Does smoking influence outcome after autologous chondrocyte implantation?

A CASE-CONTROLLED STUDY


Smoking is known to have an adverse effect on wound healing and musculoskeletal conditions. This case-controlled study looked at whether smoking has a deleterious effect in the outcome of autologous chondrocyte implantation for the treatment of full thickness chondral defects of the knee.

The mean Modified Cincinatti Knee score was statistically significantly lower in smokers \((n = 48)\) than in non-smokers \((n = 66)\) both before and after surgery \((p < 0.05)\). Smokers experienced significantly less improvement in the knee score two years after surgery \((p < 0.05)\). Graft failures were only seen in smokers \((p = 0.016)\). There was a strong negative correlation between the number of cigarettes smoked and the outcome following surgery \((\text{Pearson’s correlation coefficient} \ -0.65, p = 0.004)\).

These results suggest that patients who smoke have worse pre-operative function and obtain less benefit from this procedure than non-smokers. The counselling of patients undergoing autologous chondrocyte implantation should include smoking, not only as a general cardiopulmonary risk but also because poorer results can be expected in smokers following this procedure.

Autologous chondrocyte implantation (ACI) is increasingly being used for the treatment of painful chondral defects of the knee. This technique has undergone considerable development since it was first used in the United Kingdom in 1998, and has been adapted for use in the shoulder, elbow and ankle.\(^1\)\(^4\) However, little is known about the factors that affect the outcome of such surgery.

Smoking is a well-established risk factor for cardiovascular and respiratory disease. It has also been shown to have a deleterious effect on wound healing.\(^5\)\(^6\) More recently, cigarette smoking has been associated with musculoskeletal conditions such as progression of osteoarthritis of the knee, low-back pain and degenerative disc disease.\(^7\)\(^-\)\(^10\) In orthopaedic surgery, smoking has been associated with inferior clinical results following rotator cuff repair, anterior cruciate ligament reconstruction, hind-foot fusion, spinal fusion, hemicallotasis, and hip and knee arthroplasty.\(^11\)\(^-\)\(^16\)

Cigarette smoking is associated with two phases: a volatile phase and a particulate phase. During the predominant volatile phase, nearly 500 different gases are released including nitrogen, carbon monoxide and hydrogen cyanide. In the particulate phase, almost 3500 chemicals are released, and as water is removed the particulate matter (‘tar’) that remains contains the majority of the carcino gens of cigarette smoke.\(^17\) Nicotine, the addictive component of cigarette smoke, has been implicated in the pathogenesis of a variety of diseases by increasing platelet aggregation, reducing microvascular prostacyclin levels, and perhaps, more important in surgery, inhibiting the function of fibroblasts, red blood cells and macrophages.\(^18\)\(^,\)\(^19\)

However, despite these reports, a comprehensive literature review failed to identify any publications on the effects of smoking on the outcome following ACI for the treatment of chondral defects of the knee. The aim of this paper was to test the hypothesis that smoking adversely affects the outcome of ACI.

Patients and Methods

From a retrospective audit of our prospectively compiled database of all patients who had undergone ACI with a synthetic type I/III collagen scaffold or matrix-carried procedure, we identified 48 smokers, 66 non-smokers and 15 ex-smokers. In addition, we quantified the mean number of cigarettes smoked per day, as well as the number of years smoked, to deduce the number of pack-years, an indication of lifetime exposure to cigarette smoke. The inclusion
and exclusion criteria for this operation have been previously described. All the operations had been performed by the four senior authors (GB, RWJC, JAS, TWRB) between 2003 and 2006, and all patients followed a standardised programme of rehabilitation. An independent reviewer evaluated the functional outcome following surgery in all the patients and was blinded to their smoking status.

**Evaluation.** All patients were assessed according to the Modified Cincinnati Knee score, the Stanmore Functional Rating score and a visual analogue scale (VAS) before and after surgery. In addition, their demographic data, including weight and height, were also recorded. Patients were reviewed at six weeks, 12 weeks, six months and nine months after surgery, and then at one year, and yearly thereafter. Arthroscopy was scheduled for approximately one year after surgery, and the graft was assessed according to the International Cartilage Repair Society grading system. If possible, a biopsy was taken from the centre of the graft using a Jamshidi needle of 2.5 mm diameter to quantify the amount of hyaline cartilage formed in the graft.

**Statistical analysis.** An earlier pilot study enabled us to perform sample size calculations. With $\alpha = 0.05$ and $\beta = 0.2$ (hence a power of 80%), a total of 90 patients would be required to detect a difference of ten points in the modified Cincinnati Scale. Statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, Illinois). Paired t-tests were used to compare knee scores before and after surgery and Fisher’s exact test was used to compare the proportion of excellent and good results achieved in both groups. The level of significance was set at $p = 0.05$. Regression analysis was performed to determine whether there was a relationship between lifetime exposure to cigarette smoke as judged by the pack-years and the modified Cincinnati score two years after surgery.

**Results**

The two groups were matched for age, gender, body mass index (BMI), proportion of ACI or matrix-carried procedures, the duration of symptoms, the number of previous operations and the size of lesions (Table I). Figure 1 demonstrates the improvement in the mean modified Cincinnati scores. There was a statistically significant difference in the pre-operative as well as the post-operative mean modified Cincinnati score at two years in smokers and non-smokers ($p = 0.037$ and $p = 0.05$, respectively). Non-smokers also experienced a significantly higher increase in Cincinnati scores two years after surgery.

Arthroscopically, there was a higher proportion of excellent and good results according to the International Cartilage Repair Society scale in non-smokers than in smokers. Smokers were less likely to form hyaline or mixed hyaline and fibrocartilage than non-smokers (Table II), although this was not statistically significant owing to the low numbers of biopsies performed. Graft failures were only seen in smokers, and this was significant ($p = 0.016$).

There was a strong negative correlation between the number of cigarettes smoked in mean pack-years and the outcome following surgery measured by the mean Cincinnati score at two years. Pearson’s correlation coefficient was -0.65, and this was statistically significant ($p = 0.004$).

**Discussion**

We believe this to be the first study to assess the effect of smoking on the outcome of ACI. The results showed that...
patients who smoke and ex-smokers have worse pre-operative function and derive less benefit from this procedure than do non-smokers (Fig. 1). A greater proportion of fibrous tissue or fibrocartilage was formed in smokers. It is unclear why smoking should affect outcome after ACI. Articular cartilage is avascular and does not rely on constituents in the blood for repair. It receives its nutrition and oxygen supply by diffusion from the synovial fluid and subchondral bone.\textsuperscript{23,24} The partial pressure of oxygen in synovial fluid (50 mmHg to 60 mmHg)\textsuperscript{25} is approximately half that in arterial blood (80 mmHg to 100 mmHg), and in osteoarthritic joints the oxygen tension is further reduced.\textsuperscript{26} In animal models, long-term hypoxia has been shown to alter gene expression levels of structural proteins and growth factors in articular cartilage in the knee.\textsuperscript{27} This articular cartilage also expresses the hypoxia-inducible factor 1α (HIF-1α) which helps tissue function at low oxygen tensions. Smoking has been shown to reduce its expression in other tissues,\textsuperscript{28} and perhaps a similar mechanism is applicable in cartilage. Smoking has also been shown to delay chondrogenesis in a mouse model of fracture healing in the tibia. Mice exposed to smoke exhibited less type II collagen in the fracture callus and a delay in the chondrogenic phase of fracture healing in the tibia.\textsuperscript{29} Tissue hypoxia may have been a major factor in the impaired production of cartilaginous callus in mice exposed to smoke. Perhaps a reduced or delayed type II collagen synthesis as a result of smoking, as well as tissue hypoxia in the synovial joint, led to the deleterious effects of smoking on cartilage repair in our patients. This could also explain why all the graft failures occurred in the smoking group.

Several reports have suggested that smokers experience more musculoskeletal pain than non-smokers.\textsuperscript{7,11,12,30} In a longitudinal study assessing the degree of cartilage loss in male smokers and non-smokers as judged by MRI, men who smoked at the baseline of the study had statistically significant higher pain scores as judged by a VAS than non-smokers.\textsuperscript{7} They were also found to have an increased risk for cartilage loss at the medial tibiofemoral and the patellofemoral joints. Pain constitutes one-fifth of the modified Cincinnati score; the other activities being assessed are walking, jumping, running, stairs, overall activity, and symptoms of swelling and giving way. Therefore, our cohort of smokers experienced not only greater pain but also global restriction of function. Smokers have also been reported to have higher levels of pre-operative pain and lower levels of function prior to rotator cuff repair and to experience less improvement following open repair than non-smokers.\textsuperscript{11} Similarly poorer outcomes were reported among smokers following anterior cruciate ligament reconstruction.\textsuperscript{12} Although pain was not an issue in these patients, smokers were less likely to return to their original level of pre-injury sport and had worse functional knee scores than non-smokers. Animal studies have suggested that reduced cellular density and type I collagen expression in mice with a medial ligament injury exposed to smoke may provide an explanation for poor healing of knee ligaments.\textsuperscript{31}

ACI is not a universally successful procedure, with reported rates of graft failure ranging from 7% to 25%, delamination from 8% to 22%, and graft hypertrophy from 0% to 36%.\textsuperscript{32,33} An important study has shown several prognostic factors that may be associated with poor outcome following ACI. These include greater age, patients with lower pre-operative Cincinnati scores, longer duration of symptoms, multiple defects, and multiple procedures prior to the index procedure.\textsuperscript{34} This case-controlled study has highlighted smoking as a possible cause of failure. Smoking has been shown to be the single most important risk factor for the development of complications after elective arthroplasty of the hip or knee.\textsuperscript{13} Wound complications have also been shown to be related to smoking habits, and smokers are more likely to need further surgery.\textsuperscript{35} Observational studies suggest that prolonged abstinence from smoking reduces the risk of many peri-operative complications.\textsuperscript{36} The results of ACI in ex-smokers were intermediate between those of smokers and non-smokers (Fig. 1).

The counselling of patients undergoing ACI should include smoking, not only as a general cardiopulmonary risk, but also because poorer results can be expected following this procedure. Patients should be encouraged to enrol in smoking-cessation programmes and at the very least to stop smoking six to eight weeks before surgery and during the period of rehabilitation.\textsuperscript{37}

Table II. Clinical and histological outcomes

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th>Non-smokers</th>
<th>Ex-smokers</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Excellent/good clinical results</td>
<td>35.6</td>
<td>66.1</td>
<td>66.7</td>
<td>0.0019</td>
</tr>
<tr>
<td>% Excellent/good arthroscopic results</td>
<td>56</td>
<td>87.8</td>
<td>75</td>
<td>0.0137</td>
</tr>
<tr>
<td>% Hyaline or mixed cartilage from biopsy</td>
<td>30</td>
<td>40.9</td>
<td>33.3</td>
<td>0.46</td>
</tr>
</tbody>
</table>

* p-values are derived from comparisons between smokers and non-smokers.

References


