Effect of 6-week walking exercise program on the level of fitness, pain and inflammatory biomarkers

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Abstract:

Background: Knee arthritis (KOA) is a prevalent condition causing pain and disability in older adults worldwide. Despite several guidelines recommending moderate aerobic exercises, the

compliance rate is very low. Preliminary data from Dr. Wen Liu and his team has revealed that interval walking (IW) has higher compliance rate with greater improvement in decreasing visual analog scale (VAS) pain compared to continuous walking group (CW). Additionally, they observed similar cardiovascular and functional improvement in both groups. Therefore, the results indicates that interval training is as effective as continuous training and may have better compliance with less pain provocation. The OA disease progression is regulated by inflammatory process but the real-time association of biomolecular changes in response to exercises is still elusive. The aim of this study is to investigate the potential difference of inflammatory status with IW and CW programs in individuals of KOA and how it may relate to the difference of symptom modulation and adherence rate.

Methods: Qualified participants with KOA between 60-79 years old were recruited and randomized into two groups: IW (2 bouts of 15 minutes) and CW group (1bout of 30 min). Both walking groups were prescribed 3 time/week for 6 weeks. Blood samples were collected before and post intervention for each participant. Serum derived proinflammatory biomarkers including C-reactive protein (CRP), interleukin- (IL-) 6, IL-8, and IL-1β, and anti-inflammatory IL-10 were measured from the processed blood samples.

Discussion: This study will aim to explore the biomolecular mechanism of superior pain management with IW compared to CW by examining associated inflammatory biomarkers. This will provide critical information in understanding the pathogenesis of KOA at biomolecular level

and identifying a timelier detection of joint irritation prior to cartilage degradation when exploring a pragmatic dosage of exercises in this population.

Key words: knee arthritis, aerobic exercise, inflammatory biomarkers, interval walking, continuous walking,

Introduction:

Knee osteoarthritis is the most common musculoskeletal progressive condition leading to pain and disability worldwide.[1] The cartilage loss, subchondral bone changes and narrowing of joint space is driven by both biomechanical and proinflammatory factors. [1,2] There are increasing yet still limited understanding of the underlying inflammatory mechanism of the cartilage degradation in the pathogenesis of OA. Biomarkers readily detectable in blood provide real-time objective measurements to reflect disease relevant biological process in response to interventions including exercise based therapy.[3-5] This would enhance our ability to determine the appropriate mechanical loading with closely monitored disease progression.

It is well known that proper amount of physical exercises is beneficial to modulate inflammatory process, decrease pain and improve functional mobility. While excessive joint loading is likely to increase the risk of articular tissue degradation, resulting in worsening of the clinical symptoms of OA based on physical stress theory.[6] Aguiar et al. has found that exercise therapy can reduce inflammatory biomarker, decrease pain, and improve function.[7] However, it is remained undetermined what is the most optimal exercise parameters for individuals with

KOA taking in consideration of pain reduction, functional improvement, adherence rate and associated inflammatory change.

Despite several guidelines recommended aerobic exercises at moderate intensity to be beneficial in patients with KOA, the compliance rate is very low.[8,9] Therefore, it is imperative to research if there are alternative parameters that would increase compliance rate while maintaining similar or better functional improvement.

Pilot studies from Dr. Wen Liu and his team indicates that the effect of IW exercise on fitness level and cardiovascular system are comparable to that of the CW exercise. In addition, the IW group presented higher compliance rate and better pain reduction in individuals with KOA. However, the effect of IW and CW exercise on inflammatory biomarkers has not been studied systematically.

There has been many inflammatory biomarkers reported to has associated with knee OA but there is lack of consistency among literature and there is also lack of understanding of the mechanisms and pathways with this process.[3-5,10-18] Interleukin 6 (IL-6) has been suggested to have an important role in OA structural damage,[19] although antibodies against IL-6 showed no clinical difference.[20] C-reactive protein (CRP) has also been shown to be independently associated with the incidence and progression of OA.[21] In addition, proinflammatory IL-8, IL-1β and anti-inflammatory IL-10 also have altered serum concentration in KOA population.[22]

In this project, we will look into the inflammatory biomarkers to help us better understand why pain increase for longer walking time, but decrease for shorter walking time, both immediately after the walking exercise and in long-term, i.e., 6 weeks of walking program. We

would like to explore the correlation between pain and inflammatory biomarkers. In addition, we want to go beyond the superficial correlation and explore the underlying mechanism of intervention by assessing additional up or down stream proteins.

Methods: Study design, Inclusion and Exclusion criteria, experimental procedure (this section is provided by Dr. Wen Liu's team)

Study design:

Our pilot trial was conducted at the Neuromuscular Research Laboratory and the Kirmayer Fitness Center at the University of Kansas Medical Center (KUMC). We recruited 21 participants and randomly assigned them into an IW or CW group. There were 3 dropouts and 18 participants who completed either IW (n=9) or CW (n=9) intervention and post-intervention assessment. The details of study protocol can be found in our previous submission[23]. In the following a brief description of study protocol and procedures are provided.

Inclusion and exclusion criteria

Inclusion criteria includes people with KOA, who are between 60-79 years old. Participants must be sedentary according to 2011 Compendium of Physical Activities questionnaire[24,25], and have mild to moderate pain (0.5-7.5 cm on 10 cm VAS) in most days of the past month[26-28]. Participants who have CVD, low back pain, or hip pain that prevent them from participating in walking exercise were excluded. Participants who are pregnant, have two or more incidents of fall history during the past 6 months, underwent any lower extremity surgical procedure during the last 6 months, use beta blocker medication, or diagnosed with other rheumatoid arthritis, gout, neurological diseases were excluded. Participants who were unable to

walk without assistive device or attend exercise program 3 times/week or more at the Kirmayer fitness center were excluded. The detailed selection process is shown in Figure 1.

Experimental procedure

Intervention:

Two types of walking exercises were prescribed for the participants 3 times/week for 6 weeks. In the CW group, the participants were asked to walk for 30 minutes continuously without taking any rest. In the IW group, the participants were asked to walk for 30 minutes with a resting interval of 30-40 minutes after the first 15-minute bout of the walking exercise, and then completed second bout of 15-minute walking exercise.

Assessments:

To assess level of CRP, IL-6, IL-8, IL-1β and IL-10 biomarkers, blood sample was collected for each participant at baseline and post-intervention assessments. The participants were asked to limit their physical activity level in the 24 hours prior to their assessment day. Ten milliliters of venous blood sample were collected from each participant. Thirty minutes after blood withdrawal, centrifugation at 1,000xg at +4°C was used to process the blood sample to separate serum from cells. The serum was collected and kept in a freezer at -80◦C until assaying. The serum was assayed after one thawing to avoid losing the needed molecules due to going through several freezing and thawing process. The serum sample of IL-6, IL-8, IL-1β and IL-10 were assayed by Eve Technologies (Millipore, St. Charles, MO, USA) using the multiplex assay "Human High Sensitivity T-Cell 14 plex Discovery Assay® Array (HDHSTC14)". Eve Technologies protocol uses the Bio-Plex™ 200 system (Bio-Rad Laboratories, Inc., Hercules, CA, USA) and a Milliplex Human High Sensitivity T-Cell panel (Millipore, St. Charles, MO, USA). The Eve Technologies assay is sensitive (0.11 – 3.25 pg/ml) to these biomarkers. The

serum samples of CRP were assayed at the University of Kansas Medical Center – Kansas Intellectual and Developmental Disabilities Research Center using CRP Sandwich ELISA (Alpco, Salem,NH,USA). The assay is 0.124 pg/mL sensitive to CRP biomarker.

Statistical analysis:

To compare blood biomarkers between the two groups at baseline, independent t-test was used for continuous variables. At the end of the intervention, paired t-test was used to compare withing group change of the biomarker levels from the baseline to post-intervention, and independent t-test was used to compare the changes of CRP, IL-6, IL-8, IL-1β and IL-10 between CW and IW group at the end of the intervention.

Results: (this section is provided by Dr. Wen Liu's team)

Nine participants in each group completed the study. There were no significant differences between the two groups in comparison of the demographic data (table 1).

Twenty-two participants were recruited and randomly assigned into an IW (n=12) or CW group (n=10). The mean age of the participants was 70.89 and 67.44 in the IW and CW group, respectively. Demographic and anthropometric data are presented in Table 1. There was no significant difference between the two groups in age (p=0.22), BMI (p=0.59), or waist circumferences (p=0.38).

Nine participants from each group completed the intervention program, resulting in the 25% and 10% dropout rate for IW and CW groups, respectively. Fisher test shows no significant difference between IW and CW groups in dropout rate (p=0.50). The averaged compliance in the

IW and CW groups was 96.29% and 78.39%, respectively. The difference in the compliance between groups was statistically significant ($p<.001$). The most missing sessions in the CW group occurred after day 12, especially in the last two days (day 17 and 18).

There was no significant difference ($p=0.82$) between IW and CW groups in the VAS score at baseline (Table 2). Pain level significantly decreased from the baseline to post-intervention in both IW ($p<0.001$) and CW ($p<0.05$) groups, while changes of VAS score at post-intervention in IW group was significantly greater ($p<0.05$) than that in the CW group.

There was no significant difference between the two groups in the IL-6 at baseline ($p=0.55$). The average of IL-6 in the IW and CW group decreased post intervention by -0.74 and -0.72, respectively. There was no significant change in IL-6 within groups post intervention in IW ($p=0.21$) and CW ($p=0.31$). There was no significant difference between groups in the change of the IL-6 post intervention ($p=0.97$) (table 2).

There was no significant difference between the two groups in the IL-8 at baseline ($p=0.95$). The average of IL-8 in the IW and CW group decreased post intervention by -0.81 and -1.12, respectively. There was no significant change in IL-8 within groups post intervention in IW ($p=0.12$) and CW ($p=0.47$). There was no significant difference between groups in the change of the IL-8 post intervention ($p=0.32$) (table 2).

There was no significant difference between the two groups in the IL-10 at baseline or post intervention (table 2). The average of IL-10 in the IW and CW group changed post intervention by 0.47 and -0.36, respectively. There was no significant change in IL-10 within groups post intervention in IW ($p=0.50$) and CW ($p=0.72$).

There was no significant difference between the two groups in the IL-1β at baseline or post intervention (table 2). The average of IL-1β in the IW and CW group changed post

intervention by 0.03 and -0.13, respectively. There was no significant change in IL-1β within groups post intervention in IW (p=0.76) and CW (p=0.36).

There was no significant difference between the two groups in the CRP level at baseline or post intervention (table 2). There was no significant change in CRP level within groups post intervention in IW (p=0.86) and CW (p=0.95).

Discussion

In this pilot study, we examined the effect of IW exercise on the serum CRP, IL-6, IL-8, IL-1β and IL-10 of participants with KOA compared with CW exercise. The biomarker measurements were conducted on blood samples collected from the participants during rest at baseline and post-intervention after the 6-week IW or CW program. There were no significant changes in CRP, IL-6, IL-8, IL-1β and IL-10 post- intervention in both groups. The current study is the first study investigating the changes in CRP and inflammatory cytokines after either IW or CW program in people with KOA.

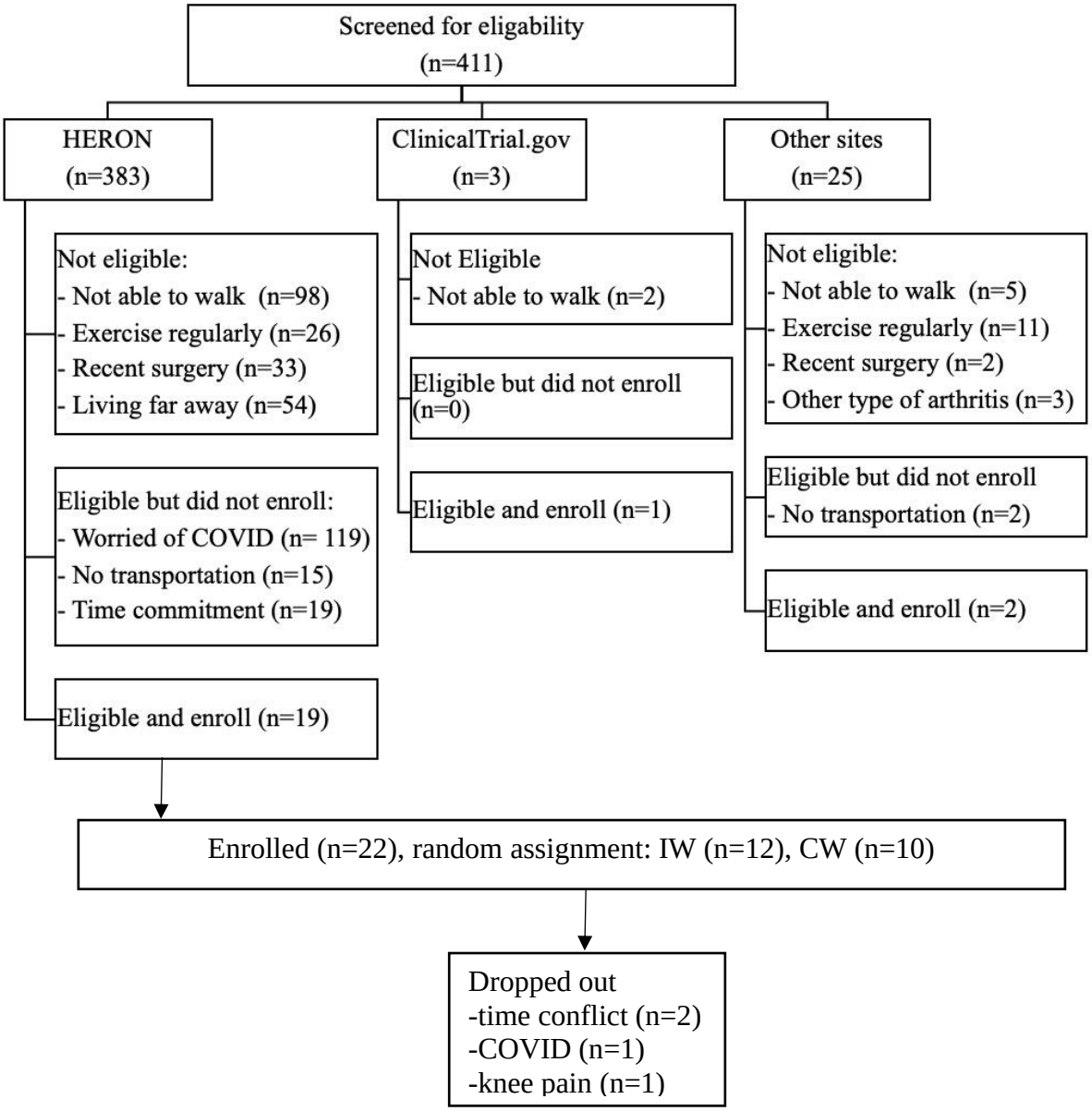
Although there are no significant cytokine changes detected between IW and CW in this pilot study, there are several factors that might contributes to the results. There is higher dropout rate in CW (25%) and IW (10%) which may attenuate the differences between IW and CW. Additionally, small sample size in this study might not be enough to show statistically significant difference, power analysis will be applied to determine appropriate subjects for future studies that might indicate a more meaning change. Another limitation of this study is that there is no measurement of biomarkers immediately after the walking program. Cytokines in general have short half life. Specifically, IL-10 has a half-life of 60min[29], indicating the importance of timely measurement of the anti-inflammatory and inflammatory biomarkers. We might have missed the

real-time change of inflammatory biomarkers immediately after each exercise intervention. Another limitation is that we did not include assessment of upstream proteins such as damage associated molecular patterns (DAMPs), which might reveal a faster response to mechanical loading preceding inflammatory biomarkers. Zhao et al. has reported that High mobility group box1 (HMGB1), a paradigm of DMPAs, is released to the extracellular matrix in tendon and initiates an inflammatory cascade in response to mechanical overloading in a mouse model.[30] S100A8/9, another DAMPs, has been shown to be an important mediator of pain response in the knee during the acute phase of inflammation in mice model via assessment of gait deviation and gene expression in dorsal root ganglia (DRG).[31] Additionally, biomarkers associated with articular cartilage may help us explain the better pain modulation with IW compared to CW group . A study by Jayabalan et al. showed the important role by cartilage oligomeric matrix protein (COMP) for exercise-induced pain increase.[32] And matrix metalloproteinases (MMPs), which is a catalyzers of extracellular matrix breakdown has been shown with increased level in the serum in response to joint loading.[33] Lastly, the outcome measurements only included biomarkers at the protein level and did not assess mRNA change at transcriptional level.

Conclusion

We found no significant changes in the CRP or inflammatory cytokines in our participants with KOA after either IW or CW exercise. Future studies to assess different types and settings of walking exercise on the level of inflammatory biomarkers with immediate measurement after each session. Upstream proteins such as DAMPs, articular biomarkers and associated mRNA level should be assessed to facilitate a better understanding of the molecular pathway of how exercises impact the disease pathogenesis of KOA.

Figure 1



List of tables:

Table 1: Participant demographic and other relevant data.

Characteristic	IW	CW
Age (years), mean ± SD	70.89 ± 5.34	67.44± 6.16
Gender: M/F	1/8	4/5
BMI (Kg/m^2), mean ± SD	31.9778 ± 8.20	30.12 ±5.75
Waist Circumference	104.66±16.43	99.11±8.64
Race: White/African-American/other	9/0/0	6/2/1
Smoker: Yes/no	0/9	1/8
Hypertension: Yes/no	5/4	2/7
Diabetes: Yes/no	1/8	0/9
Affected knee: right/left	7/2	9/0

Table 2: Measurement results of IL-6 at baseline and post intervention.

	IW	CW	P-value
IL-6 baseline	9.88±15.15	14.85±19.72	.55
Change of IL-6	-.74±1.64	-.72±2.03	.97
IL-8 baseline	31.21±38.24	32.45±45.80	.95
Change of IL-8	-3.81±6.57	-1.21±4.79	.32
IL-10 baseline	8.48±1.94	8.32±3.65	.91
Change of IL-10	.47±2.01	-.36±2.91	.49
IL-1β baseline	1.62±.89	2.29±1.38	.24
Change of IL-1β	.03±.35	-.13±.42	.36

CRP baseline	5454.11±6504.92	4588.88±4153.31	.74
Change of CRP	256.44±4511.04	-34.33±1617.65	.85

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