OOPHORECTOMY PREDISPOSES TO DEGENERATIVE SPONDYLOLISTHESIS

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We performed a case-control study on the influence of oophorectomy on the development of degenerative spondylolisthesis, including a clinical review and determination of serum oestradiol levels. We also compared the radiological appearance of the lumbar spine at L4/5 in patients with and without spondylolisthesis and with and without oophorectomy. Oophorectomy was a risk factor for degenerative spondylolisthesis with an odds ratio of 7.5 (95% confidence interval, 1.6 to 46). The incidence of degenerative spondylolisthesis in 69 oophorectomised patients was about three times higher than in 69 non-oophorectomised matched control subjects. There was also a difference in spinal variation between oophorectomised and non-oophorectomised patients with spondylolisthesis. A high incidence of sagittal-plane orientation of the L4/5 facet and an increase in pedicle-facet angle were seen in both groups and are typical radiological features of this disease. An increase in lumbosacral angle and in disc-space narrowing was seen only in the non-oophorectomised patients with this condition.

Our results suggest that the abrupt decrease in oestradiol level caused by oophorectomy may be a predisposing factor in degenerative spondylolisthesis at L4/5.

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The suggested causes of degenerative lumbar spondylolisthesis include an increased pedicle-facet angle (Junghanns 1930; Macnab 1950), sagittal-plane facets (Junghanns 1930; Allbrook 1957; Sato et al 1989), an increased promontory angle (Rosenberg 1975) and degeneration of the facet joint (Newman and Stone 1963). Many authors have reported a female predominance (Junghanns 1930; Allbrook 1957; Newman and Stone 1963; Rosenberg 1975; Cauchoix, Benoist and Chassaing 1976; Epstein et al 1983; Matsunaga et al 1990; Postacchini and Perugia 1991), but we could find no epidemiological study of the influence of sex hormones on the incidence.

We have therefore investigated whether oophorectomy has an effect on the pathogenesis of the lesion.

PATIENTS AND METHODS

We reviewed a total of 217 patients with low-back pain who had been diagnosed as having degenerative spondylolisthesis at the Toyama Medical and Pharmaceutical University Hospital between 1981 and 1991. There were 52 men of mean age 63.4 years (39 to 80) and 165 women of mean age 59.1 years (41 to 78). Degenerative spondylolisthesis was evaluated by the compass test of Morgan and King (1957) on a lateral radiograph taken in the neutral upright position, and diagnosed when there was a slip of 3 mm or more.

Case-control study. The 165 women with degenerative spondylolisthesis all completed a questionnaire on gynaecological disease, history of oophorectomy, age at operation, age of menopause, and history of low-back or leg pain. All reported gynaecological operations were reconfirmed from hospital records. This detailed medical information was obtained from 105 women, 8 in the fifth decade, 46 in the sixth decade, 46 in the seventh decade and 5 in the eighth decade of life. We then collected a control series of 105 patients, with no degenerative spondylolisthesis and matched by age, gender and occupation, chosen at random from orthopaedic inpatients treated between 1980 and 1990. The diagnoses in the 105 control patients were lumbar spondylisisis (37), osteoarthritis of hip or knee (27), rheumatoid arthritis (18), limb fractures (5) and miscellaneous joint diseases (18). These control subjects also completed the questionnaire. We used the case-control pairs to calculate the influence of oophorectomy on the incidence of degenerative spondylolisthesis.

Degenerative spondylolisthesis and serum oestradiol levels in oophorectomised and non-oophorectomised groups. We studied 69 patients, none involved in the case-control study, who had had bilateral oophorectomy before their menopause with no hormonal replacement therapy in our hospital between 1979 and 1989. Their mean age at review was 53.8 years (36 to 70); their mean age at oophorectomy was 47.4 ± 5.6 years and the mean period between oophorectomy and review was 6.3 ± 2.8 years. The indications for oophorectomy were uterine myoma in
38, uterine carcinoma in 10, ovarian cyst in 7, endometriosis in 4, ovarian tumour in 4 and other causes in 6. We then selected a matched control group of 69 non-oophorectomised patients of mean age 53.6 years (36 to 70) by random sampling from orthopaedic inpatients during the same period. All the patients in both groups had a direct interview and physical and radiological examinations. The serum oestradiol concentration was measured in all of the oophorectomised group and in the 42 postmenopausal women of the 69 in the non-oophorectomised group by radioimmunoassay (DPC oestradiol kit; Diagnostic Products Corporation, Los Angeles, California).

Radiography of the lumbar spine in oophorectomised and non-oophorectomised patients. We analysed skeletal variation at L4 and L5 vertebrae in 198 patients in four groups:

- group I was oophorectomised patients with degenerative spondylolisthesis at L4/5 (n = 23);
- group II was non-oophorectomised patients with degenerative spondylolisthesis (n = 68);
- group III was oophorectomised patients with no degenerative spondylolisthesis (n = 49); and
- group IV was non-oophorectomised patients with no degenerative spondylolisthesis (n = 58).

On the anteroposterior views we noted the incidence of a sagittal plane facet at L4/5 (Allbrook 1957; Rosenberg 1975; Sato et al 1989). On the lateral views the pedicle-facet angle of L4 and the lumbosacral angle were measured using Newman and Stone’s method (1963) and Junghanns’ method (1930), respectively. Disc-space narrowing at L3/4 and L4/5 levels was determined by Brandner’s method (1972). That at the L4/5 level of spondylolisthesis was assessed with reference to the L3/4 intervertebral disc space. The level of the iliac crests (Jacoby line) on an anteroposterior radiograph was recorded as being in the area of the L4 vertebral body, the L4/5 intervertebral disc or the L5 vertebral body.

Statistical analysis. In the case-control study, we estimated the possibility of oophorectomy causing degenerative spondylolisthesis using McNemar’s test to express the risk of degenerative spondylolisthesis as an odds ratio. The 95% confidence interval (CI) of the odds ratio was calculated using tables based on the binomial distribution.

We compared the incidence of degenerative spondylolisthesis in oophorectomised and non-oophorectomised groups using a chi-squared test for independence with correction by Fisher’s exact probability test. The pedicle-facet angles and lumbosacral angles in the four groups were compared by one-way analysis of variance. Disc-space narrowing was compared between two groups using a t-test with Welch’s correction. The location of the Jacoby line in the four groups was compared by the Wilcoxon-Mann-Whitney test. Differences were regarded as significant when the p value was less than 0.05.

RESULTS

Age and gender differences. In the patients with degenerative spondylolisthesis the mean age of the 165 women at diagnosis was 59.1 years ± SD 8.5. This was significantly younger than the 52 men (63.4 ± 8.8; p < 0.005). In men, degenerative spondylolisthesis was rarely seen before 55 years of age, but a high proportion of women were in their 40s or 50s at the time of diagnosis (Fig. 1). Of the 217 patients, 125 were light manual workers (9 men and 116 women), 31 were moderate manual workers (13 men and 18 women), and 61 were heavy manual workers (30 men and 31 women). There were few female heavy manual workers.

Case-control study. In the case-control study, the mean

![Age distribution of patients with degenerative spondylolisthesis at L4/5](image)
age of the 105 women with degenerative spondylolisthesis was 58.8 ± 6.49 years (41 to 74), and the mean age of the 105 matched control subjects was 58.7 ± 6.54 (41 to 74). The frequencies of potential risk factors for degenerative spondylolisthesis in the patients and control subjects are shown in Table I. The incidence of oophorectomy was significantly higher in the spondylolisthesis cases than in the controls (p < 0.01). The odds ratio of a positive history of oophorectomy as a risk factor for degenerative spondylolisthesis was 7.5 (95% CI, 1.61 to 46.24; Table II). Subdivision into bilateral and unilateral oophorectomy showed that bilateral oophorectomy was a risk factor at an odds ratio of 8.0 (95% CI; 1.01 to 38.36).

**Spondylolisthesis and serum oestradiol concentration.**
Degenerative spondylolisthesis was found in 29.0% (20 of 69) of the patients in the oophorectomised group and 8.7% (6 of 69) of the non-oophorectomised group (p < 0.005; Fig. 2). The serum oestradiol concentration in the oophorectomised group was approximately 15 pg/ml or not detectable, but in the non-oophorectomised group it was 15 to 85 pg/ml in five of the 42 patients tested (Table III).

**Spinal variation at L4/5.** Facets in the sagittal plane were commonly found at L4/5 in patients with degenerative spondylolisthesis (groups I and II), regardless of oophorectomy or no oophorectomy. The incidences were 60.9% in group I, 54.4% in group II, 10.2% in group III and 24.2% in group IV (p < 0.01; Table IV). The mean pedicle-facet angles in groups I and II were 120.9° and 118.5°, respectively. These angles were significantly lower in the non-spondylolisthetic groups (mean 115.3°) and IV (mean 117.7°) (Table V).

The average lumbosacral angle was significantly greater in group II (spondylolisthesis, no oophorectomy) than in groups III and IV (p < 0.01; Table V). Degenerative spondylolisthesis in oophorectomised patients (group I) was not necessarily associated with an exaggerated lumbosacral angle. The disc space of L4/5 in group II was significantly narrower than that of L3/4 (p < 0.005). In group I, however, we did not find disc-space narrowing of L4/5 (Fig. 3). We found no statistical significance in the level of the Jacoby line; it was usually at the L4/5 intervertebral disc level in each of the four groups.

**DISCUSSION**
It is generally accepted that there is a female predominance in patients with degenerative spondylolisthesis, and we found about a threefold increase. Rosenberg (1975) suggested that there may be a menstrual-cycle-related laxity of the paraspinous ligaments in this disease but there have been no precise confirmatory data. In our female patients, the mean age at diagnosis was significantly younger than that in men and the age distribution of diagnosis of degenerative spondylolisthesis was centred around the menopausal period. Most of the men with this condition were heavy manual workers while most of the women were light manual workers. The level of physical activity appears to be less important in the onset of degenerative spondylolisthesis in women.

Our case-control study shows that oophorectomy is a risk factor for degenerative spondylolisthesis, and this was supported by our clinical review of oophorectomised patients which indicated that they have a high incidence of spondylolisthesis.

In experiments on the elastic properties of the capsular ligament of the hip (Yamamuro et al 1977; Shikata et al...
Table II. Oophorectomy as a risk factor for degenerative lumbar spondylolisthesis

<table>
<thead>
<tr>
<th>Discordant case-control pairs</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/−*</td>
<td>−/+†</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>15</td>
</tr>
<tr>
<td>Unilateral</td>
<td>8</td>
</tr>
<tr>
<td>Serum oestradiol</td>
<td>120.9 ± 24.2</td>
</tr>
<tr>
<td>Non-oophorectomised</td>
<td>117.7 ± 3.8</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>No</td>
<td>37</td>
</tr>
</tbody>
</table>

* +/−, discordant pair in which only the case and not the control was exposed to the risk factor
† −/++, discordant pair in which only the control was exposed to the risk factor

Table III. Serum oestradiol level (pg/ml) in the oophorectomised and the postmenopausal non-oophorectomised patients

<table>
<thead>
<tr>
<th>Serum oestradiol</th>
<th>Oophorectomised (n = 69)</th>
<th>Non-oophorectomised (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to 85</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Not detectable to 14</td>
<td>69</td>
<td>37</td>
</tr>
</tbody>
</table>

Table IV. Incidence of facet orientation in the sagittal plane at L4/5 in four groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Oophorectomy</th>
<th>Degenerative spondylolisthesis at L4/5</th>
<th>Facets in sagittal plane</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n = 23)</td>
<td>Yes</td>
<td>14°</td>
<td>60.9</td>
</tr>
<tr>
<td>II (n = 68)</td>
<td>No</td>
<td>37°</td>
<td>54.4</td>
</tr>
<tr>
<td>III (n = 45)</td>
<td>Yes</td>
<td>5°</td>
<td>10.2</td>
</tr>
<tr>
<td>IV (n = 58)</td>
<td>No</td>
<td>14°</td>
<td>24.2</td>
</tr>
</tbody>
</table>

* a-c, a-d, b-c, b-d, (a+b)-(c+d); p < 0.01 (chi-squared test)

Table V. Pedicle-facet and lumbosacral angles (mean ± SD in degrees) in four groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Oophorectomy</th>
<th>Degenerative spondylolisthesis at L4/5</th>
<th>Pedicle-facet angle*</th>
<th>Lumbosacral angle †</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n = 23)</td>
<td>Yes</td>
<td>Yes</td>
<td>120.9 ± 5.4°</td>
<td>142.7 ± 11.5°</td>
</tr>
<tr>
<td>II (n = 68)</td>
<td>No</td>
<td>Yes</td>
<td>118.5 ± 5.4°</td>
<td>148.7 ± 13.2°</td>
</tr>
<tr>
<td>III (n = 49)</td>
<td>Yes</td>
<td>No</td>
<td>115.3 ± 5.7°</td>
<td>141.1 ± 8.3°</td>
</tr>
<tr>
<td>IV (n = 58)</td>
<td>No</td>
<td>No</td>
<td>117.7 ± 3.8°</td>
<td>140.2 ± 10.1°</td>
</tr>
</tbody>
</table>

* a-c, p < 0.01; b-c, p < 0.05
† f.g. f-h; p < 0.01 (one-way analysis of variance)

1979), the arterial wall (Fischer and Swain 1977), periodontal tissues and the uterus (Dyer, Sodek and Heersche 1980), oestrogen was proved to have a considerable influence on collagen and elastin synthesis. Fischer and Swain (1977) found that oestrogen reduced the collagen content and increased the elastin content of the arterial wall in rats. Shikata et al (1979) in an experimental study on hip dislocation stated that oestrogen deficit after oophorectomy induced a loss of elasticity of the capsular ligament.

In patients, oophorectomy has been shown to provoke an abrupt decrease in serum oestrogen level (Aksel et al 1976) and a deficit of testosterone and androstenedione which are also secreted by the ovary (Sitteri and MacDonald 1973; Vermeulen 1976). By contrast, the physiological menopause causes a gradual decrease in oestradiol secretion; the levels of testosterone and androstenedione are maintained and both of these are converted into oestradiol. Oestrogen is still produced by the postmenopausal ovary (Poliaik, Jones and Woodruff 1971), and there is no abrupt decrease in serum oestrogen in the physiological menopause. The evidence of these experimental studies and of clinical outcomes appears to show that oestrogen affects the elasticity of fibrous connective tissues.

In our study, facet orientation in the sagittal plane and an increased pedicle-facet angle appeared to be common characteristic features of the spine developing spondylolisthesis. By contrast, exaggerated lumbosacral angles and narrowing of the disc at the involved segment were observed only in non-oophorectomised patients with degenerative spondylolisthesis. Thus it seems that an exaggerated lumbosacral angle and disc-space narrowing are

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REFERENCES


