MUSCLE ARCHITECTURE IN PATIENTS WITH SJÖGREN’S SYNDROME

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Background: Although fatigue and skeletal muscle involvement is not rare in Sjögren’s Syndrome (SS) patients, there is not much data about the macroscopic structure of the skeletal muscle.

Objectives: 1) To investigate if ultrasonographic muscle architecture and muscle strength differed in SS patients 2) To investigate if these changes correlated with disease activity, fatigue, anxiety and depression.

Methods: Assuming 2.40 mm mean difference and 2.5 mm SD of thickness at vastus lateralis muscle with 80% power and 5% significance 19 SS patients and 19 healthy controls (HCs) were recruited (1). Disease activity was measured by EULAR Sjögren Disease Activity Index (ESSDAI), anxiety and depression were assessed with the Hospital Anxiety Depression Scale (HADS), fatigue with Multidimensional Assessment of Fatigue scale (MAF), quality of life with Health Assessment Questionnaire (HAQ). A single rheumatologist, blind to the participants' group assignment, performed the ultrasonographic evaluation using a multi-frequency linear probe. Thickness of bilateral quadriceps femoris, gastrocnemius and soleus muscles, pennation angle and fascicle length were measured. Isokinetic knee and ankle muscle strength tests were performed at 60°-180°/s and 30°-120°/s respectively by a calibrated isokinetic testing machine.

Results: Patients with SS scored higher than HCs for depression, anxiety, quality of life and fatigue (p<0.0001). At dominant leg, pennation angle of vastus medialis muscle was significantly lower in SS group than HCs (10.26±3.63 SD deg vs 14.15±6.36 SD deg, p=0.006). In addition, fascicle length of gastrocnemius medialis muscle was significantly shorter in SS group than HCs (42.26±10.33 SD mm vs 49.25±8.27 SD mm, p=0.036). Peak torque/body weight of knee and ankle muscles in SS group did not differ from that of HCs. However, in SS group, at dominant leg, ESSDAI score was negatively correlated with knee extension strength at velocities 60°/s and 180°/s (r=-0.572, p=0.010; r=-0.617, p=0.05 respectively), knee flexion strength at 60°/s velocity (r=-0.492, p=0.033), ankle plantar flexion strength at 30°/s velocity (r=-0.730, p=0.001). Similarly at non-dominant leg, ESSDAI score was negatively correlated with knee extension strength at velocities 60°/s and 180°/s (r=-0.575, p=0.010, r=-0.508, p=0.026 respectively) and ankle plantar flexion strength at 30°/s velocity (r=-0.508, p=0.027). Fatigue was negatively correlated with ankle plantar flexion strength at 120°/s velocity (r=-0.484, p=0.036) at dominant leg, knee extension strength at 180°/s velocity (r=-0.521, p=0.022) knee flexion at 60°/s velocity (r=-0.585, p=0.011) at non-dominant leg. There was no correlation between anxiety, depression and muscle strength.

Conclusion: Patients with SS have some minor structural changes on ultrasonographic evaluation. Although there was no difference in isokinetic muscle strength measurements between groups, knee strength and endurance had a moderate negative correlation with disease activity in SS patients.

REFERENCE:

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CLINICAL EFFICACY OF LEFLUNOMIDE/HYDROXYCHLOROQUINE COMBINATION THERAPY IN PRIMARY SJÖGREN’S SYNDROME IS PREDICTED BY SERUM PROTEOME BIOMARKERS – RESULTS FROM REPURPSS-I

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Background: Despite major efforts to treat primary Sjogren’s syndrome (pSS) advances in pSS treatment remain disappointing. Treatment strategies effective in other immunological conditions lack an effect in pSS. Hence, there is a huge unmet need in finding an effective treatment, let alone to have the ability to predict who responds to what treatment. Based on the unique immunosuppressive properties of leflunomide (LEF) and hydroxychloroquine (HCQ), we recently conducted a randomized, double-blind, placebo-controlled proof of concept study.

Objectives: To evaluate the efficacy, safety and tolerability of LEF/HCQ therapy in patients with pSS and to predict treatment response by molecular profiling using baseline serum proteomics.

Methods: Clinically active (European SS disease activity index ESSDAI score ≥5) pSS patients (n=29) were randomized to receive LEF 20 mg daily and HCQ 200 mg twice daily or placebo/placebo (2 verum:1 placebo) for 24 weeks. Clinical and safety outcomes were assessed at baseline, 8, 16 and 24 weeks. Clinical response was defined by a decrease in ESSDAI of ≥3 points at 24 weeks. In addition, at baseline 386 proteins involved in inflammation, immune response, metabolism and cardio-metabolism were measured in serum of all patients using the Olink platform (for panels, see Olink website).

Results: Overall, LEF/HCQ was safe and well-tolerated and significantly reduced ESSDAI scores, the primary endpoint (p<0.0001). Furthermore, LEF/HCQ treatment was associated with improvement of oral dryness, ESSPRI, Physician’s and Patient’s Global Assessment, serum IgG, IgM rheumatoid factor, C3 and C4 levels (all at least p<0.05), which was not observed in the placebo group. Clinical response was observed in 11 out of 21 patients receiving treatment, providing a unique opportunity to examine biomarkers to predict response. However, except for C3 levels, clinical markers at baseline were not significantly different between responders and non-responders, underscoring the challenges in prediction of therapy response. Olink proteomic analysis revealed 43 significantly differentially expressed proteins between responders and non-responders. Unsupervised hierarchical clustering using the most differentially-expressed analytes (p-value based) demonstrated distinct serum proteomes in responders vs. non-responders. Using multidimensional scaling, based on all measured analytes, a high degree of dissimilarity of responders and non-responders was observed. Next a random forest machine-learning model was established to identify the proteins that best predict response to treatment using the baseline serum proteome. The results were validated using 500 leave-7-out iterations. The highest mean accuracy (84%) was achieved using a set of 16 differentially expressed analytes, indicating a 96% chance to robustly predict responders and a 74% chance to correctly identify non-responders.

Conclusion: We demonstrated a clinical response in pSS patients treated with the combination of leflunomide and hydroxychloroquine. Strikingly, a set of 16 circulating proteins predicts response to therapy with clinically meaningful accuracy. Given the exciting but preliminary nature of these observations a follow-up RCT aimed at replication of these results is warranted.

REFERENCE:

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