Is hormone replacement therapy protective for hand and knee osteoarthritis in women?: The Chingford study

T D Spector, D Nandra, D J Hart, D V Doyle

Abstract

Objectives—To explore whether hormone replacement therapy (HRT) has a protective role for osteoarthritis (OA) of the hand and knee in a cross sectional study of women in the general population.

Methods—1003 women aged 45–64 (mean age 54.2) from the Chingford Study were asked details of HRT use. Standard anteroposterior radiographs of hands, knees were taken and scored according to the methods of Kellgren and Lawrence (grade 2+ positive for OA), and using individual features of osteophytes and joint space narrowing. Analysis compared ever use (> 12 months) versus never use, and current use (> 12 months) versus never use. Only 606 definitely postmenopausal women were included in the analysis. Odds ratios and 95% confidence intervals were calculated using logistic regression for risk of user versus non-user at each site, adjusted for age, height and weight, menopausal age and for bone mineral density of the femoral neck.

Results—For current users (n=72) there was a significant protective effect of HRT for knee OA (defined by Kellgren and Lawrence grade or osteophytes 0.31 (95% CI 0.11, 0.93), and a similar but not significant effect for moderate joint space narrowing of the knee, 0.41 (95% CI 0.05, 3.15) and for distal interphalangeal OA 0.48 (95% CI 0.17, 1.42). No clear effect was seen for the carpometacarpal joint, CMC OA 0.94 (95% CI 0.44, 2.03). When analysing ever users (n=129) the protective effect was reduced. For ex-users of >12 months (mean duration 40.7 months), there was no overall protective effect of HRT for OA. Additional adjustment for hysterectomy, physical activity, social class, and smoking made little difference to the results.

Conclusions—These data show an inverse association of current HRT use and radiological OA of the knee suggestive of a protective effect. The effect was weaker in the hand joints. The mechanism of the protection is unclear but has important implications for aetiology.
Hormone replacement therapy and osteoarthritis in women

Comparison of the groups. No difference was seen for age, height, weight, and BMI. As expected the 129 women in the ever HRT group had a significantly increased mean (SD) femoral neck BMD (0.79 (0.12) v 0.76 (0.12), p=0.03) and higher rates of hysterectomy. Levels of smoking and physical activity were similar. There were significant differences in social class between the groups. Only women who were clearly postmenopausal at the time of the radiography were included in the HRT analysis (n=606). If women had undergone hysterectomy and bilateral oophorectomy (n=65), their age at menopause was taken as the age at operation. Women under 55, with hysterectomy alone (n=165), were excluded. Prevalence and risk of OA at each site by HRT status is shown in Table 2 adjusted for age, height weight, menopausal age, and bone density. For current users there was a threefold significant protective effect of knee OA as defined by osteophytes OR 0.31 (95% CI 0.11, 0.93), and a twofold non-significant protective effect for the DIP OR 0.48 (95% CI 0.17, 1.42). No clear effect was seen at the CMC joint OR 0.94 (95% CI 0.44, 2.03). For joint space narrowing at the knee, there was no clear effect for mild (grade 1) narrowing, but a suggestion for more severe narrowing OR=0.41 (95% CI 0.05, 3.15), although numbers were small in this latter group. When analysing ever users the protective effect was generally lessened and non-significant. There were only a small number (57) of ex-HRT users and no suggestion of a protective effect was seen. Additional adjustment for further potential confounders such as social class, hysterectomy, oophorectomy, physical activity, and knee injury did not further change the results.

A nurse administered questionnaire was used to obtain demographic and environmental details. Where information on timing and duration of HRT use or age at menopause was unclear, additional information was obtained by subsequent telephone survey and postal questions. Current users were defined as more than 12 months of use at the time of radiography and ex-users more than 12 months at least 24 months previously. Age at menopause was defined as last recalled regular menses or oophorectomy. Women were defined as postmenopausal if their periods had stopped at least 12 months previously, or if they had a total hysterectomy, or hysterectomy alone and were aged over 55. Odds ratios and 95% confidence intervals were calculated using multiple logistic regression (EGRET, SERC, Seattle) for the risk of OA in users versus never users adjusting for potential confounders, age, height, weight, menopausal age, femoral neck BMD, as well as hysterectomy physical activity, recalled knee injury, and social class.

Results

Subjects were divided into three exposure categories; current users (more than 12 months, mean duration (SD) 33.4 months (26.5) n=72), ever users (a combination of ex-users (at least two years before radiography) and current users for more than 12 months, mean duration (SD) 36.6 months (29.5) n=129) and never users (including those users of less than 12 months) (n=874). The types of HRT were recorded and the majority of users had taken conjugated oestrogens, Prempak-C or Premarin 0.625 at some time. Table 1 shows a comparison of the groups. No difference between HRT groups was seen for age, height, duration HRT, weight, height, and social class. Differences between HRT groups were seen for weight, bone density and smoking. For current users there was a threefold significant protective effect of knee OA as defined by osteophytes OR 0.31 (95% CI 0.11, 0.93), and a twofold non-significant protective effect for the DIP OR 0.48 (95% CI 0.17, 1.42). No clear effect was seen at the CMC joint OR 0.94 (95% CI 0.44, 2.03). For joint space narrowing at the knee, there was no clear effect for mild (grade 1) narrowing, but a suggestion for more severe narrowing OR=0.41 (95% CI 0.05, 3.15), although numbers were small in this latter group. When analysing ever users the protective effect was generally lessened and non-significant. There were only a small number (57) of ex-HRT users and no suggestion of a protective effect was seen. Additional adjustment for further potential confounders such as social class, hysterectomy, oophorectomy, physical activity, and knee injury did not further change the results.

Table 1 Basic characteristics of women, presented as mean (SD) or number (%)

<table>
<thead>
<tr>
<th>Age (y) (SD)</th>
<th>Current (n=72)</th>
<th>Current (n=72)</th>
<th>Ex-users (n=57)</th>
<th>Ex-users (n=57)</th>
<th>Ever (n=129)</th>
<th>Ever (n=129)</th>
<th>Never (n=874)</th>
<th>Never (n=874)</th>
<th>p Value ever v never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) (SD)</td>
<td>53.5 (4.53)</td>
<td>54.6 (6.1)</td>
<td>53.9 (5.29)</td>
<td>54.3 (6.13)</td>
<td>0.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age menopause (y) (SD)</td>
<td>48.7 (3.73)</td>
<td>46.3 (5.6)</td>
<td>48.5 (3.77)</td>
<td>48.9 (4.18)</td>
<td>0.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration HRT (months) (SD)</td>
<td>33.4 (26.46)</td>
<td>40.7 (32.7)</td>
<td>36.6 (29.49)</td>
<td>48.9 (4.18)</td>
<td>0.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm) (SD)</td>
<td>161.9 (6.02)</td>
<td>161.74 (5.86)</td>
<td>161.8 (5.93)</td>
<td>161.6 (6.0)</td>
<td>0.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg) (SD)</td>
<td>66.3 (11.60)</td>
<td>66.3 (11.60)</td>
<td>66.3 (11.60)</td>
<td>67.0 (11.88)</td>
<td>0.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>25.3 (6.48)</td>
<td>25.4 (3.47)</td>
<td>25.33 (4.18)</td>
<td>25.6 (4.32)</td>
<td>0.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysterectomy (%)</td>
<td>32 (44.4)</td>
<td>32 (44.4)</td>
<td>32 (44.4)</td>
<td>32 (44.4)</td>
<td>0.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking (%) ever</td>
<td>30 (41.7)</td>
<td>30 (41.7)</td>
<td>30 (41.7)</td>
<td>30 (41.7)</td>
<td>0.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity group (%)</td>
<td>4 (5.6)</td>
<td>4 (5.6)</td>
<td>4 (5.6)</td>
<td>4 (5.6)</td>
<td>0.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social classes (%)</td>
<td>8 (11.1)</td>
<td>8 (11.1)</td>
<td>8 (11.1)</td>
<td>8 (11.1)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD femoral neck (SD) (g/cm²)</td>
<td>0.80 (0.13)</td>
<td>0.77 (0.11)</td>
<td>0.79 (0.12)</td>
<td>0.76 (0.12)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion

These data show that current use of HRT is associated with a threefold reduction in risk of knee OA, as defined by osteophyte or Kellgren and Lawrence and a modest reduction in DIP but not CMC OA. There was a suggestion of an effect when defining knee OA by moderate joint space narrowing but not mild, although numbers were small. This effect was not mediated by change in bone density or explained by measured confounders. We had insufficient numbers of long duration users to accurately assess dose response. The differences between the effects of past and current HRT use are

Table 1 Basic characteristics of women, presented as mean (SD) or number (%)
and ideally a randomised trial. As previous studies have shown bone density is higher in women with OA, a reasonable hypothesis was that HRT use could lead to a greater risk of OA. 

The cross sectional nature of the study makes it difficult to be sure of the importance of the timing of HRT use, and whether early or subclinical disease was present. These results taken together suggest that HRT has a metabolic action that is only effective if given continuously, perhaps by preventing disease initiation; once HRT is stopped there might be a ‘rebond’ effect, explaining the rapid return to normal risk. In OA the mechanisms by which HRT might act are highly speculative, but could entail changes in cartilage repair or bone turnover, perhaps with cytokines such as interleukin 6, for example. The study of knee OA in elderly women by Hannan et al lacked sufficient numbers of current users to resolve the issue of timing. A case control study of knee OA by Samanta et al examined HRT use as one of a number of potential risk factors and found a non-significant protective effect but did not distinguish timing of HRT use. A recently published study by Nevitt et al from the Study of Osteoporotic Fractures cohort of 4366 white women reported that in current users the risk of hip OA was 0.62 (95% CI 0.49, 0.86), with a weak trend for increasing protection with disease severity. As in this study no clear effect for past use was seen. In observational studies of HRT use such as this, selection bias is a potential problem that is impossible to completely eliminate by adjustment. Although we found no major differences in our data other than for social class, studies have shown that long term HRT users are more likely to be health conscious, have better diets, and be better informed about preventive medicine. Nevertheless the size of the effect, the increasing use of HRT, and the public health importance of OA warrant confirmatory prospective studies.

Table 2 Prevalence of OA and risk of OA by HRT group presented as odds ratios and 95% confidence intervals

<table>
<thead>
<tr>
<th>Joint site and OA grade</th>
<th>Current users (n=72)</th>
<th>Never users (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affect (%)</td>
<td>Cases Controls</td>
</tr>
<tr>
<td>Knee osteophytes</td>
<td>143 (14.5)</td>
<td>4 68</td>
</tr>
<tr>
<td>Knee narrowing</td>
<td>359 (36.7)</td>
<td>20 52</td>
</tr>
<tr>
<td>Gd1+</td>
<td>34 (3.5)</td>
<td>1 71</td>
</tr>
<tr>
<td>Gd2+</td>
<td>140 (14.2)</td>
<td>4 50</td>
</tr>
<tr>
<td>Distal interphalangeal joint OA</td>
<td>160 (16.2)</td>
<td>9 50</td>
</tr>
</tbody>
</table>

*Adjusted for age, height, weight, menopausal age, femoral neck BMD.

We are grateful to Sabeha Attia, Maxine Daniels, and Elizabeth Arden for their input as well as the staff of Chingford Hospital and the staff and patients of the Handsworth Avenue Health Partnership.

References

Is hormone replacement therapy protective for hand and knee osteoarthritis in women?: The Chingford study
T D Spector, D Nandra, D J Hart and D V Doyle

doi: 10.1136/ard.56.7.432

Updated information and services can be found at:
http://ard.bmj.com/content/56/7/432

These include:

References
This article cites 10 articles, 5 of which you can access for free at:
http://ard.bmj.com/content/56/7/432#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Menopause (including HRT) (54)
- Degenerative joint disease (4641)
- Musculoskeletal syndromes (4951)
- Osteoarthritis (931)
- Clinical diagnostic tests (1282)
- Epidemiology (1367)
- Radiology (1113)
- Radiology (diagnostics) (750)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/