■ ASPECTS OF CURRENT MANAGEMENT

Chronic inflammation, joint replacement and malignant lymphoma

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This paper considers the increased risk of the development of lymphoma in patients with chronic inflammatory disease who undergo metal-on-metal arthroplasty.

Patients with inflammatory conditions have twice the risk of developing lymphoma. This seems to be further increased if they have a metal-on-metal joint replacement. Prospective studies should be undertaken in patients with chronic systemic inflammatory conditions after the implantation of a metal-on-metal implant to investigate lymphocyte function and the risk of developing haematopoietic malignancies.

Register studies

One method of analysing the risk of developing lymphoma after joint replacement would be to screen large cohorts of patients for tumours over an extended period. The Scandinavian joint registers and national cancer statistics make this possible, but there are difficulties with the statistical evaluation of this type of study.¹

Lewold et al² from Sweden and Paavolainen et al³ from Finland reported a significant increase in lymphoma after knee replacement. In the Swedish study, osteoarthritis (OA) and rheumatoid arthritis (RA) were separated. Men with RA, followed for 3180 person years, had the highest risk of a lymphoma with a standardised rate of mortality (observed *vs* expected) of 4.7 after 60 months.² There was no increase in patients with OA. In the Finnish study with a mixed population the standardised incidence rate was 1.4 for non-Hodgkin's lymphoma.³

In a Danish study of hip and knee replacement for OA, no increase in haematopoietic cancer was found.⁴ Gillespie et al⁵ from New Zealand and Visuri et al⁶ from Finland found a three- to fourfold risk for tumours of the lymphatic and haematopoietic systems after total hip replacement (THR) compared with that in a community control group, but neither study separated OA from RA. Two other studies using

patient admission registers to investigate the relationship between THR and cancer found no significant increase in lymphatic tumours.^{7,8} The highest risk of lymphoma (standardised incidence rate 4) was found in a Finnish study which analysed a metal-on-metal replacement, namely the McKee-Farrar implant.⁹ None of these studies, however, separated OA from chronic inflammation. It is notable that RA, with the highest risk of the development of lymphoma, is present in only 3% to 5% of an arthroplasty population.^{10,11} The high risks of development of lymphoma in RA were confirmed by studies on rheumatoid patients and from the Swedish cancer register¹² analysing haematopoietic malignancies, which verified earlier studies that showed patients with RA had more than twice the risk of developing lymphoma than community control groups.¹³⁻¹⁶ It is not clear whether modern treatment with tumour necrosis factor (TNF)-blocking agents or methotrexate increases the risk for lymphoma or if this is simply an effect of advanced disease.¹³⁻¹⁶ Recent data have also suggested a doubled risk in patients with systemic lupus erythematosus.¹⁷ The highest risk is in those with Sjögren's syndrome, in which 10% develop lymphoma,^{18,19} and when lymphoma predictors such as the CD4+/CD8+ ratio were used the risk increased to over 30%.²⁰

There are no register-cohort studies on the relative risk (standardised incidence rate or rate of mortality) of lymphoma in patients with a chronic systemic inflammatory condition, with reference to the activity and stage of the disease and whether the patient had undergone arthroplasty, especially a metal-on-metal prosthesis. This could only be done by cross-referencing different registers and probably only in the Nordic countries where personal identification numbers are used and arthroplasties have been registered for more than 30 years.^{10,11}

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Cellular toxicity and the immune system

There are many tests for studying the carcinogenic effects of new materials for clinical use in cell or bacterial cultures. The toxicity of cobalt and chromium, both of which constitute an important part of prosthetic alloys, is well documented.²¹⁻²⁵ In tribological failures with catastrophic wear this may even lead to systemic cobalt poisoning.²⁶

The most important questions are whether safe levels of metal ions can be determined for successful implants and if there are subgroups of patients with joint replacements who are at an increased risk of developing tumours, especially of the lymphatic system.²⁷⁻²⁹

Occupational environmental and animal testing data are of limited value, and ultimately clinical data on patients are required.³⁰ A recent review has summarised the potential toxicity of metals released from alloys used in modern orthopaedics.³¹ As far as can be estimated from published clinical studies, the only combination which is likely to give significantly increased ion levels under normal conditions is cobalt-chromium alloys articulating against themselves.³² With the renewed popularity of metal-on-metal bearings, especially in younger patients, the focus has hitherto been on measuring cobalt ion concentrations in blood and urine. However, whether such measurements should be made on whole blood, plasma, serum or erythrocytes in addition to urine is unclear.³³ A recent study has indicated that serum and whole blood levels are not equivalent.³⁴

Retrieval analysis of metal-on-metal explants has shown, after a post-operative run-in period, annual wear of up to 5 μm .³⁵ In such patients, the serum cobalt levels were three to five times higher than those of control subjects.³⁵ In some studies, there was a late (four years) reduction of chromium but not of cobalt ions.³⁶ New sensitive and reliable methods of determining trace metals by high-resolution inductively-coupled plasma mass spectrometry have stimulated long-term repeated measurements.³⁷⁻⁴⁰ It could be inferred that patients with metal-on-metal implants have significantly higher serum and urine cobalt concentrations in the long-term than those with conventional metal-on-polyethylene bearings.⁴¹⁻⁴⁴ Loose metal-on-metal implants may raise the level by factors of 50 to 300 compared with control groups.⁴⁵ It has also been shown that there is a reversible exercise-related rise in plasma cobalt levels^{46,47} with variation between different metal-on-metal devices and sizes of femoral head.⁴⁸⁻⁵⁰ In a study on ten women with a metal-on-metal implant, transplacental transfer and increased levels of cobalt were found in the umbilical cords of their infants.⁵¹

A recent report of 73 patients with metal-on-metal THRs showed an excellent probability of prosthetic survival at a minimum follow-up of ten years.⁵² Elevated serum metal levels were found by atomic absorption spectrometry which is less reliable, but were the same at short and intermediate follow-up. The authors reported four primary malignancies and stated that there was no evidence of increased risk. However, only 4% of their patients had an

inflammatory arthritis. Wear particles from peri-prosthetic tissue after metal-on-metal implantation have been analysed by Catelas et al⁵³ up to two years post-operatively. Rounded chromium particles were seen initially, and subsequently a greater proportion of cobalt-chromium-molybdenum particles were found. In one study, a prominent feature in the tissue of patients with metal-on-metal implants was perivascular particle infiltration of lymphocytes which was not seen in those with metal-on-polyethylene bearings.⁵⁴ In a recent study, CD 20-positive B-lymphocytes and a distinct infiltration were found in the neocapsular tissue of 46 patients who had undergone revision of a metal-on-metal implant.⁵⁵ In two cases, lymphatic follicles with both T- and B-lymphocytes were detected. Patients with RA and infection had been excluded and the median time until revision was only 14 months.

Pearle et al⁵⁶ investigated lymphocyte gene expression in response to metal particles. They showed a non-specific innate activation of the immune system by polymethyl-methacrylate particles whereas metal particles promoted induction of T-lymphocyte-specific gene expression.

Ladon et al⁵⁷ showed a significant increase not only in serum levels of chromium and cobalt but also in chromosomal translocation and aneuploidy in peripheral blood lymphocytes at 6, 12 and 24 months after implantation of a metal-on-metal prosthesis. Also, Hart et al⁵⁸ showed a statistically significant decrease in the level of CD8+ T cells in asymptomatic patients after implantation of a metal-on-metal prosthesis which was well fixed. Theander et al²⁰ found that patients who did not have an implant, but had Sjögren's syndrome with CD4+ T cell lymphocytopenia or a disturbed CD4+/CD8+ ratio had a significantly-increased risk of later development of a lymphoma. Such a study has not been performed in patients with a metal-on-metal implant. It would be of value if a threshold could be established for serum levels of cobalt and chromium which would not cause lymphocytopenia in patients with a specific metal-on-metal bearing. Dunstan et al⁵⁹ studied 25 patients who received metal-on-metal bearings between 1965 and 1979 with a mean age at operation of 33 years and a mean follow-up of 35 years. They used the 24-colour fluorescent *in situ* hybridisation chromosomal painting technique on peripheral leucocytes to map chromosomal changes and aberrations. They found a significant difference in structural aberrations between a metal-on-polyethylene control group and the metal-on-metal group. Also, there were significantly more structural aberrations in the metal-on-metal group than in a revised metal-on-metal group after exchange to a conventional metal-on-polyethylene joint. There was no difference between the control and revised groups. Dunstan et al⁵⁹ stated that the normal genetic repair mechanisms may be overloaded or damaged by the metal ion load.

The immune system can be subdivided into innate and adaptive systems. Macrophages, neutrophils and mast cells are the major active cells in the innate immune response to

environmental agents such as metal ions. The adaptive system provides a memory for the original challenge and generates an enhanced response on re-exposure, largely through T and B cells.⁶⁰

Follicular lymphoma is the second most common form of non-Hodgkin's lymphoma, accounting for approximately 25% of cases.⁶¹ Dave et al⁶² studied the gene expression profile in 191 biopsy specimens from patients with untreated follicular lymphoma. Unexpectedly, they found that the gene-expression signatures which predicted survival were derived from non-malignant cells in the tumour. This observation points to an important interplay between the host immune system and malignant cells. It is therefore possible that non-malignant lymph node cells, which include T cells, macrophages and follicular dendritic cells, promote proliferation of existing malignant cells.

Immunological high-risk factors for patients undergoing metal-on-metal implantation are therefore advanced RA, systemic chronic inflammation of connective tissue, ongoing anti-TNF treatment, severely impaired renal function and, in women, foreseeable pregnancy.

In conclusion, in patients with chronic systemic inflammatory conditions, there are no prospective studies which follow disease-activity lymphocyte function, measure ion concentrations and evaluate the risk of developing primary haematopoietic malignancy or lymphoma after metal-on-metal arthroplasties. Such studies are necessary to establish whether patients with high-risk factors should undergo such a procedure.

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