The Benefits of Intra-Articular High Molecular Weight Hyaluronic Acid Injections Compared to Low Molecular Weight Intra-Articular Hyaluronic Acid in the Reduction of Pain, Disability, and Stiffness in Adult Patients with Osteoarthritis of the Knee

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The Benefits of Intra-Articular High Molecular Weight Hyaluronic Acid Injections Compared to Low Molecular Weight Intra-Articular Hyaluronic Acid in the Reduction of Pain, Disability, and Stiffness in Adult Patients with Osteoarthritis of the Knee

Abstract

Introduction: Osteoarthritis (OA) of the knee is a common disorder affecting adults and continues to be a growing concern as the current population ages. Intra-articular (IA) injections of hyaluronic acid (HA) are currently used as a viscosupplementation and have shown to provide symptomatic relief. Recently the formulation of differing molecular weight HAs have been produced to provide a further decrease in pain and stiffness, and increase physical function. The formulations include high molecular weight HA (HMW-HA) and low molecular weight HA (LMW-HA). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) has been used as a validated tool to assess the improvements in knee OA.

Hypothesis: If pain, disability, and stiffness are affected by specific molecular weight HA, then intra-articular injections of HMW-HA will benefit patients suffering from OA of the knee.

Study Design: A systematic review of current randomized controlled trials.

Methods: An exhaustive electronic literature search was performed for relevant published, randomized controlled trials in MEDLINE, CINAHL, Evidence-Based Medicine Reviews Multifile, and PubMed from January 2002 to March 2009. Inclusion criteria included randomized controlled trials comparing the effects of intra-articular injection of high molecular weight hyaluronic acid with that of intra-articular injection of a low molecular weight to treat osteoarthritis of the knee were included in this systematic review. Outcome measures of pain, physical function, and stiffness based on the WOMAC had to be available. Exclusion criteria included trials having no randomization and no pain, disability, or stiffness (WOMAC) classification.

Results: Pooled data reveal an allocation of 1321 patients to a HMW-HA, LMW-HA, or placebo group. The average age of patients ranged from 41 to 82 years (mean 65.3 years). Of the 4 studies reviewed only one revealed a significant difference. All others reported no significant decrease in pain and stiffness, and improvement in physical function. Most studies demonstrated an improvement in all three variables from baseline, independent of the molecular weight HA used.

Conclusion: Based on this systematic review of four RCTs the use of HMW-HA does not provide an absolute clinical benefit to adult patients suffering from knee OA.

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Bradley E. Scott

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR For the Masters of Science Degree, August 15, 2009

Faculty Advisor: Latha Reddy MS, PA-C Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC
Biography

Bradley Scott was raised in the great state of Florida and received Bachelor of Science and Master of Science degrees in Exercise Physiology from Florida State University (Go Noles!). Upon completion he moved to Portland, OR and worked in obesity research at Oregon Health & Science University. He now resides in Bend, OR with his wife Kirsten and their son CJ. Interests include spending time with family, mountain biking, running, and working towards owning one or more Porsches.
Abstract

**Introduction:** Osteoarthritis (OA) of the knee is a common disorder affecting adults and continues to be a growing concern as the current population ages. Intra-articular (IA) injections of hyaluronic acid (HA) are currently used as a viscosupplementation and have shown to provide symptomatic relief. Recently the formulation of differing molecular weight HAs have been produced to provide a further decrease in pain and stiffness, and increase physical function. The formulations include high molecular weight HA (HMW-HA) and low molecular weight HA (LMW-HA). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) has been used as a validated tool to assess the improvements in knee OA. **Hypothesis:** If pain, disability, and stiffness are affected by specific molecular weight HA, then intra-articular injections of HMW-HA will benefit patients suffering from OA of the knee. **Study Design:** A systematic review of current randomized controlled trials. **Methods:** An exhaustive electronic literature search was performed for relevant published, randomized controlled trials in MEDLINE, CINAHL, Evidence-Based Medicine Reviews Multifile, and PubMed from January 2002 to March 2009. Inclusion criteria included randomized controlled trials comparing the effects of intra-articular injection of high molecular weight hyaluronic acid with that of intra-articular injection of a low molecular weight to treat osteoarthritis of the knee were included in this systematic review. Outcome measures of pain, physical function, and stiffness based on the WOMAC had to be available. Exclusion criteria included trials having no randomization and no pain, disability, or stiffness (WOMAC) classification. **Results:** Pooled data reveal an allocation of 1321 patients to a HMW-HA, LMW-HA, or placebo group. The average age of patients ranged from 41 to 82 years (mean 65.3 years). Of the 4 studies reviewed only one revealed a significant difference. All others reported no significant decrease in pain and stiffness, and improvement in physical function. Most studies demonstrated an improvement in all three variables from baseline, independent of the molecular weight HA used. **Conclusion:** Based on this systematic review of four RCTs the use of HMW-HA does not provide an absolute clinical benefit to adult patients suffering from knee OA.

**Keywords:** Hyaluronic acid, viscosupplementation, osteoarthritis, knee
Acknowledgements

To Kirsten C. Scott, Thank you for being my best friend and beautiful wife. Without your loving support this journey would not have been possible.

To my son CJ, I hope being a Physician Assistant provides you with a better quality of life and gives you the tools to pursue your dreams and desires.

I would like to dedicate this clinical project to my Dad, Robert L. Scott. He always wanted the best for me and I know he is watching down on me in great enjoyment of my accomplishments.
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List of Abbreviations

HA……………………………………………………………………...…Hyaluronic acid
OA..................................................................................................................Osteoarthritis
HMW………………………………………………………………High Molecular Weight
LMW……………………………………………………………….Low Molecular Weight
IA...........................................................................................................Intra-articular
The Benefits of Intra-Articular High Molecular Weight Hyaluronic Acid Injections Compared to Low Molecular Weight Intra-Articular Hyaluronic Acid in the Reduction of Pain, Disability, and Stiffness in Adult Patients with Osteoarthritis of the Knee

INTRODUCTION:

Osteoarthritis (OA) of the knee is a common disorder and continues to be a growing concern in an aging population. Recent estimates reveal that 46.4 million American adults (21%) are diagnosed with OA. These numbers represent approximately 11.7 million ambulatory care visits a year. It is estimated that by 2020 OA will affect 59.4 million adults in the United States. Due to this expected increase and its public health impact, management is paramount.

The goals for management of OA of the knee are to decrease pain, improve function, and increase joint mobility. Management options include analgesics (opioids, acetaminophen, and non-steroidal anti-inflammatory drugs), intra-articular (IA) corticosteroid injections, joint arthroplasty, and physiotherapy, to include quadriceps strengthening and dynamic muscle balance.

One other therapeutic treatment option is IA hyaluronic acid (HA) injections. Hyaluronic acid, in the form of hyaluronan and hylan, is a major component of the synovial fluid matrix, and aids in joint homeostasis. Hyaluronic acid is a polysaccharide and has been shown to influence tissue hydration, interact with extracellular macromolecules, and act upon cell receptors, specifically CD44. The therapeutic value of HA has been proposed to have a protective effect on chondrocytes and to improve the structural matrix within synovial fluid. These benefits may be due to an anti-inflammatory effect such as a decrease of phagocytosis, prostaglandin synthesis, chemotaxis, and removal of free radicals.

In patients with knee OA, hyaluronic acid is cleared from the synovial fluid at higher rates, thus producing a decreased concentration and molecular weight. Intra-articular injections of HA, referred to as viscosupplementation, have been shown to provide benefits after a single treatment. Proposed
mechanisms include in-situ stimulation of synovial synthesis of HAs, decreased cartilage matrix degradation, and suppression of inflammatory responses.4

The formulation of differing molecular weight HAs, have been produced to compensate for the decreased molecular weights due to OA and to provide a joint viscosity closer to that of biological synovial fluid. Currently, there are five HA formulations approved in the United States for viscosupplementation of knee OA: Synvisc®, Euflexxa™, Orthovisc®, Supartz™, and Hyalgan® (Table 1).

The most widely used tool to assess knee OA, is the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Moreover, the WOMAC index uses 24 parameters to monitor the course of the disease and/or to determine the effectiveness of anti-rheumatic medications (Table 3). Scoring is based on patient response to three overall categories, which include pain, physical function, and stiffness. Total maximum score is 98 with 20 from pain, 68 from physical function, and eight from stiffness. The WOMAC index has been validated and deemed a reliable tool for assessing knee OA.5

PURPOSE:

The aim of this systematic review is to elucidate the therapeutic and functional benefits of intra-articular, high molecular weight hyaluronic acid injections for osteoarthritis of the knee in adults, compared to low molecular weight hyaluronic acid.

HYPOTHESIS:

If pain, stiffness, and the level of physical function are affected by specific molecular weight HA, then intra-articular injections of high molecular weight hyaluronic acid (HMW-HA) will benefit adult patients suffering from OA of the knee.
SIGNIFICANCE:

The findings of this review will aid clinicians and healthcare providers in determining proper care for adult men and women suffering from OA of the knee. Moreover, this review will determine if there is a beneficial effect to using a HMW-HA in the reduction of pain, disability, and stiffness in patients suffering from knee OA compared to low molecular weight hyaluronic acid (LMW-HA).

METHODS:

An exhaustive electronic literature search was performed for relevant published, randomized controlled trials in MEDLINE, CINAHL, Evidence-Based Medicine Reviews Multifile, and PubMed from January 2002 to March 2009. The search terms, “viscosupplementation”, “osteoarthritis”, “knee”, “hyaluronic acid”, and its synonyms were used to refine the search. Further limitations to the search criteria included humans, English language, and full text. Each article was reviewed and assessed a Jadad score as a quality rating method (Table 2).

Inclusion Criteria

Only randomized controlled trials comparing the effects of intra-articular injection of high molecular weight hyaluronic acid with that of intra-articular injection of a low molecular weight to treat osteoarthritis of the knee were included in this systematic review. Outcome measures of pain, physical function, and stiffness based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) had to be available. Studies must have been published within the last seven years (January 2002 to March 2009). Participants must have been over 40 years of age and have radiographic confirmed OA of the knee.

Exclusion criteria

Trials having no randomization and no pain, disability, or stiffness (WOMAC) classification were excluded from this systematic review. Moreover, general review and meta-analysis articles were excluded from the results, but referred to for background and discussion purposes only.
RESULTS:

Based on the above search criteria, four randomized controlled trials (RCTs) were identified and found eligible for this systematic review (Table 2). Each eligible study used the WOMAC index for scoring treatment effect and included all sub-categories of pain, physical function, and stiffness. Trial durations range from 6 to 27 weeks and only patients with a radiological confirmed diagnosis of knee OA were recruited. Pooled data reveal an allocation of 1321 patients to a HMW-HA, LMW-HA, or placebo group. The average age of patients ranged from 41 to 82 years (mean 65.3 years). Listed below are the specific results for each study in this systematic review.

Raman et al

The high molecular (HW) hylan G-F 20 (Synvisc®) group contained 199 patients and 193 were allocated to the low molecular (LM) sodium hyaluronate (Hyalgan®) with predominantly grade III OA, 61% and 59%, respectively. The age range was 42 to 82 years with a mean age of 67.2 years (p = 0.54). The gender ratio of male:female was 1:2.1 (p = 0.61). The WOMAC scoring index demonstrated a significant improvement in pain scores for the HMW compared to the LMW group at 3, 6, and 12 months (p<0.05). Physical function WOMAC scores were significantly better in the HMW group compared to the LMW at 6 and 12 months (p<0.05). There was no intergroup statistical difference for WOMAC stiffness, but both groups showed improvement from baseline at 3, 6, and 12 months. Knee pain assessed by visual analogue scale (VAS) revealed a statistical difference (p<0.05) between groups at 6 weeks, 6 months, and 12 months. Adverse events were noted in 69 patients (39 HMW and 30 LMW). All adverse events, except one, were minor. The major adverse event was a patient with pseudosepsis, which was treated per trial protocol, and subsequently excluded from the results.
The study evaluated IA injections of hylan (HMW), avian HA (medium molecular weight), and bacterial HA (LMW). There were 660 patients randomly assigned to each group: HMW = 222 patients, MMW = 219, and LMW = 219. The majority of patients (57% - 60%) had confirmed moderate knee OA. The mean age was 63.4 years. Results indicated no statistical difference between groups for WOMAC pain score at 3 and 6 months. Similar trends were seen for WOMAC physical function and stiffness scores. There were no statistical differences between groups for VAS.

There were 59 patients randomly assigned to HMW (21), LMW (20), and placebo (18). The mean age was 59.5 years. The gender ratio of male:female was 1:8.5. The HMW and LMW groups each exhibited a significant (p<0.05) decrease in WOMAC pain, physical function, and stiffness scores from baseline to 27 weeks. No statistical difference was demonstrated between groups for WOMAC pain, physical function, and stiffness at all time points.

There were 210 patients randomly assigned to HMW (77), LMW (76), and placebo (57). The mean age was 71.3 years. The majority of the patients were women (68%). The majority of the patients had grade I OA (59%). There were no statistical difference between groups at all time points (12 and 26 weeks) for WOMAC pain, physical function, and stiffness. Similarly, no statistical differences between groups were seen for VAS at all follow-up time points.

DISCUSSION:

Viscosupplementation with intra-articular HA injections are a treatment option for knee OA. Previous studies have shown a benefit using intra-articular HA when compared to placebo. Recent interest has been shown in the use of HMW-HAs and their added benefits compared to lower molecular weight HAs. Benefits in knee OA have been quantified by using the WOMAC index, which
evaluates decreases in pain and stiffness, and increases in physical function (Table 3). The WOMAC index is a standardized and validated scoring system used in the determination of clinical improvement.5

Findings of this systematic review suggest no definitive benefits, based on the WOMAC index, in symptoms related to knee OA with the use of HMW-HA when compared to LMW-HA. Three of the four studies found no intergroup statistical difference for pain, physical function, and stiffness based on the WOMAC index.3,7-8 One reviewed study, Raman et al6, demonstrated an intergroup difference in WOMAC pain and physical function between Synvisc® (HMW-HA) and Hyalgan® (LMW-HA).

**WOMAC Pain Index**

Three of the four reviewed studies found no intergroup differences for pain based on the WOMAC index. Raman et al6 demonstrated an intergroup difference when administering Synvisc® (6.0 mDa) (HMW) and Hyalgan® (0.5 – 0.7 mDa) (LMW). One possible explanation for this intergroup difference is the use of two HA formulations at the extreme ends of the molecular weight spectrum. The three other studies administered Synvisc® (6.0 mDa), but compared it to other viscosupplements of varying molecular weights (Table 1). Moreover, Jüni et al3 and Kotevoglu et al7 compared Synvisc® to Orthovisc® (1.0 – 2.9 mDa), which has a higher molecular weight than Hyalgan® used by Raman et al6. The use of different formulations could be one possible explanation for the lack of intergroup differences.3,7-8

Current data show a reduction in pain with the use of viscosupplementation, independent of the molecular weight HA used.3,6-8 Similar results have been reported when comparing HA and a saline placebo IA injection.2,10 One possible explanation is the partial removal of catabolites involved in inflammation. Only one of the reviewed studies specifies methodology on the injection technique.
Moreover, an injection technique using aspiration of synovial fluid prior to HA injection may elicit benefits independent of the viscosupplement administered.

WOMAC Physical Function Index

As previously mentioned, improving trends have been reported for LMW and HMW intra-articular injections.\textsuperscript{3,6-8} More specifically, these data represent an improvement in physical function from baseline. These reported improvements, include ascending and descending stairs, rising from sitting, standing, and squatting.\textsuperscript{6,8} Most studies revealed an increase in physical function during early follow-up, 6 to 12 weeks, though these were not statistically significant.\textsuperscript{7,8} These results are independent of the molecular weight viscosupplement administered.

Raman et al\textsuperscript{6} did exhibit an intergroup difference for physical function when comparing Synvisc\textsuperscript{®} and Hyalgan\textsuperscript{®}. As mentioned above, this could be attributed to the extreme difference in molecular weight between the two viscosupplements, although the severity of knee OA is not clearly stated and could be a possible limitation in extrapolating these results to clinical practice.

WOMAC Stiffness Index

All reviewed studies demonstrated an intragroup improvement in stiffness from baseline. These results are consistent with published data from the administration of HA compared to placebo, independent of the molecular weight HA used.\textsuperscript{2,9} Reported improvements include decreased morning and evening stiffness.

Only one study to date has shown a significant improvement between the use of HMW HA compared to LMW HA.\textsuperscript{6} Other studies have been unable to reproduce these results. The most likely explanation is the use of varying molecular weight HAs. Raman et al\textsuperscript{6} administered Synvisc\textsuperscript{®} and Hyalgan\textsuperscript{®}, while other studies used Synvisc\textsuperscript{®} and a HA in the mid-range of molecular weight, mainly Orthovisc\textsuperscript{®} (1.0 – 2.9 mDa). Moreover, the study was powered only by the primary outcome, which could lead to bias in the statistical analysis.\textsuperscript{6}
Strengths of Study

The strength of this systematic review lies in the inclusion of studies incorporating the WOMAC index for the assessment of a therapeutic effect in knee OA. By assessing one primary outcome this provides homogeneity and makes the study reproducible. All studies were RCTs and blinded, thus again adding integrity to the results. Furthermore, each reviewed article was assessed a Jadad score, and these scores ranged from two to five out of a maximum of five.

Limitations of Study

The current systematic review has several limitations. First, unpublished studies were not searched. Studies with negative results or limited methodology tend to be unpublished; exclusion of these studies may introduce the likelihood that a treatment effect is skewed in the positive direction due to publication bias. Second, the four included studies differed in the viscosupplement administered. Most used Synvisc® as a HMW, but differed in the LMW comparison agent. Third, there was no concise standardization of knee OA severity. Current data suggest a benefit to using HMW HA in patients with moderate to severe knee OA. The four reviewed studies stated mild to moderate knee OA and used two different classification systems, the Kellgren-Lawerence and Ahlbäck systems, to define these. This produces heterogeneity in the results and makes it difficult to determine a therapeutic effect. Lastly, by only focusing on one primary outcome, the WOMAC index, this current review may be overlooking other evaluation tools to reveal improvements in knee OA. Other common assessment tools include the VAS, Oxford knee scores, and the EuroQol-5D index. The WOMAC was used as a primary outcome measure based on its validity and incorporation of pain, physical function, and stiffness, and their subgroups (Table 3).

Recommendations for Future Studies

More well-designed RCTs with high methodological quality are needed to fully elucidate the benefits of HMW HA in the treatment of knee OA. Furthermore, double-blinded, RCTs comparing
Synvisc® to all varying molecular weight HAs and placebo would benefit the clinician in determining the best treatment for knee OA in adult patients. The current study has noted more female patients than male patients enrolled in the four reviewed studies. Future studies could analyze data to elicit a possible gender effect associated with the administration of HMW-HA and/or LMW-HA.

Synvisc-One™ is a new viscosupplement touted to give benefits up to six months. Future studies comparing this, to track proven HA agents would shed more light on the treatment options available to clinicians. Furthermore, Synvisc-One could show clinical benefits by reducing the number of injections patients need, decreasing adverse events, and reducing out-of-pocket cost.

CONCLUSION

Based on this systematic review of four RCTs, the use of HMW-HA does not provide an absolute clinical benefit to patients suffering from knee OA. Furthermore, there is no definitive therapeutic effect of HMW-HA compared to other proven modalities, such as NSAIDs, IA corticosteroid injections, physiotherapy, and joint arthroplasty. The current recommendations for knee OA are to begin with noninvasive therapies (NSAIDs and physiotherapy) and progress to more invasive techniques (IA corticosteroid and HA injections). Lastly, total joint arthroplasty is a definitive treatment for knee OA, but is reserved for patients suffering from severe OA.
TABLE 1: Current FDA Approved Hyaluronic Acid Products in the United States

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>Molecular Weight (Daltons)</th>
<th>Dosage per Injection</th>
<th>Number of Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synvisc® (Hylan G-F 20)</td>
<td>$6.0 \times 10^6$</td>
<td>16mg/2mL</td>
<td>3</td>
</tr>
<tr>
<td>Euflexxa™ (1% sodium hyaluronate)</td>
<td>$2.4 - 3.6 \times 10^6$</td>
<td>10mg/2mL</td>
<td>3</td>
</tr>
<tr>
<td>Orthovisc® (Hyaluronan)</td>
<td>$1.0 - 2.9 \times 10^6$</td>
<td>30mg/2mL</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Supartz™ (Sodium hyaluronate)</td>
<td>$0.6 - 1.2 \times 10^6$</td>
<td>25mg/2.5mL</td>
<td>3 or 5</td>
</tr>
<tr>
<td>Hyalgan® (Sodium hyaluronate)</td>
<td>$0.5 - 0.7 \times 10^6$</td>
<td>20mg/2mL</td>
<td>3 or 5</td>
</tr>
</tbody>
</table>
### TABLE 2: Study Characteristics of Four Reviewed Articles

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Study Type</th>
<th>Patients</th>
<th>HA Administered</th>
<th>Outcomes</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raman et al 2008</td>
<td>Prospective RCT, Investigator blinded</td>
<td>n = 380</td>
<td>Synvisc x 3 (HMW) Hyalgan x 5 (LMW)</td>
<td>WOMAC, VAS, &amp; Oxford Knee Score</td>
<td>3</td>
</tr>
<tr>
<td>Jüni et al 2007</td>
<td>RCT, Patient blinded</td>
<td>n = 330</td>
<td>Synvisc x 3 (HWW) Orthovisc x 3 (MMW) Ostenil x 3 (LMW)</td>
<td>WOMAC &amp; VAS</td>
<td>2</td>
</tr>
<tr>
<td>Kotevoglu et al 2004</td>
<td>RCT &amp; Double blinded</td>
<td>n = 59</td>
<td>Synvisc x 3 (HMW) Orthovisc x 3 (LMW)</td>
<td>WOMAC</td>
<td>3</td>
</tr>
<tr>
<td>Karlsson et al 2002</td>
<td>RCT, Double blinded, Placebo controlled</td>
<td>n = 242</td>
<td>Synvisc x 3 (HMW) Artzal x 3 (LMW)</td>
<td>WOMAC, VAS, &amp; Lequesne</td>
<td>5</td>
</tr>
</tbody>
</table>

HMW = high molecular weight; MMW = medium molecular weight; LMW = low molecular weight; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = visual analogue scale
<table>
<thead>
<tr>
<th>Sub-Categories</th>
<th>Pain</th>
<th>Physical Function</th>
<th>Stiffness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking</td>
<td></td>
<td>Descending stairs</td>
<td>Morning stiffness</td>
</tr>
<tr>
<td>Stair climbing</td>
<td></td>
<td>Ascending stairs</td>
<td>Stiffness occurring later in the day</td>
</tr>
<tr>
<td>Nocturnal</td>
<td></td>
<td>Sitting</td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td>Rising from sitting</td>
<td></td>
</tr>
<tr>
<td>Weight bearing</td>
<td></td>
<td>Standing</td>
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<tr>
<td></td>
<td></td>
<td>Lying</td>
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<tr>
<td></td>
<td></td>
<td>Riding from bed</td>
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<tr>
<td></td>
<td></td>
<td>Bending to floor</td>
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<tr>
<td></td>
<td></td>
<td>Walking on flat</td>
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<tr>
<td></td>
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<td>Getting in and out of car</td>
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<tr>
<td></td>
<td></td>
<td>Going shopping</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Putting on socks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Taking socks off</td>
<td></td>
</tr>
</tbody>
</table>

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
References


