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# Use of magnetic resonance imaging for screening for avascular necrosis post-SARS

## Key Messages

1. Avascular necrosis (AVN) can occur following use of low-dose corticosteroids, though the risk increases with increase in dosage.
2. The relative risk of AVN increases non-linearly with total dosage and total dosage per kg body weight.
3. The steroid dosage does not correlate with the extent of involvement.
4. Early AVN is relatively stable in the medium term.

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## Aims and objectives

1. To study the incidence of osteonecrosis and its relationship to drug treatment and other possible factors in patients who survived severe acute respiratory syndrome (SARS).
2. To study steroid dosage and its relationship to avascular necrosis (AVN).

## Introduction

During the outbreak of SARS in 2003, most of the affected patients in Hong Kong were treated with antiviral agents and corticosteroids. Some survivors developed AVN after recovery. The dosage of steroids varied from patient to patient, and from hospital to hospital, depending on the severity of illness and the experience of the doctors managing the SARS patients. Avascular necrosis was first noticed in post-SARS patients about 6 months after illness onset. The relationship between steroid dose, patient predisposition, and the development of AVN is not fully understood. In order to ascertain the magnitude of the problem, a screening programme was organised for all SARS survivors at 6-to-9 months post-discharge. This particular timing was based on a consensus among Hospital Authority (HA) radiologists and orthopaedic surgeons.

## Methods

Patients recovering from SARS aged 10 years or above were invited for screening by magnetic resonance imaging (MRI) at 6 to 9 months after their illness. Non-ambulatory patients or those with known AVN before SARS were excluded. The scanning was based on a protocol common to all HA radiologists. Staging of AVN of the hip was achieved using a modified version of the University of Pennsylvania Staging System.[1] From the SARS databases and clinical information systems of the HA, patient demographics including: age, sex, steroid therapy details (dosage and type); polymerase chain reaction and serology results for SARS-coronavirus; $PaO_2/FiO_2$ ratio, neutrophil level, lactate dehydrogenase level at illness onset and at peak illness severity within 28 days from onset, body weight, and other risk factors of AVN (alcoholism, connective tissue disease, rheumatologic conditions, and history of significant trauma) were retrieved.

Examinations were performed at HA centres with 1 to 1.5 Tesla superconductive scanners with a basic screening sequence. When an abnormality was detected or suspected, a detailed examination of the involved joint(s) was performed at the same setting or on another date within 1 month to characterise and confirm the lesion. Plain radiographs were referred to for any bone changes. All MRI scans and plain radiographs were reported to radiologists. Controversial results underwent panel review by musculoskeletal radiologists and a final diagnosis was reached by consensus. Patients' clinical and drug histories were blinded to radiologists. All abnormalities of more than 3 mm at different sites were recorded. Diagnosis of AVN was established when a typical ring of low signal surrounding a central fatty marrow signal was found on T1-weighted images at subchondral marrow; and was further confirmed with T2-weighted images. The extent of involvement at the hip was estimated as the percentage of volume involved and at the knee as the maximum area of the lesion in the coronal plane.

The recruited adult patients were stratified into seven groups, according to the body weight–adjusted total steroid dosage received during and post-SARS hospitalisation (ie total steroid dosage per kg of body weight). Whilst SARS patients received a variety of corticosteroids (hydrocortisone, prednisolone, or methylprednisolone), all steroid dosages were converted to equivalent dosages of prednisolone; 20 mg hydrocortisone = 5 mg prednisolone = 4 mg methylprednisolone.[2] Pulsed steroid treatment was defined as equivalent to 625 mg or higher of prednisolone per day, for any period. The incidence and relative risk of subchondral AVN (at the hip or knee or both), hip AVN, and knee AVN relating to different steroid dosage groups were determined.

Patients with AVN were referred to the orthopaedic clinic for follow-up. Data analysis was performed to ascertain factors that might contribute to the development of AVN, including the dosage of steroids, the severity of illness, and the degree of respiratory insufficiency. All knees affected by AVN were tracked for follow-up with MRI at 18 to 24 months after steroid treatment. Findings of MRI and any temporal changes of lesions were retrieved from databases.

## Results

A total of 1203 SARS survivors (75 children, 1128 adults) were screened by MRI for osteonecrosis at the hip and knee, whereas 227 other survivors did not attend for their scan and were not screened. Data pertaining to adult patient groups were analysed to determine associated risk factors for AVN.

The prevalence of AVN in SARS survivors treated with treatment was 13.7%; being 9.5% and 7.0% in the hip and knee, respectively. In all, 31 (30%) of 104 post-SARS patients with AVN at the hip also developed AVN at knee whilst only 5% (n=46) free from hip AVN developed AVN at knee. When they were screened (6-9 months post-SARS), patients with hip AVN had 6.4 times the risk of manifesting knee AVN compared to those free from hip AVN.

Avascular necrosis occurred in patients receiving a total (cumulative) dosage equivalent to 720 mg of prednisolone (14.9 mg/kg). The risk of AVN increased with increased steroid dosage. The relative risk of AVN increased non-linearly with total dosage and total dosage per kg body weight.

The proportion of patients with subchondral AVN increased from 1.5% in the group who received equivalent to 0 to 25 mg/kg of prednisolone to 47% in those who received the equivalent of 200 mg/kg or more. Patients who received equivalent to a 25 to 50 mg/kg dose were 6 times more likely to develop subchondral AVN than those who received doses equivalent to less than 25 mg/kg, and the risk ratio was 28 when the dosage exceeded the equivalent of 200 mg/kg. Further analysis showed that steroid dosage was not associated with extent of the involvement.

The association of neutrophilia with AVN found in univariate and multivariate analysis requires further evaluation and analysis.

Multivariate analysis revealed that high steroid dosage, high peak neutrophil count, and a history of having had a prior serious injury were independent risk factors for subchondral AVN.

Fifty patients with AVN of the knees (bilateral in 35 and unilateral in 15) discovered at the 6-to-9 months post SARS screening consented to undergo MRI follow-up 18 to 24 months after receiving their steroids. Among these patients, 25 (50%) had no change in their affected knees. Of the 85 affected knees, 50 (59%), 32 (38%), 3 (4%) showed no change, decreased size, and progression of the lesions, respectively. However, in the 32 knees whose lesion sizes had decreased, only four showed resolution of some of them.

## Discussion

Avascular necrosis is a well-known and serious complication related to steroid therapy. The mechanism of corticosteroid-induced osteonecrosis is not known, and could be multi-factorial. Apoptosis may play a role, but its contribution remains uncertain. The prevalence of steroid induced of the femoral head ranges from 5 to 50%, while that of steroid induced AVN of the knee is not well-established. Avascular necrosis rarely presents within the first 6 months following steroid treatment. Attempts have been made to identify a relationship between corticosteroid dose and osteonecrosis, but the results of different studies are conflicting.

Due to the initially unknown and poor understanding of SARS in terms of its pathogenesis and because of its high morbidity and mortality, various doses of steroids were given to patients during the early course of the disease. This produced a large group of patients who had received very heterogeneous cumulative steroid doses. Screening by MRI demonstrated AVN at an earlier stage than older studies based on X-rays.

Whilst the use of steroids was significantly related to AVN, according to both univariate and multivariate analyses the total cumulative dose was significantly associated with the risk of developing this pathology. The relative risk increased significantly with increased cumulative dosage; those who received more than 200 mg/kg equivalent of prednisolone had a relative risk of 28 compared to those who received 0 to 25 mg/kg. The corresponding relative risk was about 26 for AVN of the hip and 63 for AVN of the knee.

Although we hypothesised that hypoxia might contribute to the development of AVN, only univariate

analysis showed a statistically significant association. Multivariate analysis did not show such a correlation. Similarly, laboratory confirmation of SARS and its severity as reflected by lactate dehydrogenase levels revealed no statistically significant association with AVN in both the univariate and multivariate analyses. Nor were neutrophil counts associated with the development of AVN, according to the univariate and multivariate analyses. Steroid dose-dependent neutrophilia and its contribution to AVN have not been reviewed in previous studies and further exploration of this area is needed.

A history of previous injury to the hip and knee requiring surgery was marginally associated with the occurrence of AVN. Although there may be a theoretical risk of disturbance of the vascular supply to the femoral head, nearly all surgery or trauma-related AVN was associated with recent trauma or recent surgical interventions. Unlike cohorts in previous studies, steroid treatment for SARS patients was not long-term and was discontinued rapidly after disease resolution. Thus, subsequent cumulative dosing contributing to the development of AVN was not an issue.

## Conclusions

Development of AVN was associated with high doses of steroid therapy; it occurred after total (cumulative) doses equivalent to prednisolone 720 mg and 14.9 mg/kg (ie <25 mg/kg). There was a six-fold increase in the risk after a total dose equivalent to 25 to 50 mg/kg, and 28-fold if the total dose was equivalent to 200 mg/kg or more. The extent of involvement was not associated with the steroid dosage. Knee AVN was relatively stable in the medium term.

The results of this study might benefit former SARS patients who develop AVN with few or no symptoms, by facilitating future clinical follow-up and management. The study also establishes a point of reference and supports the need for carefully titrating steroid dosage to minimise the risk of osteonecrosis.

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