Determination of serum levels of cobalt and chromium in 17 patients undergoing metal-on-metal THR

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Purpose. To assess cobalt and chromium concentrations in serum and urine in 17 patients that underwent total hip replacement (THR) with a metal-on-metal bearing and to determine their correlation with radiographical findings.
Materials and methods. Cobalt and chromium concentrations were measured in 17 patients by means of atomic absorption spectrophotometry before implantation of a metal-on-metal THR, between the first and second year post-op and between the third and fourth year post-op. Cobalt and chromium concentrations in urine were also determined at the end of follow-up. The post-op radiological study was compared with that carried out at the end of follow-up. Mean patient age was 57 ± 6 years and mean follow-up was 31 ± 9 months.
Results. Mean cobalt concentration did not rise during the first and second year post-op with respect to the mean pre-op concentration, but it did increase between the third and fourth year. Mean chromium concentration rose between the first and second year and they went on to drop slightly between the third and fourth year post-op. No relationship was found between the appearance of radiolucent lines or a varus or valgus position of the stem and the cobalt and chromium levels in serum and urine. Eighty-five percent of cups with an inclination > 56° showed cobalt and chromium concentrations in serum in excess of the mean pre-op value.
Conclusions. The increase in mean serum cobalt and chromium concentrations detected in our study was lower than that shown by other authors. This increase occurred mainly between the first and second year post-op. The series under study shows that the more vertically the cup is placed the higher the cobalt and chromium levels present.

Key words*: total hip replacement, metal-on-metal bearing, metal ions, cobalt, chromium.*

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Determinación de los niveles en suero de cobalto y cromo en 17 pacientes tras el implante de una prótesis total de cadera con par metal-metal

Objetivo. Valorar los niveles de cobalto y cromo en suero y orina en 17 pacientes tras el implante de una prótesis total de cadera (PTC) con par de fricción metal-metal y su correlación con los hallazgos radiológicos.
Material y método. Se determinaron en 17 pacientes, mediante espectrofotometría de absorción atómica, las concentraciones de cobalto y cromo en suero antes de la implantación de una PTC metal-metal, entre el primer y segundo año, y entre el tercer y cuarto año tras la intervención, y las concentraciones de cobalto y cromo en orina al final del seguimiento. Se comparó el estudio radiológico postoperatorio con el realizado al final de seguimiento. La edad media de los pacientes fue de 57 ± 6 años, y el tiempo medio de seguimiento de 31 ± 9 meses.
Resultados. La concentración media de cobalto no se elevó durante el primer y segundo año tras la intervención respecto a la concentración media preoperatoria, y sí lo hizo entre el tercer y cuarto año. La concentración media de cromo se elevó durante el primer y segundo año, para descender ligeramente entre el tercer y cuarto año tras la intervención. No se evidenció ninguna relación entre la aparición de líneas de radiolucencia o la colocación del vástago en varo o valgo con los niveles de cobalto y cromo en suero y orina. El 85% de los cotilos con una inclinación superior a 56° presentaron concentraciones de cobalto y cromo en suero por encima de la media preoperatoria.
Conclusiones. El incremento de las concentraciones medias de cobalto y cromo en suero detectado en nuestra serie fue menor respecto a otros estudios. Este incremento se produjo principalmente entre el primer y segundo año tras la intervención. En la serie estudiada se aprecia un incremento de los niveles de cobalto y cromo en relación con la verticalización del cotilo.

Palabras clave*: prótesis total de cadera, par de fricción metal-metal, iones metálicos, cobalto, cromo.*

The failure of total hip replacement (THR), whether due to the wear of articular components or to loss of bone fixation, is one of the most frequently found complications in orthopedic surgery. This situation has given rise to renewed interest in the research and study of the workings of the various types of bearings, with the purpose of increasing implant longevity[1].

The realization that polyethylene wear debris caused by the friction that occurs between a metal head and an ultra-high-molecular-weight polyethylene component (the most commonly used bearing surface) is the main cause of periprosthetic osteolysis and implant failure has resulted in the advent of new types of bearings, the metal-on-metal kind being among them. THR with metal-on-metal bearings has been shown to undergo a lower degree of linear and volumetric wear, and may prove to be an alternative to implants with polyethylene bearings insofar as it reduces the degree of wear and the chances of osteolysis brought about by polyethylene debris particles. However, there is an increase of the concentration of metal ions–mainly cobalt and chromium–subsequent to a metal-on-metal THR, with possible long-term effects, both at the local and systemic levels, caused by the exposure to high concentrations of these ions[2].

The purpose of this study is to assess serum and urine levels of cobalt and chromium in patients undergoing metal-on-metal THR, and to determine their correlation with radiographic findings.

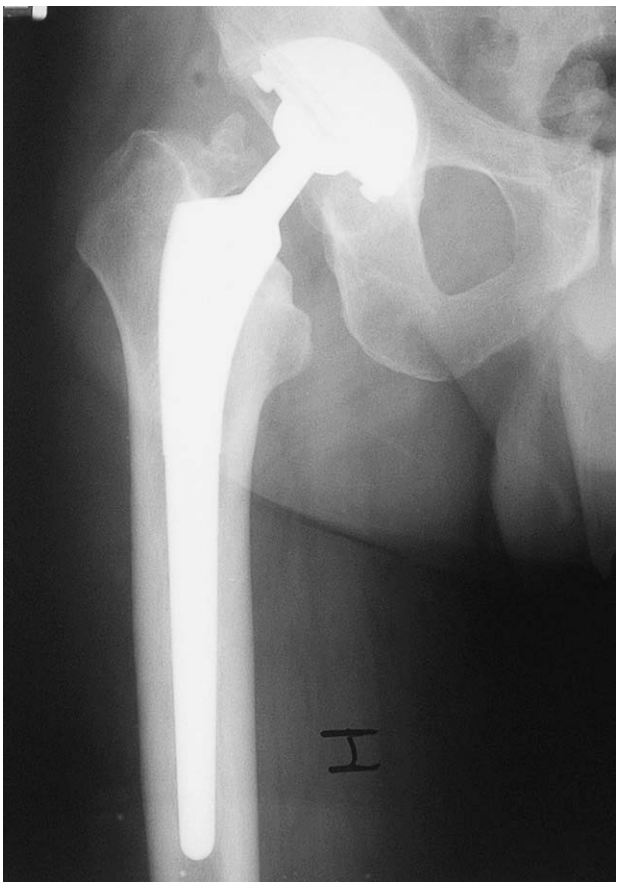

Figure 1. *Antero-posterior x-ray of the M2a metal-on-metal bearing.*

MATERIALS AND METHODS

Between January 2001 and June 2003, 22 M2a metal-on-metal (Biomet Merck)® prostheses were implanted in 20 patients undergoing THR in our center (fig. 1).

The characteristics of the components were the following: a hemispheric plasma-sprayed porous coated press-fit cup having four non-rotational fins and allowing for the addition of directional screws; a cup liner made of new-generation polyethylene and a chromium-cobalt-molybdenum alloy; a chromium-cobalt-molybdenum head containing a high degree of carbon (0.08%); a four-sided press-fit stem, made with a titanium alloy (Ti-6 Al-4V), with anterior and posterior ridge, and with a wide and profiled lateral fin. The surface topography of the stem is of three kinds: the proximal third is a porous titanium alloy layer covered with sprayed plasma; the medial third is a textured Interlok® surface; the distal third is polished.

Three patients had to be excluded because they had undergone contralateral THR (one of them had a metal-polythene bearing and the other two had a metal-on-metal bearing), and thus 17 patients remained in the study group. None of these had undergone a prior replacement procedure, nor did had they had any other joint implantation. We studied 13 male and 4 female patients with a mean age, at the time of surgery, of 57 ± 6 years, and an average weight of 74 ± 9kg. The pre-op diagnosis was primary hip arthritis in 12 cases and avascular necrosis in 5 cases. The right hip was treated in 5 cases and the left hip in 12.

All the stem implants were uncemented, cups required fixation with screws in 9 cases, and the femoral heads were made of metal and 28mm in diameter. Mean follow-up was 31 ± 9 months (minimum 17, maximum 46). Serum cobalt concentrations and urine chromium concentrations were determined by atomic emission spectrophotometry /mass spectrophotometry, while serum chromium concentrations and urine cobalt concentrations were determined by atomic absorption spectrophotometry/graphite chamber (Reference Laboratory S.A. Barcelona). The relevant reference values were the following: a) cobalt concentration in serum was 1.0 micrograms per liter (mcg/l) in exposed individuals at the end of the working week; b) chromium concentration in serum was up to 2 mcg/l in unexposed individuals; c) cobalt concentration in urine was 15mcg/l in exposed individuals at the end of the working week; and d) chromium concentration in urine was 30mcg/l creatinine in exposed individuals at the end of the working week.

Serum concentrations of cobalt and chromium were determined, prior to implantation of the metal-on-metal bearing, between the first and second year and, subsequent to the implantation, between the third and fourth year, whereas cobalt concentrations in urine were determined at the end of follow-up.

The minimum detection values were 0.5 mcg/l cobalt in serum; 0.2 mcg/l chromium in serum, and 2 mcg/l cobalt in urine. Concentrations below these values were established for statistical analysis at 0.25 mcg/l cobalt in serum; 0.1 mcg/l chromium in serum; and 1 mcg/l cobalt in urine, as has been done by other authors[3-5]. For each sample, we worked out mean and percentiles of 25 and 75%.

On comparing the post-op x-ray study with a study carried out at the end of follow-up, we observed radiolucent lines surrounding the femoral stem, which we classified them following Gruen's zones[6], and around the cup, distributed into the areas described by DeLee and Charnley[7]. We also analyzed any osteolytic areas and determined whether the stem had been implanted in varus or valgus. Cup inclination was measured in degrees and three groups were established: group I (inclination equal to or under 40°), group II (inclination between 41 and 55°) and group III (inclination equal to or over 56°).

The data were analyzed using the SPSS 7.0 statistical software, and quantitative variables were compared by means of the paired Student's «t» test. Threshold values for p were equal to or under 0.01.

RESULTS

Mean pre-op concentration of cobalt in serum was 0.52 ± 0.35 mcg/l, and it practically did not increase during the first and second post-op years, the mean levels being 0.51 ± 0.39 mcg/l, but it did increase during the third and fourth post-op years reaching a mean concentration of 0.95 ± 0.30 mcg/l (fig. 2), and indicating a significant difference with respect to pre-op values (p = 0.01) and to first and second year post-op values (p = 0.003).

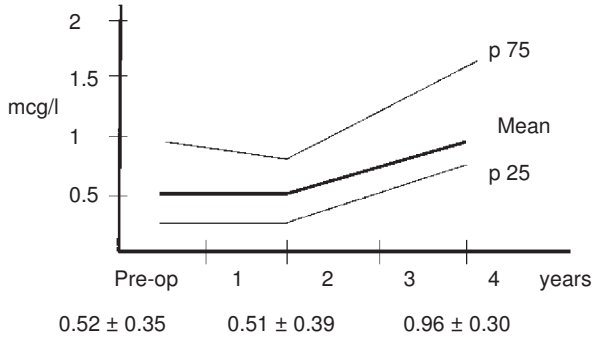

Figure 2. *Evolution of mean serum cobalt concentrations and of 25/75 percentiles.*

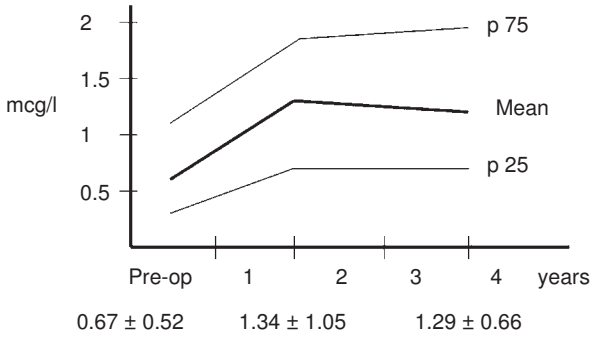

Figure 3. *Evolution of mean cobalt chromium concentrations and of 25/75 percentiles.*

The mean chromium concentration in serum, however, increased from pre-op levels of 0.67 ± 0.52 mcg/l to 1.34 ± 1.05 mcg/l during the first and second post-op years, and then fell slightly during the third and fourth years reaching a concentration of 1.29 ± 0.66 mcg/l (fig. 3), thus evincing a statistically significant difference between post-op and pre-op values (p < 0.0001).

The mean cobalt concentration in urine at the end of follow-up was 2.92 ± 2.25 mcg/l, and the chromium concentration in urine was 1.92 ± 1.36 mcg/g creatinine.

The increase in the cobalt concentration in serum coincided with an increase in the cobalt concentration in urine in only 7 cases (41%); and the increase of the respective chromium concentrations coincided in only 4 cases (23%).

At the end of follow-up, we observed radiolucent lines surrounding the femoral stem in 9 patients (53%), with a higher frequency in zones 4 (8 cases) and 5 (3 cases), and with a lower frequency in zones 3 (2 cases), 11 (2 cases), 10 (1 case) and 12 (1 case). Only one case presented with radiolucent lines in zone 1 of the cup. We observed malalignment of the femoral implant stem in six patients (35%): 4 were in valgus and 2 in varus. Five of these patients (83%) presented with radiolucent lines.

There was no correlation between the serum and urine levels of cobalt and chromium and the presence or absence of radiolucent lines, nor was there any correlation with an adequate implantation or a valgus or varus implantation of the femoral stem.

As regards cup inclination, we found 1 case in group I (≤40°), 9 cases in group II (41-55°), and 7 cases in group III (? 56°), plus 4 cases of 58°, 1 case of 60° and 1 case of 62° (fig. 4). In group III, 85% of the patients presented above the average serum levels of cobalt and chromium, while 55% of the patients in group II exhibited an increase in cobalt levels and 44% in chromium levels. On the other hand, only 28% of the cases in group III presented with increased cobalt and chromium levels in urine.

None of the implants revealed x-ray signs of osteolysis. There was one case of aseptic loosening that was revised 25 months later. This case presented serum cobalt levels of 2.2

Figure 4. *Anteroposterior x-ray image of 58° cup inclination, 1.4 mcg/l serum levels of cobalt and 4 mcg/l chromium.*

mcg/l and chromium levels under 0.5 mcg/l; furthermore, it presented with radiolucent lines in femoral zones 10, 11 and 12, and a 62° cup inclination. While it presented no x-ray signs of osteolysis, it did reveal an increased uptake on a bone scan.

Three patients were left out of the study: one of them had undergone THR with a metal-polyethylene bearing, and the other two had undergone THR with a metal-on-metal bearing. In these two cases the prostheses were implanted contralaterally, at 14 and 21 months respectively. Prior to the second implantation, these two patients presented with high serum levels both for cobalt (4.8 mcg/l and 3 mcg/l) and for chromium (2 mcg/l and 0.7 mcg/l); after a two-year follow-up, subsequent to the second implantation, they presented with similar serum levels for cobalt (4.6 mcg/l and 3.3 mcg/l) but higher levels for chromium (3.5 mcg/l and 2.6 mcg/l).

DISCUSSION

Several kinds of metal-on-metal bearings were developed and used in the 60's; however, they were discarded and replaced by metal-polyethylene bearings in the mid 70's. This was due to the following reasons: the satisfactory initial results obtained with the Charnley prosthesis; a high rate of aseptic loosening; the possibility of a toxic effect; carcinogenesis and hypersensitivity related to metal particles; the high rate of infection and the increase of the rate of fatigue in the periprosthetic bone[8]. These prostheses were reintroduced at the end of the 80's, due to the problems generated by polyethylene wear debris. Although the results for today's metal-on-metal bearings only have short and middle term follow-ups–there are yet no publications of results for the long term–they must be considered as a feasible alternative to other bearings owing to the possibility they offer of reducing volumetric wear, the number of particles released and the likelihood of osteolysis[2,9].

An increase in the concentration of metal ions in serum and urine, mainly cobalt and chromium, was detected following metal-on-metal THR. Tables 1, 2 and 3 show results obtained by different authors with respect to the mean concentrations of cobalt and chromium in serum and urine in relation to metal-on-metal THR evolution time. There are increased cobalt and chromium levels and these prove to be higher in patients with a metal-on-metal bearing than in

Table 1. Atomic-absorption spectrophotometry*** of mean serum concentrations of cobalt** in mcg/l* following metal-on-metal THR, according to various authors.

	Pre-op	Evolution (years)						
		1	2	3	4	5	7	25
Jacobs[10]								0.9
Brodner[3]		1.1						
Gleizes[11]		2.63 (44.6 nmol/l)						
Brodner[4]	0.15	1	0.75	0.6	0.9	0.7		
Clarke[12]			1.3 (22 nmol/l)					
Delaunay[13]	3.6					3.8	2	
Gandía	0.52	0.51	0.96					

*Jacobs[10] in parts per million, Gleizes[11] and Clarke[12] in nmol/l (1 nmol Co = 0.059 mcg Co).
**Delaunay[13] total in blood.
***Clarke[12] with ICP-MS *(inductively coupled plasma mass spectrophotometry)*.

Table 2. Atomic-absorption spectrophotometry** of mean serum concentrations of chromium** in mcg/l* following metal-on-metal THR, according to various authors.

	Pre-op	1 year	2 years	3 years	4 years	25 years
Jacobs[10]						1.28
Maezawa[14]		0.9				
Clarke[12]			0.98 (19 nmol/l)			
Maezawa[5]		1.05 ± 0.76	1.46 ± 0.91	1.61 ± 1.31		
Brodner[15]					1.1	
Gandía	0.67 ± 0.52	1.34 ± 1.05		1.29 ± 0.66		

*Jacobs[10] in parts per million and Clarke[12] in nmol/l (1 nmol Cr = 0.052 mcg Cr).
**Clarke[12] with ICP-MS (*inductively coupled plasma mass spectrophotometry).*

Table 3. Mean urine concentrations of chromium in micrograms per liter (mcg/l) following metal-on-metal THR

	1 year	3 years	25 years
Jacobs[10]			1.22
Maezawa[14]	2.2		
Gandía		1.92 ± 1.36	

those with a metal-on-polyethylene bearing or a ceramic-on-polyethylene bearing[3,4]. However, the metal-on-metal bearing is not the only kind that increases the serum levels of metal ions; metal-on-polyethylene bearings have also been known to have this effect[16].

The increases in the mean cobalt and chromium concentrations in our series have been lower than those found in other studies. This could be accounted for by the fact that the bearings we used contained a high degree of carbon in the coating of the femoral head and cup, which provides greater resistance to wear[1,2]. Chan et al[9] researched into the wear performance of metal-on-metal bearings using a hip simulator and they observed a lesser degree of wear in bearings with a high carbon content.

Our observations, similarly to others that have been published, confirm the hypothesis that the increase in serum concentrations is produced mainly in the first and second post-op years. The graphs for volumetric wear published by Chan et al[9] showed that implants presented a common accelerated initial wear period during the first million cycles (one million cycles is deemed the average one-year activity in patients with joint implants). There was eventually a marked decrease in the wear rate, which approached low values in a state of equilibrium. Other authors observed that serum chromium levels increased during the first and second post-op years[5], and those of cobalt in serum during the period between 6 months and a year after replacement[4], or after a period of 18 months following replacement[11].

An interesting issue that arises out of these findings concerns whether high levels of metal ions can be said to predict negative prosthetic performance.

Clinical and radiological results do not seem to indicate–at least up to the present moment–any differences between the various kinds of bearings. Neither clinical nor radiological differences have been found between groups of patients with metal-on-metal bearings and groups with metal-polyethylene or ceramic-polyethylene bearings[17]. Metal-on-metal bearings are recommended for young patients[4,18]. A prospective randomized study with a two-year follow-up compared metal-on-metal with ceramic-on-polyethylene THR's radiologically (computer-assisted method). In the cases of metal-on-metal prostheses, the cranio-caudal migration of the acetabulum was noticeably less than in the cases of ceramic-on-polyethylene bearings, which indicated a satisfactory primary fixation[19]. Both satisfactory and excellent clinical results have been published for 97% of the cases with a six-year follow-up[13], and 98.2% survivorship after a 7-year period following metal-on-metal THR[20].

In our series, we have not found any correlation between cobalt and chromium levels and the appearance of radiolucent lines or stem positioning. Other studies have observed higher levels of metal ions in cases of revision due to aseptic loosening[21]. In our case of aseptic loosening, we found that the serum cobalt level was above average. Other authors have not found radiological evidence of high volumes of particle debris in the metal-metal interface of the implantations they revised surgically[22]. Another study found that the use of a metal-on-metal bearing could be associated with a risk of aseptic loosening that was lower than that of the metal-on-polyethylene bearing, though the values were not statistically significant[23].

In the present study we found an increase in the cobalt and chromium levels in those cases in which the cup had an inclination above 56°. Brodner et al[15] researched the influence of cup inclination on the levels of cobalt and chromium subsequent to a metal-on-metal THR, considering 3 groups on the basis of degree of inclination, and did not find statistically significant differences. Notwithstanding this, 3 patients with marked inclinations (58, 61 and 63°) did show higher than average serum levels of cobalt and chromium. Delaunay[13,24] establisheds a correlation between the increase of cobalt concentrations and a cup anteversion of over 25°.

Some authors refer to another feature of the functioning of metal-on-metal THR's stating that they provide greater cup stability and a lower dislocation index (0.9%) than other kinds of bearings (6.2-8.2% dislocation index); they put this down to the adhesive-suctional effect of the metal-on-metal bearing.

A second issue to be cleared up is whether the increase of ions and their systemic dissemination constitute a toxic potential or a risk of carcinogenesis or hypersensitivity.

Some authors report having found high levels of cobalt in patients with a chronic kidney condition[4] and they have considered the possibility that this kind of condition could be a contraindication for metal-on-metal THR; however, they believe that neither the determination of cobalt levels nor a routine monitoring of the kidney are necessary, unless a patient with a metal-on-metal bearing develops a kidney condition.

Metal particles have been detected post mortem in the liver, spleen, and abdominal lymphatic nodes of patients with THR, with a major prevalence in patients that had undergone revision than in patients with primary arthroplasty, yet the long-term effects of the accumulation of metal wear particles are still unknown[26]. Moreover, the levels of metal ions observed in the different studies are markedly below the toxic concentrations described in exposed workers[11].

It is not possible, from the information in the published literature, to reach a conclusion regarding the risk of cancer. Visuri et al[27] contrast the number of cases of cancer in the general population of Finland with the number of cases after metal-on-metal THR, and observe an incidence of 0.95 (15.7 years follow-up); also, the number of cases of cancer in patients with metal-on-polyethylene prostheses was contrasted with that of the population at large and an incidence of 0.76 was observed (12.5 years follow-up). The carcinogenetic risk in the metal-on-metal group was 1.23 times greater than in the metal-polyethylene group. The incidence of leukemia in the metal-on-metal cases was slightly higher, but statistically irrelevant. No sarcomas were observed at the site of implantation. Regarding the presence of other forms of cancer, there were no significant differences with the population at large. If we compare the variations that have been observed in the incidence of the different kinds of cancer in patients with THR with those of the general population, we can conclude that other factors play a more decisive role than THR in the emergence of cancer. Gillespie et al[28] show the results of two cohort studies and a control study carried out in the United States and in Scotland, and conclude that the results show a greater risk of lymphoma or leukemia after arthroplasty.

It has been found that the prevalence of cutaneous sensitivity in patients with a replaced joint, especially in those in which the implantation has failed, is higher than in the population at large; however, until the roles of hypersensitivity development and immune response are not clearly defined, the risk run by patients should be esteemed to be minimum[29]. Histological studies of periprosthetic tissue carried out in revisions of metal-on-metal THR show perivascular infiltration of lymphocytes and plasma cells with metal wear particles[30,31]. These findings seem to suggest that the immunological hypersensitivity reaction to metal may be responsible for osteolysis and aseptic loosening, both frequently associated with metal-on-metal bearings[32,34].

A final point to make concerning the increase of metal ions after metal-on-metal THR, is that it would be interesting to research the reaction of these ions following a resurfacing metal-on-metal THR. Clarke et al[12] measured the cobalt and chromium levels in 22 patients with resurfacing THR and compared them with those of 22 patients with a metal-on-metal 28mm head THR, observing significantly higher levels in the cases of resurfacing THR. Skipor et al[35] have also observed an increase with respect to pre-op levels in the serum and urine chromium levels and in the serum cobalt levels 3, 6 and 12 months after replacement with this kind of bearing.

In conclusion, we have confirmed that there is an increase (though of a lower degree than that found in other studies) in the chromium and cobalt concentrations, mainly in the first and second years after arthroplasty. We may ascertain that it is the verticalization of the acetabular component that causes the increase in these concentrations.

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Conflict of interests

The authors have declared that they have no conflict of interests.