Official Title: Effects of Metformin on Low Back Pain

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Scientific Background

Low back pain is one of the most common musculoskeletal conditions requiring medical care and contributing to patient impairment and disability, with over 25% of the general population reporting low back pain at any given time and a lifetime incidence exceeding 80%. However, the care of low back pain represents one of the greatest challenges facing musculoskeletal care today. Current care for low back pain relies on a trial and error approach, with increasingly aggressive options considered after each failed treatment. This results in exposure of patients to unnecessary risks associated with treatments that are unlikely to be helpful, significant wasted resources, and delays in symptom improvement (1). In addition, disc degeneration is ubiquitous in our aging population (2-3), in whom standard treatments, including injections, surgery, and current medication options (particularly NSAIDs and opioids), carry increased risk. With increasing interest in the anti-aging effects of metformin, and potential effects in the intervertebral disc related to inflammation, anabolic activity and cell senscence (4), the favorable side effect profile and low cost make metformin an attractive therapeutic candidate for the treatment of low back pain. In addition, preliminary observational data in patients with low back pain taking metformin suggest an improvement in pain score compared to patients not taking metformin and over time (see below). With the suggested effects of metformin on the pain experience, inflammatory cascade (5), and microbiome (6), exploring the associations of these key biomarkers with response to oral metformin may reveal sub-populations of subjects more likely to respond to treatment as well as novel targets for future therapeutics. In addition, because degenerative changes and low back pain increase with age, and aging is associated with systemic inflammation, older adults may have an even greater response to a medication such as metformin, underscoring the potential opportunity of this treatment approach.

We have previously demonstrated associations of protein and genetic biomarkers with pain and function in axial low back pain (7-8). In addition, we queried the UPMC data warehouse to compare patients with low back pain who were taking metformin vs those taking other medications for their diabetes management. Diabetic patients taking metformin (n=26,077) had slightly lower average pain scores (6.2) than diabetic patients not taking metformin (n=21,540) (6.4). ESR was also lower for patients taking metformin (21.2 vs 26.4). Among patients not taking NSAID or oral steroid, average pain scores remained in favor of metformin (6.1 vs 6.4). We then queried the database to examine patient pain score one year after initial prescription of metformin (n=26,937) and demonstrated small improvement in average pain score, from 6.5 to 6.2 after one year of metformin. When these patients were limited to patients with an ESR of 10-30 (chosen based on above finding and prior evidence in low back pain (9-10), the average pain score improvement widened to 6.8 to 6.3. and was similar amongst patients without NSAID or steroid use (6.8 to 6.1). Finally, when subjects were further narrowed to patients with ESR 10-20, the pain score changed from 9 to 4, however, this resulted in extremely small sample size (n=2). These results justify to proposed prospective study (SA1), and also provide evidence of sub-phenotypes of patients who will be more likely to respond to treatment (SA2).

In addition to the above data, we have previously developed a clinical prediction model for patients with axial low back pain for response to epidural injection. While we accurately predicted 22% of the total population with this model, addition of protein and genetic polymorphism data into the predictive model as proposed herein improved the predictive capacity of the model, demonstrating the feasibility of this approach.

Study Objectives

The purpose of the current study is to determine the effects of metformin in non-diabetic patients with low back pain, and identify novel targets for future treatments.

Specific Aim 1: To examine the response in pain and pain related function to oral metformin treatment for 6 months in patients with axial low back pain.

Hypothesis: Patients with axial low back pain treated with metformin for 6 months will demonstrate a 2 point or greater improvement in numeric pain rating score and be superior to placebo in pain and functional outcome measures.

Specific Aim 2: To examine the associations of clinical characteristics, genetic, protein and microbiome biologic signatures with response to treatment, and develop a robust personalized predictive model for determining response.

Hypothesis: Polymorphisms in pain perception genes, blood based protein biomarkers, and microbiome characteristics will show significant associations with response to metformin in regard to both pain and pain related function. In addition, older patients with moderate levels of systemic inflammation will demonstrate a greater response.

Study Design & Methods

Randomized, placebo controlled, wait list controlled, clinical trial. Subjects will be randomized to one of the following groups:

-High Dose Metformin Group

-Low Dose Metformin Group

-High Dose Placebo Group

-Low Dose Placebo Group

-Wait-list Control Group (will have a 3 month "wait-list" and then be randomized to treatment group at month 3 visit)

Subjects will take study medication for a total of 6 months

Eligibility Criteria

Inclusion criteria:

-Age 18 and above

-Diagnosed with axial low back pain (low back pain more severe than pain in other parts of the body, without radiation of pain into the lower extremities).

-Women of child bearing potential must have a negative serum pregnancy test at baseline.

Exclusion criteria:

-Diagnosed with rheumatoid arthritis, lupus, other autoimmune/systemic inflammatory arthropathies

-Progressive lower extremity weakness or numbness

-Recent oral or injected steroid use (within last 3 months)

-NSAID use

-Chronic kidney disease (eGFR <60)

-Diagnosis of diabetes mellitus or elevated HbA1c at screening (> 6.5)

-Subjects must not be pregnant or breastfeeding, or planning to become pregnant or breastfeed during the course of the trial

-Unable to take an oral medication in a non crushable pill form

-Taking metformin presently or within the last 6 months

-History of allergy to metformin

-History of lactic acidosis or elevated lactate at screening (> 2.2)

-Severe Hepatic dysfunction

-Currently taking a diabetic medication such as sitagliptin, saxagliptin, linagliptin, alogliptin, sitagliptin with metformin

-Currently taking a Carbonic anhydrase inhibitor such as topiramate, zonisamide, acetazolamide, dichlorphenamide, methazolamide

-Currently taking cimetidine

Statistical Considerations

Sample size is estimated based on feasibility of subject recruitment based on prior study of axial low back pain, as well as prior studies demonstrating clinically and statistically significant change in the primary outcome of NPRS for randomized trials of NSAID in as few as 37-295 patients. For patients who met all inclusion criteria in our previous study

examining epidural steroid injection for axial low back pain, our successful recruitment rate was 72%. For this prior study, we screened 1455 subjects over a one year period, and 768 were excluded due to leg pain/radiculopathy. Therefore, we expect adequate availability of subjects to meet our recruitment goal. Formal sample size justification based on 80% power, alpha = 0.05:

Effect Sizes:

High vs. Low: 0.79

High vs. placebo: 0.79

Low vs. placebo: 0.79

Control vs. placebo: 0.86

*These are all based on two-sample t-tests with a common variance.

Per MOD19010007-009: While we retained data from the initial enrollment, they not be included in the parent statistical analysis. Therefore, this would not impact the overall analysis plan since re-enrolled patients would complete the new proposed baseline data collection (ie treated as an entirely new subject).

Since there has been sufficient wash-out period for medication and the short time enrolled in the study, re-enrolling subjects is not expected to influence results