Characterizing Gene Expression in Muscle Biopsies of Patients with Proximal Junctional Failure

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Disclosures: This work was funded by Scripps Clinic Medical Group.

INTRODUCTION:
Despite increasing attention brought to adjacent segment disease following spinal fusion surgery, proximal junctional failure (PJF) remains a prevalent complication. Paraspinal muscle quality has been shown to be associated with PJF. The purpose of this work is to investigate a possible genetic basis for the contribution of muscle composition to the development of PJF.

METHODS: This study was approved by the IRB. All consenting patients at a single institution who underwent spinal fusion surgery of at least 4 levels with fusion to the pelvis for adult spinal deformity had an intraoperative paraspinal muscle biopsy. 7 patients who developed PJF were matched by age and sex with 7 patients who did not develop PJF and their muscle biopsies were analyzed for gene expression using qPCR. Gene expression for 42 genes associated with adipogenic/metabolic, atrophic, fibrogenic, inflammatory, and myogenic pathways were measured, and differential expression between the PJF and non-PJF groups was evaluated. Principal components analyses (PCA) were used to identify gene expression clustering across clinical phenotypes. Significance was set at a p-value of < 0.05. Trends were determined to be p-values < 0.08.

RESULTS SECTION: The 14 patients were in their 5th or 6th decade of life and the demographic and comorbid characteristics of each group were similar, though there was a trend towards higher BMI in the PJF group (p-value = 0.0609) (Table 1). Across both groups, the most common upper instrumented vertebrae were L1 (21%) and T9 (21%), and the average number of levels fused was 8.2 (SD=2.9). There was no difference in degree of the proximal junctional angle on preoperative imaging between groups, though the PJF group did have greater sagittal vertical axis (p=0.0455) and global alignment values (p=0.0462) on preoperative sagittal X-ray imaging. On differential expression analysis there was a trend towards a relative decrease in expression of ADIPOQ (p-value = 0.0663). Unbiased PCA analysis showed a significant relationship between PJF and a cluster of genes defined by a contribution of MYH3, ADIPOQ, and PDGFRα ($p<0.01$), explaining 6.4% of the variance in gene expression of the sample (Figure 1).

DISCUSSION:
These preliminary works provide insight into specific gene targets for investigating muscle impairment as it contributes to PJF. These data indicate individuals who go on to develop PJF experience downregulation of the lipid metabolism associated gene ADIPOQ and fibroadipogenic progenitor gene PDGFRα, and upregulation of the myogenic gene MYH3, within their paraspinal musculature. Importantly, the tissue composition of paraspinal muscle biopsies has been shown to be of heterogeneous composition, including fatty and fibrotic infiltration. This may explain the differential expression of non-muscle specific genes (ADIPOQ and PDGFRα) across these groups. Interpreting the directionality of gene expression requires further consideration of downstream protein transcription for a better understanding of underlying mechanisms. Although upregulation of MYH3 is in contrast to an expected downregulation of muscle growth genes in this population, it may indicate an increased drive for production of contractile proteins that has not previously been translating to protein production. Limitations of this work are the small sample size and the selective array of genes analyzed. Additional work is needed to perform larger scale differential expression analyses.

SIGNIFICANCE/CLINICAL RELEVANCE: (1-2 sentences): Elucidating the biologic mechanism underlying the soft tissue contribution to PJF is an important direction to inform future less invasive or minimally invasive treatments.

	PJF (n=7)	No PJF (n=7)	p-value
Age	66.14 (15.7)	52.6 (19.8)	0.183
Female	5 (71%)	6 (86%)	1.0
BMI	25.6 (3.6)	21.8 (3.2)	0.0609
Osteoporosis	2 (29%)	2 (29%)	1.0
Current smoker	1 (14%)	0 (0%)	1.0
Revision	1 (14%)	0 (0%)	1.0

Table 1. Frequencies and means with standard deviations in parentheses.

Figure 1A.

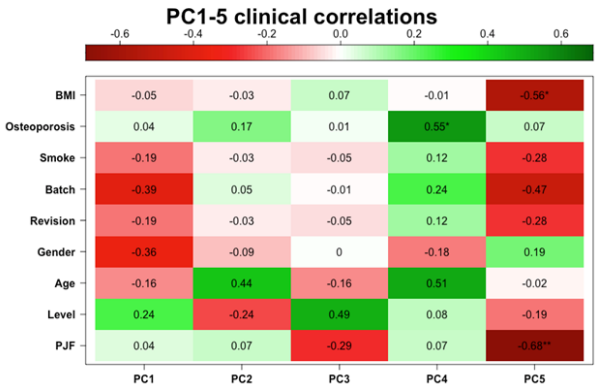

Figure 1B.