

# Human growth hormone in polymethyl methacrylate

## A controlled study of 15 hip arthroplasties

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Growth hormone-loaded polymethyl methacrylate (PMMA) was used in 15 hip replacements. The levels of growth hormone and insulin growth factor-I from the hip and the blood were measured before, and after, implanting PMMA containing 20 mg of growth hormone. Low levels of growth hormone and insulin growth factor-I were found in the femur initially, but very high local levels were found after implanting the growth hormone-loaded PMMA. These results were compared with the low levels found in 15 patients in a control group undergoing cemented or cementless

hip replacement without added growth hormone. The local levels of growth hormone and insulin growth factor-I declined rapidly during the first 72 hours and were near normal at the end of this time. Systemic levels of growth hormone and insulin growth factor-I were not affected by the implantation of growth hormone-loaded PMMA. No complications or adverse reactions were noted. However, randomized studies with long-term follow-up are mandatory before the use of growth hormone-loaded PMMA is justified.

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A number of bone growth factors including skeletal growth factor, insulin-like growth factors I and II, transforming growth factor- $\beta$ , fibroblast growth factor, platelet-derived growth factor, bone morphogenetic proteins and hematopoietic factors have been identified (Mohan and Baylink 1991). It is not known how these factors may be produced and activated, and so far their use has been limited.

The best known growth factor is growth hormone. Generally it has been postulated that there are two mechanisms for maintaining bone volume, systemic regulation by hormones that control calcium and phosphorus and local regulation. Growth hormone is metabolized in the liver to insulin growth factor-I (IGF-I). Growth hormone may also be metabolized to IGF-I directly by bone and it becomes locally active when this occurs (Rudman et al. 1990). I used polymethyl methacrylate (PMMA) as a delivery system for local application of growth hormone.

### Patients and methods

30 patients were scheduled for routine hip replacement. None had any known endocrine, metabolic or bone wasting disease. All the patients were in good health and none took medications such as insulin, L-dopa or clonidine that might influence growth hormone levels or metabolism. This study had the

approval of the hospital's ethics committee. All the patients consented to participation in the study.

Patients were evaluated by medical-history taking, physical examination, differential blood count, urinalysis, blood chemistry tests, chest radiography, and electrocardiogram prior to and after surgery. Blood pressure measurements were made three times a day in the first week following surgery and blood counts, urinalysis, and blood chemistry tests were performed daily.

20 milligrams of growth hormone (Human Growth Hormone [Protropin], Genentech Inc., San Francisco, CA, U.S.A.) in each 40 grams of polymer powder (Palacos, Richards Company, Memphis, TN, U.S.A.) were used in 15 patients. The investigation also included 15 patients who served as controls. In each case in the treated group, a cemented femoral prosthesis was used with a cementless acetabular prosthesis. The added growth hormone produced no noticeable change in the handling characteristics of the PMMA.

All the operations were performed by a surgeon who had no knowledge of whether the bone cement used during the procedure contained growth hormone. During the operation and prior to implanting the cement, blood from the medullary canal of the femur was evaluated to determine both growth hormone (GH) and IGF-I levels. After the operation, samples of blood were collected in the recovery room and at 24, 48, and 72 hours from two 3.2-mm drains that had been placed in each wound and connected to suction

Table 1. Growth hormone (ng/mL) and insulin growth factor-I (units/mL) levels. Mean (range)

	Patients		Controls	
			PMMA	No PMMA
Age	71 (65-76)		73 (65-78)	61 (58-63)
Men	6		4	3
Women	9		6	2
Weight (kg)	76 (69-83)		75 (70-81)	72 (66-84)
Diagnosis				
Arthrosis	11		6	2
Rheumatoid arthritis	1		1	1
Osteonecrosis	2		2	1
Dysplasia	1		1	1
Total PMMA quantity used (g)	31 (28-33)		31 (28-33)	0
	Patients		Controls	
	GH	IGF-I	GH	IGF-I
Blood levels				
Before surgery	1.8 (0.6-12)	0.7 (0.2-1.7)	1.1 (0.6-2.0)	0.8 (0.4-2.0)
Two weeks after surgery	1.3 (0.6-6)	0.7 (0.3-1.3)		
From hip				
During surgery	1.8 (0.6-12)	0.7 (0.2-1.7)	1.1 (0.6-2.0)	0.8 (0.4-2.0)
Hours after surgery				
1	754 (543-1174)	1.5 (0.8-3.1)	1.0 (0.8-2.4)	0.6 (0.3-0.9)
24	98 (18-364)	1.3 (0.6-1.5)	1.0 (0.8-2.1)	0.6 (0.4-0.8)
48	18 (11-32)	1.2 (0.6-1.6)	0.9 (0.7-1.8)	0.6 (0.4-0.8)
72	8 (5-18)	1.2 (0.9-1.4)	0.8 (0.6-1.7)	0.6 (0.4-0.8)

bottles. The drains were in the immediate proximity of the artificial joint and were routinely removed at 72 hours. Systemic blood levels of GH and IGF-I were measured prior to and two weeks after surgery.

Assays for growth hormone were performed at Nichols Laboratory (Nichols Laboratory, Los Angeles, CA, U.S.A.). Statistical analyses were performed using Student's *t*-test.

## Results

There were no manifestations of hypersomatotropism. Specifically, no patient developed hypertension, glucose intolerance, edema or cardiomegaly. There was no evidence of a local reaction.

Increases in the growth hormone levels were detected in the recovery room as well as at 24, 48, and 72 hours compared with levels obtained prior to surgery ( $P < 0.01$ ). The levels of growth hormone found in the wound secretions after implanting the GH-loaded PMMA were higher than in the control group ( $P < 0.01$ ). The growth hormone levels in the wound secretions were very high, particularly in the recovery room, but then fell rapidly within the first 72 hours.

Systemic blood levels of GH and IGF-I were identical to levels found in the femur prior to instrumenta-

tion. The level of IGF-I increased within minutes after implantation of GH-loaded PMMA ( $P < 0.01$ ; Table 1). This suggests that GH is metabolized in the femur to IGF-I.

## Discussion

The addition of small amounts of drugs has not been found to have adverse effects on the strength or binding capability of PMMA; 2 grams of an antibiotic may be added to PMMA before noticeable loss of strength can be appreciated. The elution characteristics of growth hormone in this study are quite similar to those found with antibiotics by many other authors (Wahlig et al. 1984, Trippel 1986).

It has been established that there is declining activity of the growth hormone/IGF-I axis with advancing age. There is also loss of bone mass with age. At least one-third of individuals over 60 years of age will have a measurable decrease in the levels of IGF-I. Treatment with growth hormone reliably reestablishes mean plasma IGF-I levels in the normal range in such individuals (Rudman et al. 1990).

Downs et al. (1990) have shown that human growth hormone elutes in measurable quantities from PMMA. In their studies of New Zealand white rabbits, growth

hormone-impregnated PMMA was shown to enhance the bone cement interface in a controlled series. On histologic section, significant increases in osteoid in contact with loaded PMMA were observed.

Koskinen et al. (1978) demonstrated that growth hormone can be helpful in healing nonunited fractures. I have demonstrated a similar response using L-dopa (Pritchett 1990). That growth hormone is probably metabolized to IGF-I directly in bone is relevant as this is a highly important growth factor which promotes cell multiplication in undifferentiated cells (Mohan and Baylink 1991). The rapid initial release of growth hormone followed by a rapid decline in levels after a few days is highly desirable since a continuous release of high concentrations of growth hormone may have unfavorable long-term effects.

Increased serum growth hormone levels did not occur after implanting growth hormone-loaded PMMA and therefore the use of PMMA as a method of delivery of growth hormone for systemic needs is not likely to be useful or harmful. To determine whether growth hormone loaded PMMA will enhance the fixation of joint prostheses will require a randomized study with a large number of patients and very long-term follow-up.

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