

both diet and the exercise interventions. Each group was tracked for 18 months, with the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) physical function scale as the primary outcome measure (Figure 2).

Subjects in the diet group lost an average of 4.9% of their body weight (4.6 kg) and achieved significant improvement in their WOMAC physical function score, but their improvement was not significantly greater than that of the healthy lifestyle control group. Only the group randomized to diet plus exercise experienced significantly more improvement than the control healthy lifestyle group. These important results do not show an effect of weight loss as dramatic as might have been anticipated from prior uncontrolled studies and small trials. Even so, they strongly suggest the efficacy of weight loss in OA, especially if it is combined with exercise.

In summary, work in the past 2 years has led to substantial new insights into the relationship between obesity and OA, with studies suggesting for the first time that weight loss, especially if accompanied by exercise, may substantially improve symptoms.

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## RISK FACTORS FOR THE DEVELOPMENT AND PROGRESSION OF HIP OSTEOARTHRITIS

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Lieveense and colleagues at the Erasmus Medical Center, Rotterdam, have published several systematic reviews that

nicely summarize the literature on risk factors for hip OA<sup>1-4</sup>. These reviews employed a common search strategy and all used the "best evidence" method of synthesizing data from observational epidemiological studies. Moderate evidence was found for a positive association between hip OA and obesity; participation in sporting activities, including running; and vocational activity, particularly involving a heavy physical workload, as characterized by farming (especially for more than 10 years) or lifting heavy loads (25 kg or more). Only limited evidence existed for a positive association between occurrence of hip OA and participation in athletics or presence of hip dysplasia in older persons.

The Rotterdam group also published a systematic review of observational studies of prognostic factors for hip OA<sup>5</sup>, in which they divided progression of hip OA into clinical progression (e.g., progressing to total hip arthroplasty) and radiographic progression. There was strong evidence for more rapid progression in subjects with superolateral migration of the femoral head and in those with an atrophic (in comparison with a hypertrophic) bone response. Limited evidence was present for a direct association between hip dysplasia and progression, and an inverse association was noted between the joint space width (JSW) and the progression to total hip arthroplasty (i.e., the smaller the JSW, the greater the risk of progression to total hip arthroplasty). Evidence for an association between progression of OA with greater age at baseline and with female sex was not consistent across studies; some found an association while others did not. There was strong evidence that neither body weight nor BMI was associated with progression. A subsequent report<sup>6</sup> noted that women had significantly more rapid structural progression than men and a significantly greater relative hazard of subsequent total hip arthroplasty; however, these relationships were no longer significant after adjustment for confounding variables.

Methods of determining structural progression in hip OA were discussed at the Osteoarthritis Research Society International (OARSI) Congress in Barcelona<sup>7</sup>. The group determined that, at this time, conventional radiography was the only adequately validated method for assessment of structural progression in clinical and epidemiological studies of hip OA. Recommendations were published on techniques for pelvic radiography in both supine and standing positions: it was felt that separate radiographs for each hip did not provide important advantages over a single standardized radiograph of the pelvis, while they presented greater problems than the latter with respect to repositioning in longitudinal studies. The preferred outcome measure for assessing progression is JSW at the narrowest point in the hip joint. Several methods for obtaining this measurement were reviewed and it was concluded that measurement could be performed either with a calibrated eyepiece (reticule) or electronic calipers, or by computer.

Maillefert and colleagues used data from a longitudinal

cohort study of patients with symptomatic hip OA to determine the relevant change in JSW (in mm) at the narrowest point needed to define radiological progression of hip OA<sup>8,9</sup>. The first analysis determined the relevant change based on the predictive validity for a subsequent decision to perform total hip arthroplasty, while the second analysis relied on consensus agreement by 2 experts about a clinically relevant change. In the first analysis, an absolute decrease in JSW  $\geq 0.4$  mm over 2 years had a sensitivity of 68% for a subsequent decision to perform hip arthroplasty and positive and negative predictive values of 50% and 80.5%, respectively<sup>8</sup>. In the second analysis, the best threshold was determined to be an absolute decrease in JSW  $\geq 0.4$  mm over 3 years, based on a sensitivity of 75% for patients with clinically relevant deterioration and a specificity of 75% for patients without clinically relevant deterioration<sup>9</sup>. Previous work by this group showed that the smallest detectable difference in JSW at the narrowest point, using the method of Bland and Altman, was 0.6 mm<sup>10</sup>. Hence, the recommended clinically relevant reduction in JSW appears to fall within the error of measurement of JSW. The implications for use of reduction in JSW as a surrogate outcome in clinical trials requires further discussion, particularly with regulatory agencies<sup>11</sup>.

Finally, there is high interest in the development and validation of biomarkers for the identification of individuals at greater risk for progressive OA. In 2001, the Group for the Respect of Ethics and Excellence in Science published recommendations for use of biochemical markers in studies of OA<sup>12</sup>. Preliminary data from a small sample of patients with hip OA, based on analysis of paired radiographs obtained at a one-year interval and urine samples collected at the time of the second radiograph, suggest that patients with rapidly progressive hip OA have higher mean urinary concentrations of C-telopeptide of type II collagen (CTX-II) than those with slowly progressive hip OA. A direct relationship was noted between log transformed levels of urinary CTX-II and minimum JSW<sup>13</sup>. A recent post-hoc analysis of data from the ECHODIAH study showed that high baseline levels of urinary CTX-II and of serum hyaluronic acid were associated with a higher risk of radiographic progression in patients with hip OA<sup>14</sup>.

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## WHO GETS OSTEOARTHRITIS AND WHY? AN UPDATE

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What has happened since our presentation, "Who Gets Osteoarthritis and Why?", 2 years ago<sup>1</sup>? Are we heading for a cure?

A few recent articles shed some hope. Recent epidemiologic studies show a pattern of heightened incidence of OA in specific joints, in Beijing Chinese in comparison with Caucasians, associated with differences between the 2 groups with respect to mechanics of activities of daily living. Coupled with genomic investigation, the work recommends a genetic joint-by-joint approach, looking for OA susceptibility in genes that control movement<sup>2</sup>. In addition, this research team has found that the effect of body weight on the progression of knee OA is dependent on limb alignment<sup>3</sup>.

The search for biomarkers of OA, telltale cartilage or bone molecules, seems to be dying out. Radiologic progres-