EXTENDED REPORTS

Relation between insulin-like growth factor-I concentrations, osteoarthritis, bone density, and fractures in the general population: the Chingford study

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Abstract

Objective—To assess the association between serum insulin-like growth factor-I (IGF-I) concentrations and osteoarthritis, and bone mineral density, and fractures in a large group of middle aged women from the general population.

Methods—761 women aged 44-64 years from the Chingford study had serum IGF-I concentrations measured; hand, hip, spine, and anteroposterior weight bearing knee radiographs taken; and dual energy α ray absorptiometry (DEXA) scans of the hip and spine. X rays were scored using the Kellgren and Lawrence system. In addition knee α rays were scored using a standard atlas for individual features of osteophytes and joint space narrowing (both graded 0-3). IGF-I concentrations were adjusted for the effects of age.

Results—In the osteoarthritis analysis results were compared to a constant group of 155 subjects with no evidence of osteoarthritis at any site. There was no significant difference in serum IGF-I between these subjects and 606 subjects with osteoarthritis at any site. When individual sites were analysed, serum IGF-I was higher in those cases with more severe bilateral knee osteoarthritis and in those with distal interphalangeal (DIP) joint disease. There was no significant association between serum IGF-I and other forms of osteoarthritis or milder forms of knee osteoarthritis. There was no correlation between IGF-I concentrations and bone mineral density at the spine or hip, nor any difference between IGF-I concentrations in subjects with and without a history of non-traumatic fracture [22.8 (SD 6.6) v 23.1 (SD 6.6) nmol litre⁻¹, $P = 0.6$]

Conclusions—There is a modest association between IGF-I concentrations and the development of DIP osteoarthritis and more severe or bilateral knee joint osteoarthritis in women from the normal

population, but no association with other forms of osteoarthritis, bone density, or fractures.

(Ann Rheum Dis 1996;55:870-874)

Osteoarthritis and osteoporosis are age related skeletal conditions characterised by an imbalance between bone or cartilage formation and breakdown. Insulin-like growth factor-I (IGF-I) is an important growth promoting peptide produced mainly by the liver which mediates the effect of growth hormone at tissue level. Unlike growth hormone, IGF-I does not have a diurnal rhythm and is therefore a convenient index of growth hormone secretion to study in large populations. Two lines of research suggest that IGF-I concentrations may be important in the development of osteoarthritis and osteoporosis. Firstly, IGF-I receptors are abundant in bone and cartilage, and in vitro work has suggested an anabolic effect of IGF-I on chondrocytes and osteoblasts.^{1,2} Secondly, IGF-I appears to be involved in the maintenance of body composition and muscle strength. Cross sectional studies have shown correlations between IGF-I concentrations, strength, and physical fitness^{3,4} and an inverse correlation with adiposity.⁵ Rudman *et al* also showed that administration of recombinant growth hormone to elderly men increased muscle mass, reduced adiposity, and increased bone density.⁶ As obesity is the strongest known risk factor for knee osteoarthritis, and weight is one of the most important variables associated with bone density, IGF-I might be expected to be important in both these conditions. However, work looking at serum IGF-I concentrations and osteoarthritis and osteoporosis has been inconclusive. High,⁷ low,⁸ and normal^{9,10} concentrations of IGF-I have been reported in osteoarthritis, and low¹¹⁻¹⁴ and normal¹⁵ concentrations in osteoporosis.

We therefore aimed to study the relations between IGF-I concentrations and osteoarthritis, bone mineral density, and fractures, using a large group of middle aged women and data on

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Accepted for publication
4 September 1996

Table 1 Characteristics of the subjects (n=761)

	Mean	SD	Range
Age (years)	54.2	6.0	44-67
Height (cm)	162	6.0	1.44-1.90
Weight (kg)	66.7	11.6	40.4-130
IGF-1 levels (nmol litre ⁻¹)	23.0	7.0	3.1-66.8
Femoral neck BMD (g cm ⁻³)	0.76	0.12	0.48-1.29
Lumbar spine BMD (g cm ⁻³)	0.97	0.16	0.54-1.53
Number ever smokers	346 (45%)		
Number ever using HRT	178 (23%)		
Number postmenopausal	463 (of 638 where status known = 61%)		
Number with history of knee injury	94 (of 668 where status known = 14%)		

HRT, hormone replacement therapy

osteoarthritis obtained at several sites. The knee was examined in detail using a system which looked at the individual features of osteoarthritis, in addition to the conventional Kellgren and Lawrence scoring system.

Methods

Seven hundred and sixty one women from the Chingford population had measurements of IGF-I, hand, hip, spine and knee x rays, and lumbar spine and femoral neck bone densitometry. The subjects formed part of an original cohort of 1003 women aged 45-64 years (mean age 54.2, SD 6.03) participating in a population study drawn from a large general practice in Chingford, north east London, which has been described in detail previously.¹⁶ Only subjects who had x rays and dual energy x ray absorptiometry (DEXA) scanning at all sites were included in the analysis. The subjects in whom full data were available were similar to those without full data in terms of age (54.2 v 54.2 years, $P = 0.9$), weight (66.7 v 67.8 kg, $P = 0.2$), and height (161.7 v 161.4 cm, $P = 0.6$). The response rate at the initial recruitment from an age/sex register at the practice was 78%. The area is predominantly middle class, 98% are white, and the population similar to United Kingdom norms in terms of heights and weights.

All x rays were performed at first visit, apart from those of the hip, which were performed at the second visit. Radiographs of the knee (anteroposterior weight bearing), hand [including proximal interphalangeal (PIP), distal interphalangeal (DIP), and first carpo-

metacarpal (CMC) joints], and spine were graded blind by a single observer (DJH) according to the traditional Kellgren and Lawrence method. Osteoarthritis was considered to be present if a joint scored two or more. In addition knee x rays were graded according to a standard atlas.¹⁷ A scale of 0 to 3 is used, with 0 representing no disease, 1 mild disease, 2 moderate disease, and 3 severe disease. The advantage of this technique over the Kellgren and Lawrence system is that it allows grading of the individual features of osteophytosis and joint space narrowing, which previous studies suggest may be of value in looking at the association of IGF-I and osteoarthritis.^{7,9} Hip osteoarthritis as graded by the Kellgren and Lawrence method has particularly poor reproducibility and therefore only an atlas definition (the presence of femoral osteophytes and joint space narrowing grade 1 or more) was used in the study. The intraobserver κ score using the atlas technique was over 0.8.¹⁸ At each site, IGF-I concentrations were compared against a constant group of 155 cases with no evidence of osteoarthritis at any site. Bone densitometry was performed at the hip and spine using a Hologic QDR 1000 machine (in 20 healthy controls scanned twice, precision at the spine was 0.8% and at the hip 1.6%). Details of fracture for the previous 10 years were obtained from self report and validated by family doctor records for Colles and hip fracture. For vertebral fracture, radiographic criteria were used. All women had a lateral thoracic and lumbar spine x ray at first visit using standardised methods. A vertebral fracture was defined as a three standard deviation deformity using the criteria of McCloskey *et al*,¹⁹ used by us previously in the Chingford study.²⁰

After storage at -20°C , IGF-I concentrations were measured using a standard technique which involves a competitive double antibody radio immunoassay, using monoclonal antibodies.²¹ The IGF-I results were normally distributed. Exercise concentrations were graded using a questionnaire which assesses weekly walking distance, daily activity, and sport, each graded on a scale of 1 to 4. Knee injury was defined as injury severe

Table 2 Mean (SD) IGF-1 levels in cases are compared to the same group of 155 control cases with no evidence of knee, hand (PIP, DIP, CMC-1), hip or spine osteoarthritis (OA). Results are in nmol litre⁻¹ and adjusted for age

	Cases	Controls	P
(i) OA knee (OA grade)			
Kellgren and Lawrence grade 2 or more either knee	24.2 (8.9) (n=96)	22.2 (7.7) (n=155)	0.1
Kellgren and Lawrence grade 2 or more both knees	27.5 (10.8) (n=41)	22.6 (7.7) (n=155)	0.002
Unilateral knee osteophytes grade 1 or more	21.5 (6.1) (n=56)	22.5 (7.7) (n=155)	0.4
Unilateral knee narrowing grade 1 or more	23.5 (7.1) (n=102)	22.7 (7.7) (n=155)	0.4
Unilateral knee osteophytes or narrowing grade 2 or more	21.9 (6.0) (n=13)	22.9 (7.7) (n=155)	0.7
Bilateral knee osteophytes grade 1 or more	25.3 (10.2) (n=50)	22.6 (7.7) (n=155)	0.06
Bilateral knee narrowing grade 1 or more	24.1 (8.0) (n=189)	22.6 (7.7) (n=155)	0.1
Bilateral knee osteophytes grade 2 or more	27.3 (11.1) (n=14)	22.8 (7.7) (n=155)	0.05
Bilateral knee narrowing grade 2 or more	30.0 (14.2) (n=19)	22.9 (7.7) (n=155)	0.001
Bilateral knee narrowing or osteophytes grade 2 or more	24.8 (9.7) (n=61)	22.7 (7.7) (n=155)	0.1
Bilateral knee narrowing and osteophytes grade 2 or more	29.7 (18.3) (n=8)	22.9 (7.7) (n=155)	<0.0001
(ii) IGF-1 levels at other sites (site)			
DIP joint	24.4 (6.9) (n=106)	22.2 (7.7) (n=155)	0.006
PIP joint	24.7 (5.6) (n=33)	22.6 (7.7) (n=155)	0.2
CMC-1 joint	22.8 (6.7) (n=122)	22.3 (7.7) (n=155)	0.6
Spine	23.2 (6.5) (n=487)	22.5 (7.7) (n=155)	0.2
Hip	23.4 (7.9) (n=10)	22.9 (7.7) (n=155)	0.8
Any site	23.2 (6.8) (n=606)	22.5 (7.7) (n=155)	0.3

enough to require at least one week's rest. Smoking history and hormone replacement therapy (HRT) use were defined on the basis of whether the subjects had ever smoked or had used HRT for more than six months.

Analysis of covariance using SPSS software was used to compare IGF-I concentrations in groups with each osteoarthritis feature against a constant group of controls from the population with no evidence of osteoarthritis at any of the sites studied. There was a strong negative correlation between IGF-I concentrations and age ($r^2 = -0.2$, $P = <0.001$) and

therefore all results were adjusted for the effects of age. Partial correlation analysis was performed to assess the association between IGF-I concentrations and bone mineral density, again with adjustment for age. In addition subjects were also divided into quartiles of bone mineral density and IGF-I concentrations compared in the highest and lowest quartiles using analysis of covariance.

Results

The characteristics of the subjects are shown in table 1. The mean age was 54.2 years. There was an association between IGF-I concentrations and the more severe grades of knee osteoarthritis: bilateral Kellgren and Lawrence grades of 2 or more; osteophytes graded 2 or more either side or bilaterally; and joint space narrowing graded 2 or more either side or bilaterally. The strongest association was seen in eight subjects with bilateral narrowing and osteophytes graded 2 or more. There was also an association between IGF-I concentrations and DIP joint disease graded 2 or more (table 2). When IGF-I concentrations were adjusted for bone mineral density, height, and weight as well as for age, the difference between cases and controls was lost in those cases with osteophytes graded 2 or more and in those with DIP disease (table 3).

Crude correlations showed a modest positive relation between IGF-I concentrations and lumbar spine bone mineral density ($r^2 = 0.1$, $P = 0.006$) but not between IGF-I concentrations and femoral neck bone mineral density ($r^2 = 0.06$, $P = 0.08$) (table 4). After adjustment for age, the correlation between IGF-I and lumbar spine bone mineral density was no longer significant ($r^2 = 0.03$, $P = 0.5$) and the correlation between IGF-I and femoral neck bone mineral density became less significant ($r^2 = -0.01$, $P = 0.7$). There was no significant correlation between IGF-I concentrations and weight, height, smoking history, exercise, or knee injury.

Subjects were also divided into highest and lowest quartiles of bone mineral density. No significant differences in IGF-I concentrations were seen at the lumbar spine [23.3 (SD 6.6) v 22.4 (6.5) nmol litre⁻¹, $P = 0.2$] or femoral neck [23.0 (7.3) v 23.5 (6.8) nmol litre⁻¹, $P = 0.5$] between the subjects in the highest and lowest quartiles.

A positive association was found between the presence of osteoarthritis at any site and bone mineral density after adjustment for age, weight, height, and IGF-I concentrations. Osteoarthritis cases ($n = 606$) had higher bone

Table 3 IGF-I concentrations in osteoarthritic (OA) knee and other joints. IGF-I concentrations (SD), nmol litre⁻¹, in cases compared with the same group of 155 controls adjusted for age; age and bone mineral density (BMD); age, BMD, weight and height

OA grade/type	Cases	Controls	P
Kellgren and Lawrence grade 2 or more either knee	24.2 (8.9) (n=96)	22.2 (7.7) (n=155)	0.1
	24.2	22.2	0.1
	23.6	22.6	0.4
Kellgren and Lawrence grade 2 or more both knees	27.5 (10.8) (n=41)	22.6 (7.7) (n=155)	0.002
	26.8	22.8	0.02
	27.5	22.6	0.003
Unilateral osteophytes grade 1 or more	21.5 (6.1) (n=56)	22.5 (7.7) (n=155)	0.4
	21.4	22.6	0.3
	20.9	22.8	0.1
Unilateral narrowing grade 1 or more	23.5 (7.1) (n=102)	22.7 (7.7) (n=155)	0.4
	23.6	22.6	0.3
	23.5	23.5	0.4
Bilateral osteophytes grade 1 or more	25.3 (10.2) (n=50)	22.6 (7.7) (n=155)	0.06
	25.5	22.5	0.06
	24.8	22.8	0.2
Unilateral osteophytes or narrowing grade 2 or more	21.9 (6.05) (n=13)	22.9 (7.7) (n=155)	0.7
	23.0	22.8	0.9
	23.6	22.8	0.7
Bilateral narrowing grade 1 or more	24.1 (8.0) (n=189)	22.6 (7.7) (n=155)	0.1
	24.0	22.7	0.1
	23.9	22.9	0.2
Bilateral osteophytes grade 2 or more	27.3 (11.1) (n=14)	22.9 (7.7) (n=155)	0.05
	27.1	22.9	0.07
	25.0	23.1	0.4
Bilateral narrowing grade 2 or more	30.0 (14.2) (n=19)	22.9 (7.7) (n=155)	0.001
	30.0	22.9	0.001
	29.7	22.9	0.003
Bilateral narrowing or osteophytes grade 2 or more	24.8 (9.7) (n=61)	22.2 (7.7) (n=155)	0.1
	24.8	22.7	0.1
	24.3	22.8	0.3
Bilateral narrowing and osteophytes grade 2 or more	39.6 (18.3) (n=8)	22.9 (7.7) (n=155)	< 0.0001
	39.6	22.9	< 0.0001
	38.8	22.9	< 0.0001
DIP OA	24.4 (6.9) (n=106)	22.2 (7.7) (n=155)	0.006
	24.3	22.2	0.06
	24.2	22.2	0.09
PIP OA	24.7 (5.6) (n=33)	22.6 (7.7) (n=155)	0.2
	24.5	22.6	0.2
	24.4	22.7	0.3
CMC-1 OA	22.8 (6.7) (n=122)	22.3 (7.7) (n=155)	0.6
	22.8	22.3	0.6
	22.7	22.4	0.7
Spine OA	23.2 (6.5) (n=487)	22.5 (7.7) (n=155)	0.2
	23.2	22.5	0.2
	23.2	22.5	0.2
Hip OA	23.4 (7.9) (n=10)	22.9 (7.7) (n=155)	0.8
	23.3	22.9	0.9
	22.9	22.9	0.9
Any form of OA	23.2 (6.8) (n=606)	22.5 (7.7) (n=155)	0.3
	23.2	22.5	0.3
	23.5	22.6	0.3

Table 4 Crude correlations of IGF-1

Variable	r^2	P
Age	- 0.2	< 0.001
Weight	+ 0.02	NS*
Height	+ 0.007	NS
Femoral neck BMD	+ 0.06	NS
Lumbar spine BMD	+ 0.1	< 0.01
Smoking history	+ 0.03	NS
Exercise levels	0.006	NS
Knee injury	- 0.06	NS

* (NS = $P > 0.01$).

BMD, bone mineral density

mineral density than controls with no osteoarthritis ($n = 155$) at the lumbar spine [$0.97 (0.16) v 0.94 (0.16) \text{ g cm}^{-3}$, $P = 0.003$] and femoral neck [$0.76 (0.13) v 0.74 (0.11) \text{ g cm}^{-3}$, $P = 0.04$]. The significant difference in bone mineral density was also present without adjusting for serum IGF-I.

IGF-I concentrations were also analysed in relation to confirmed vertebral and peripheral fractures not related to road traffic injuries sustained in the previous 10 years. In the 73 subjects who had sustained such fractures, IGF-I concentrations were similar to those subjects who had not suffered fractures, after adjusting for age [$22.8 (6.6) v 23.1 (7.1) \text{ nmol litre}^{-1}$, $P = 0.6$].

Discussion

Our study shows a modest association between higher serum IGF-I concentrations and the presence of DIP joint osteoarthritis and more severe grades of knee osteoarthritis. At the knee the fact that the significance increased with more severe and bilateral grades of osteoarthritis and was present using two grading systems suggests that it is unlikely to be a chance finding due to multiple testing. Why an association was found at these two sites and not at others, nor for the group with any form of osteoarthritis, is not clear. One possibility is that knee and DIP osteoarthritis represent a subgroup of osteoarthritis with a different pathological basis. To explore this further, IGF-I concentrations were also analysed in the 41 subjects with Kellgren and Lawrence knee osteoarthritis graded 2 or more bilaterally who also had DIP joint osteoarthritis graded 2 or more, and compared to the control group with no osteoarthritis. IGF-I concentrations were significantly higher in the group with both forms of osteoarthritis [$27.5 (7.7) v 22.6 (10.8) \text{ nmol litre}^{-1}$, $P = 0.02$]. This may support the concept of "generalised osteoarthritis"; possibly IGF-I plays a greater role in this subgroup. It is noteworthy that the addition of height and weight (a measure of obesity) reduced the significance of the relation between IGF-I concentrations and DIP osteoarthritis and knee osteoarthritis. This may be related to the important relation between osteoarthritis and obesity.²² Indeed, patients with osteoarthritis at these sites had significantly higher body mass indices than the controls [$30.9 v 24.6 \text{ kg m}^{-2}$, $P = < 0.001$, for bilateral grade 2 or more osteophytes, and $26.0 v 24.2 \text{ kg m}^{-2}$, $P = < 0.001$, for DIP osteoarthritis].

Our findings partly support the work of Schouten *et al.*⁷ In a longitudinal study they found that both the growth and the size of osteophytes were associated with IGF-I concentrations, although cartilage loss was not. Just over half their subjects were women, with a mean age of 58 years at the start of the 12 year follow up. In contrast, a smaller study by Denko *et al* showed lower concentrations of IGF-I in 34 elderly white males and females with osteoarthritis (defined with particular regard to osteophytes) than in the same number of age matched controls. Paradoxically,

they also found osteoarthritis to be associated with raised growth hormone concentrations.⁸ A previous study showed no association between severity of individual features of osteoarthritis and IGF-I concentrations in 78 elderly subjects (mean age 72 years) compared to 78 age and sex matched individuals.¹⁰ There are several differences between this study and ours: the subjects were older and fewer in number, with more severe disease, and included men. Hochberg *et al* used an alternative knee osteoarthritis grading system similar to ours to examine 101 women of similar age to ours, and again found no significant association between serum IGF-I and osteoarthritis, although after adjustment for age, concentrations were non-significantly higher in both sexes in subjects with osteoarthritis.⁹ It is possible that the larger numbers in our study allowed us to show a modest association where this study did not.

The natural experiment of acromegaly suggests a causal association between supraphysiological IGF-I concentrations and osteoarthritis, although the high incidence of osteoarthritis in the condition has recently been challenged. However, against IGF-I concentrations being involved in skeletal development in normal subjects is our finding that there was no relation with height or weight, as one would expect subjects with higher concentrations to attain greater adult stature. It is possible, though speculative, that some individuals may maintain their peak IGF-I concentrations longer into middle age and thus be prone to more florid osteoarthritic changes. This might explain the relation between osteophyte growth rather than cartilage loss seen by Schouten, although we were unable to show a clearer association with osteophytosis over joint space narrowing. Why both cartilage loss and osteophytes should be associated with serum IGF-I is not clear; it is possible that the anabolic effect of IGF-I is more potent in relation to bone than to cartilage. Middleton and Tyler²³ showed upregulation of IGF-I gene expression in cartilage from osteoarthritic joints, and an explanation for raised IGF-I concentrations in subjects with osteoarthritis may be local production from affected joints. However, if local production contributed significantly to serum concentrations we would have expected IGF-I concentrations to be higher in the large group of subjects with any form of osteoarthritis.

No association was seen between serum IGF-I and bone density in our subjects, nor did we find an association with fractures. In adults with growth hormone deficiency, IGF-I concentrations have been shown to correlate with bone density,²⁴ and treatment with growth hormone leads to an increase in bone density.^{25,26} The picture is less clear, however, in otherwise normal adults with osteoporosis. Four previous studies have suggested that IGF-I concentrations are low in patients with osteoporosis¹¹⁻¹⁴ and one has shown no difference compared to normal individuals.¹⁵ These studies focused on individuals with the severest disease and used different disease defi-

nitions. Our study examined a much larger number of women and avoided the difficulties of defining osteoporosis by arbitrary bone density concentrations. Nevertheless, by comparing serum IGF-I in those subjects with the lowest and highest bone mineral densities in addition to looking at fracture we would still expect to include subjects with very low bone density. There is no obvious reason (apart from possible publication bias) why our results differ from these previous studies.

In view of the attractive indirect evidence for a role of IGF-I in the development of osteoarthritis and osteoporosis, it is perhaps surprising that we failed to find a stronger association between either disease and IGF-I concentrations. There are several possible explanations for this. Firstly, tissue concentrations of IGF-I may not correlate with serum concentrations. Dequeker *et al.*²⁷ have shown that the presence of hand osteoarthritis correlated with iliac bone concentrations of IGF-I. However, adjustment for age was not made and the authors point out that other potentially important factors not under the control of growth hormone, including IGF-II and transforming growth factor β (TGF β), were also raised in the same cases. IGF-I activity is also affected by the presence of binding proteins which we did not measure.²⁸ In addition, bone and cartilage turnover is under the control of a number of other local factors, including local cytokines, all of which may have cumulative and interactive effects.²⁹

In summary, we have found that serum IGF-I concentrations do not reflect a systemic tendency to osteoarthritis, osteoporosis or fractures in this population. There is a suggestion that they are associated with severe or bilateral knee osteoarthritis and hand osteoarthritis, which may be a secondary phenomenon.

We gratefully acknowledge the help of the staff and women of the Chingford study, Highams Park Medical Practice, and Patricia Wiltshire, Maxine Daniels, Eugene McCloskey, and Nigel Arden for their contributions. Supported in part by grants from the Arthritis and Rheumatism Council and the North Thames Regional Health Authority.

- 1 Morales TI, Hascall VC. Factors involved in the regulation of proteoglycan metabolism in articular cartilage. *Arthritis Rheum* 1989;32:1197-201.
- 2 Froesch ER, Schmid C, Swander J, Zapf J. Actions of insulin-like growth factors. *Annu Rev Physiol* 1985; 47:443-67.
- 3 Florini JR. Hormonal control of muscle bulk. *Muscle Nerve* 1987;10:577-98.
- 4 Kelly PJ, Eisman JA, Stuart MC, Pocock NA, Sambrook PN, Gwinn TH. Somatomedin-C, physical fitness and bone density. *J Clin Endocrinol Metab* 1990;70:718-23.
- 5 Rudman D, Kutner MH, Rogers CM, Lubin MF, Fleming GA, Bain RP. Impaired growth hormone in the adult population: relationship to age and adiposity. *J Clin Invest* 1981;67:1361-9.
- 6 Rudman D, Feller AG, Hoskote SN, Gergans GA, Lalitha PY, Goldberg AF, *et al.* Effects of growth hormone in men aged over 60 years old. *N Engl J Med* 1990;323:1-6.
- 7 Schouten JSAG, Van den Ouweland FA, Valkenburg HA, Lamberts SWJ. Insulin-like growth factor-1: a prognostic factor of knee osteoarthritis. *Br J Rheumatol* 1993;32:274-80.
- 8 Denko CW, Boja B, Moskowitz RW. Growth promoting peptides in osteoarthritis: insulin, insulin-like growth factor-1, growth hormone. *J Rheumatol* 1990;17:1217-21.
- 9 Hochberg MC, Lethbridge-Cejku M, Scott WW, Reichle R, Plato CC, Tobin JD. Serum concentrations of insulin-like growth factor 1 in subjects with osteoarthritis of the knee. Data from the Baltimore Longitudinal Study of Ageing. *Arthritis Rheum* 1994;37:1177-80.
- 10 McAlindon TE, Teale JD, Dieppe PA. Levels of insulin related growth factor 1 in osteoarthritis of the knee. *Ann Rheum Dis* 1993;52:229-31.
- 11 Wuster C, Blum WF, Schlemilch S, Ranke MB, Ziegler R. Decreased serum concentrations of insulin-like growth factors and IGF binding protein 3 in osteoporosis. *J Intern Med* 1993;234:249-55.
- 12 Pun KK, Lau P, Wong FHW, Cheng CL, Pun WK, Chow SP, *et al.* 25-Hydroxycholecalciferol and insulin like growth factor 1 are determinants of serum concentration of osteocalcin in elderly subjects with and without spinal fractures. *Bone* 1990;11:397-400.
- 13 Ljunghall S, Johansson AG, Burman P, Lindh E, Karlsson FA. Low plasma concentrations of insulin-like growth factor I (IGF-I) in male patients with idiopathic osteoporosis. *J Intern Med* 1992;232:59-64.
- 14 Reed BY, Zerwekh JE, Sakhaee K, Breslau NA, Gottschalk F, Pak C. Serum IGF 1 is low and correlated with osteoblastic surface in idiopathic osteoporosis. *J Bone Miner Res* 1995;10:1218-24.
- 15 Bennett AE, Wahner HW, Riggs BL, Hintz RL. Insulin-like growth factors 1 and 2: ageing and bone density in women. *J Clin Endocrinol Metab* 1984;59:701-4.
- 16 Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford population. *J Rheumatol* 1993;20:331-5.
- 17 Spector TD, Cooper C, Cushnaghan J, Hart DJ, Dieppe PA. *A radiographic atlas of knee osteoarthritis*. London: Springer Verlag, 1992.
- 18 Spector TD, Hart DJ, Byrne J, Harris PA, Dacre JE, Doyle DV. Definition of osteoarthritis of the knee for epidemiological studies. *Ann Rheum Dis* 1993;52:790-4.
- 19 McCloskey EV, Spector TD, Eyres KS, Fern ED, O'Rourke N, Vasikaram S, *et al.* The assessment of vertebral deformity: a method for use in population studies and clinical trials. *Osteoporosis Int* 1993;3:138-47.
- 20 Spector TD, McCloskey EV, Doyle DV, Kanis JA. Prevalence of vertebral fracture in women and the relationship with bone density and symptoms: the Chingford Study. *J Bone Miner Res* 1993;8:817-23.
- 21 Labib M, Teale D, Marks V. Insulin-like growth factor 1 in patients with hypoglycaemia. *Ann Clin Biochem* 1990; 27:107-9.
- 22 Spector TD. The fat on the joint: osteoarthritis and obesity. *J Rheumatol* 1990;17:283-4.
- 23 Middleton JF, Tyler JA. Upregulation of insulin-like growth factor I gene expression in the lesions of osteoarthritic human cartilage. *Ann Rheum Dis* 1992;51:440-7.
- 24 Bagge E, Eden S, Rosen T, Bengtsson B. The prevalence of radiographic osteoarthritis is low in elderly patients with growth hormone deficiency. *Acta Endocrinol* 1993; 129:296-300.
- 25 Johansson AG, Burman P, Westermarck K, Ljunghall S. The bone mineral density in acquired growth hormone deficiency correlates with circulating concentrations of insulin-like growth factor 1. *J Intern Med* 1992;232:447-52.
- 26 Degerblad M, Elgindy N, Hall K, Sjoberg HE, Thoren M. Potent effect of recombinant growth hormone on bone mineral density and body composition in adults with panhypopituitarism. *Acta Endocrinol* 1992;126:387-93.
- 27 Dequeker J, Mohan S, Finkelmann RD, Aerssens J, Baylink DJ. Generalised osteoarthritis associated with increased insulin-like growth factor types I and II and transforming growth factor beta in cortical bone from the iliac crest. *Arthritis Rheum* 1993;36:1702-8.
- 28 Shimaskai S, Ling N. Identification and molecular characterisation of insulin-like growth factor binding proteins (IGFBP -1, -2, -3, -4, -5 and -6). *Prog Growth Factor Res* 1991;3:243-66.
- 29 Manolagas SC, Jilka RL. Bone marrow, cytokines and bone remodelling. *N Engl J Med* 1995;332:305-11.