

### Hypothesis / aims of study

Corneal confocal microscopy (CCM) is a novel technique allows for the quantification of small fibers located near the center of the cornea. CCM is noninvasive and fast, and might be a useful method to confirm small nerve fiber pathology. Our objective was to assess corneal small nerve fiber morphology in patients with chronic pelvic pain (CPP) and to determine the prevalence of SFN in patients with chronic pelvic pain using CCM. The interplay between peripheral and central amplifiers is complex. Despite the established association of CPP with these other complex pain syndromes, and even though both peripheral sensitization and central sensitization have been proposed as underlying processes associated with CPP, a definitive explanation for this association according to known pain mechanisms is not well established. The lack of a common underlying mechanism or condition limits a provider's ability to either reassure the patient or offer effective treatment options. Further elucidation of the pathophysiological mechanisms in patients with refractory and multisystem pain is key to understanding these entities, and will be instrumental in developing efficacious treatment modalities for the millions of people suffering from these conditions [1].

### Study design, materials and methods

Retrospective study of prospective database. We studied 22 patients with CPP (male= 14, female = 8) and 10 healthy control subjects (table 1,2). All the participants completed different questionnaires in regards to the symptoms of chronic pelvic pain including a neuropathic pain survey. A central corneal thickness scan was obtained with a confocal microscope HRT3-RCM, Heidelberg Engineering (Heidelberg, Germany), fig. 1. This confocal microscope uses a diode helium-neon laser with a wavelength of 670 nm as a radiation source. Nerve measurements were made by a single ophthalmologist without knowledge of the clinical diagnosis.

Table 1 Patient demographics in the current population with CPP (N = 22)

CPP (+) N=22	Male=14	female=8
Age	35±13,4	
Duration of complaint, y	3.5±6.55	
BMI	25.8±8.2	
No. of prior office visits	8.0±6.2	

Table 2 Comorbidities in the current population with CPP (N = 22) by patient report or chart documentation

Mixed anxiety–depressive disorder	48%
Migraine	28%
Irritable bowel syndrome	32%
Endometriosis	10%
Interstitial cystitis	19%
Fibromyalgia	14%
Lower back pain	23%
Other chronic pain syndromes	28%



Fig. 1

### Results and interpretation

Patients with chronic pelvic pain had stromal nerve thickness of  $4.8 \pm 1.0$  micrometers (mean  $\pm$  standard deviation) significantly different from control's values ( $6.0 \pm 1.3$ )  $p = 0.01$ . Patients also had significant increase in dendritic cell density  $10 \pm 2$  vs  $3 \pm 1$  of controls  $p = 0.01$  (fig. 2). Sixteen of 22 patients with pelvic pain (73%) were positive for SFN using CCM. Patients with chronic pelvic pain have thinner corneal stromal nerves and increase in dendritic cell density when compared to healthy controls (fig. 3, fig. 4).

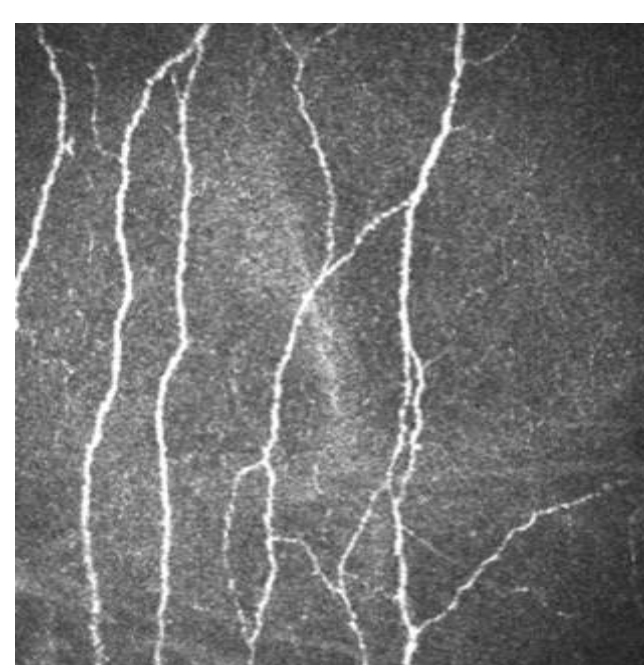


Fig.2. Confocal microscopy of the cornea of a healthy patient. The subbasal nerve plexus of the correct shape is visualized, as well as single Langerhans cells.

Fig.3. Confocal microscopy of the cornea of a patient with small fiber neuropathy. There is a decrease in the number of nerve trunks and an increase in the number of dendritic cells.

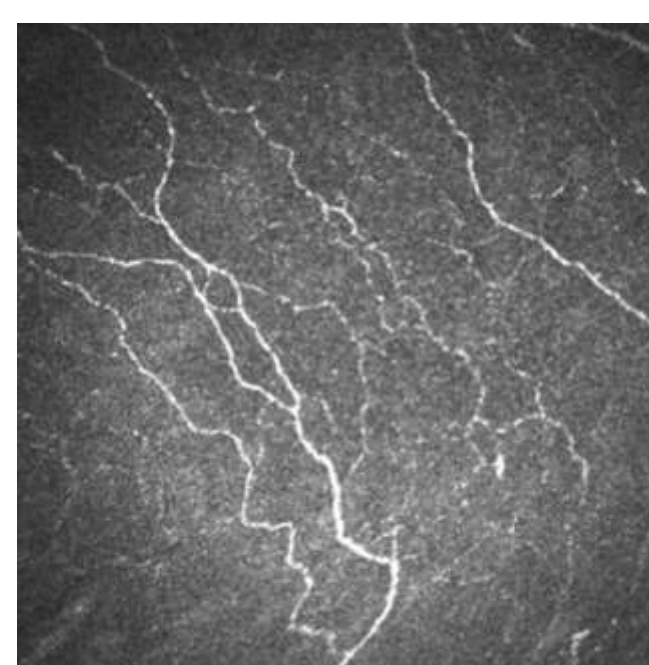
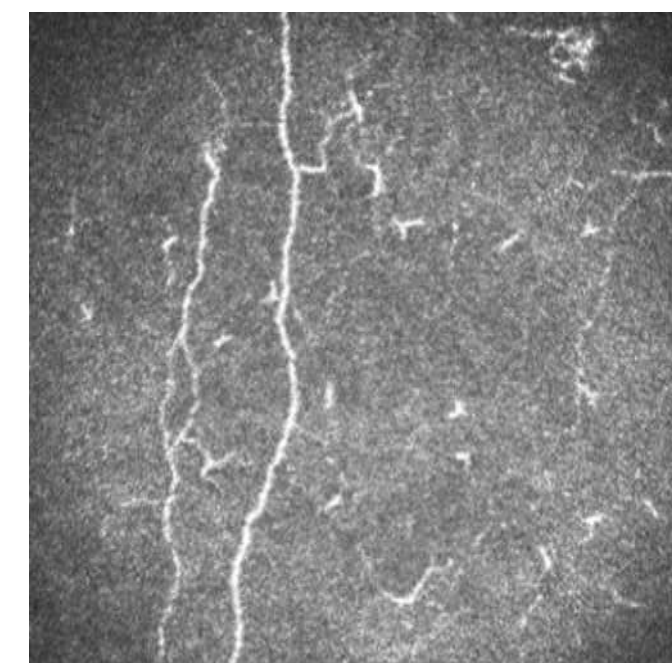


Fig. 4. Confocal microscopy of the cornea of a patient with small fiber neuropathy. The subbasal nerve plexus is visualized with pronounced tortuosity of nerve fibers and a large number of branching zones.

### Conclusions

The current view of the pathophysiology of peripheral neuropathy of small fibers indicates dysfunction of small C fibers, a-delta fibers and postganglionic sympathetic nerves. Patients with chronic pelvic pain have thinner corneal stromal nerves and increased density of dendritic cells compared to the control group.

Corneal confocal microscopy could become a useful test in the study and management of patients with chronic pelvic pain.

### References

Annie Chen, Elise De, Charles Argoff. Small Fiber Polyneuropathy Is Prevalent in Patients Experiencing Complex Chronic Pelvic Pain. Pain Med . 2019 Mar 1;20(3):521-527.