

1. Introduction

Osteonecrosis (ON), also defined as aseptic or avascular necrosis of bone, is characterized by the death of one or more segments of bone. ON may lead to severe joint pain and limitations on physical activity, with some cases culminating in surgical intervention to restore function [1]. Glucocorticoids (GC) are commonly prescribed for the treatment of patients with autoimmune inflammatory diseases, neoplastic diseases, or organ transplantation. However, glucocorticoids have been a leading cause of nontraumatic osteonecrosis [2]. Glucocorticoids have direct adverse effects on osteoblasts, osteoclasts, and osteocytes. These drugs decrease lacunar–canalicular fluid, bone vascularity, and bone strength via their effects on osteocytes [3]. Since not all patients who are treated with steroids develop ON, the presence of additional risk factors or individual variation of GC sensitivity has been suggested. A number of studies have reported that this individual difference in drug sensitivity is related to genetic polymorphisms involved in vascular occlusion, coagulopathy (thrombophilia and hypofibrinolysis) [4–7], such as PAI-1, MTHFR. Plasminogen activator inhibitor-1 (PAI-1) is a critical factor that regulates coagulation and fibrinolytic systems. Previous studies of patients with osteonecrosis found that the PAI 4G/4G genotype was closely associated with ON [8,9]. The enzyme methylenetetrahydrofolate reductase (MTHFR) plays an important role in the removal of circulating homocysteine via the methionine cycle. Many researchers report that the MTHFR C677T polymorphism is related to GC-induced ON [9–11]. GC-induced ON has been reported to be related with lipid metabolism abnormalities. Altered lipid metabolism results in emboli and infarcts in bone and that engorgement of marrow fat cells may lead to compression of bone vasculature/ischemia. Gene polymorphism of ApoA, ApoB, etc. had been reported to be associated with GC-induced ON [12–14]. It was recently suggested that this individual difference in drug sensitivity is also mediated by genetic polymorphisms in drug-metabolizing enzymes (CYP3A4, CYP3A5, CYP2D6,

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CYP2C19, UGT1A1, etc.), drug transporters (ABCB1, ABCG2, etc.) or drug target molecules (NR3C1). The transport protein P-glycoprotein (P-gp), which is encoded by the multidrug-resistance ABCB1 gene, is crucially involved in the export of drugs out of the cell. The mutations in exon 21 (G2677T) and exon 26 (C3435T) of ABCB1 are associated with alteration of P-gp expression and/or function and can be used for predicting the development of GC-induced ON. By contrast, investigations of such gene variants in GC-induced ON have generally indicated no associations in some apparently conflicting and inconclusive reports. Better definition of risk factors for GC-induced ON might permit tailoring therapy to minimize this complication. Therefore, we performed a meta-analysis to assess whether common functional polymorphisms in target genes are associated with the risk of corticosteroid-induced osteonecrosis.

2. Materials and methods

2.1. Literature search

We performed this meta-analysis in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) [15] and "Meta-analysis of Observational Studies in Epidemiology" (MOOSE) [16] guidelines. We searched the English biomedical literature via PubMed and EMBASE. We also evaluated other meta-analyses and references from related articles to identify relevant studies. The search strategy to identify all potential studies involved use of combinations of the following key words: ("osteonecrosis" OR "osteonecroses" OR "avascular necrosis of bone" OR "Kienbock Disease" OR "aseptic necrosis of bone") AND ("polymorphism" OR "SNP" OR "single nucleotide polymorphism") AND ("glucocorticoid" OR "corticosteroid" OR "steroid"). The data was last updated on 20 October 2012.

2.2. Study selection and data extraction

Studies were eligible for the meta-analysis if they fulfilled the following four criteria: (1) based on a case–control design or cohort studies; (2) evaluation of the association of genetic polymorphisms and GC-induced ON; (3) available genotype distributions of both cases and controls; and (4) genotype distribution of the control population must be in Hardy–Weinberg equilibrium (HWE). Data were extracted independently by two authors (Gong, Fang). Any disagreement was resolved by discussion or through a third investigator and consensus. We extracted data from the selected articles on the following items: the first author's last name, publication year, country of origin, mean age, gender and ethnicity of the study population, the basal diseases and related diseases, steroid dose, numbers of genotyped cases and controls.

2.3. Statistical analysis

The association between genetic polymorphisms and GC-induced ON risk was estimated by calculating odds ratios (ORs) and 95% confidence interval (CI) under an additive model, a dominant model, a recessive model and an allelic model, respectively. A random (the DerSimonian and Laird method) or fixed (the Mantel–Haenszel method) [17] effects model was used to calculate the pooled OR in the presence ($P < 0.100$) or absence ($P > 0.100$) of heterogeneity [18], respectively. Publication bias was assessed with a Begg funnel plot [19] and Egger weighted regression method [20] for those analyses with greater than three trials ($P < 0.05$ indicated significant bias). The data were analyzed with the STATA software system (version 11.0, Stata Corporation, College Station, TX).

3. Results

3.1. Search results

One hundred and twenty three studies were identified in the initial search. Among these articles, 30 publications were excluded as duplicate articles and 46 were deemed not relevant at the title/abstract level. We reviewed the full texts of the remaining 47 articles. Of these, 22 articles were excluded. A flow chart summarizing the process of study inclusion is depicted in Fig. 1. All studies identified the osteonecrosis through regular radiography, bone scans, and magnetic resonance imaging (MRI). Finally, 23 articles on 35 genes described the relationship between genetic polymorphisms and GC-induced ON [8,10,13,14,21–39]. Detailed data of the characteristics of the articles and related genes are shown in Table 1.

Meta-analyses were carried out for those SNPs with three or more eligible studies, which included four SNPs located in three genes (PAI-1, MTHFR, ABCB1). Characteristics of the individual studies involved in the meta-analysis are shown in Table 2. We calculated summary estimates for the two study types (case–control and cohort) separately, as well as in combination.

3.2. PAI genetic variations and risk of GC-induced ON

A summary of results from a meta-analysis for the association between the PAI-1 4G/5G genotype and GC-induced ON are shown in Table 3. The meta-analysis revealed that the PAI-1 4G allele was associated with an increased risk of GC-induced ON when compared with the 5G allele (for the case–control studies: OR = 2.138, 95% CI = 1.034–4.422; for the combined studies: OR = 1.932, 95% CI = 1.145–3.261; Fig. 2A). The ORs for the 4G/4G vs. 5G/5G genotype of PAI-1 were 4.130 (95% CI 1.882–9.062) for the case–control studies and 3.217 (95% CI 1.667–6.209; Fig. 2B) for the combined studies, and an association was found. To illustrate dummy variables, the 4G allele (4G/4G and 4G/5G genotypes) vs. individuals with the 5G/5G genotype and 5G allele (4G/5G and 5G/5G genotypes) vs. 4G/4G genotype were also calculated. The relative risk of GC-induced ON was increased in the 4G allele (for the case–control studies: OR = 2.307, 95% CI = 1.527–3.485; for the combined studies: OR = 2.304, 95% CI = 1.235–4.299; Fig. 2C) and 4G/4G genotype (for the case–control studies: OR = 2.935, 95% CI = 1.389–6.199; for the combined studies: OR = 2.307, 95% CI = 1.527–3.485; Fig. 2D).

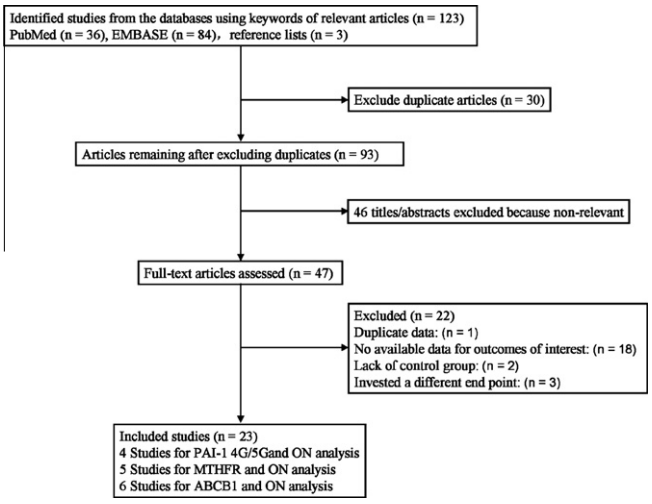

Fig. 1. Literature search and selection.