

# THE EFFECT OF CALCIUM GLYCEROPHOSPHATE (PRELIEF®) ON EPITHELIAL REGENERATION USING NMP22 AS A QUANTITATIVE EVALUATION IN THE TREATMENT OF INTERSTITIAL CYSTITIS (IC)

**Francisco M. Dubocq, MD** • **Joseph V. DiTrollo, MD** | Section of Urology, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey, USA

## NMP22 Abstract

**THE EFFECT OF CALCIUM GLYCEROPHOSPHATE (PRELIEF®) ON EPITHELIAL REGENERATION USING NMP22 AS A QUANTITATIVE EVALUATION IN THE TREATMENT OF INTERSTITIAL CYSTITIS (IC)**  
Francisco M. Dubocq, MD and Joseph V. DiTrollo, MD

**Introduction:** IC includes a major portion of the "painful bladder" disease complex. The etiology of IC remains unknown, but is likely multifactorial. Treatment of IC is empirical and most patients are treated with either systemic or intravesicular therapies. Monitoring the efficacy of treatment has been difficult due to the subjective nature of reporting symptoms such as pain, burning, discomfort, etc. The Matritech NMP22® Test Kit (Matritech, Inc.) is an FDA-approved quantitative assay for bladder cell cancer nuclear matrix proteins in voided urine, and may also serve as a useful indicator of urogenital cell inflammation.

**Study Objective:** 1. To determine the utility of measuring NMP22 during the evaluation and treatment of IC.

**Materials and Methods:** 5 patients (3 female, 2 male) previously diagnosed with IC were followed prospectively for 13-29 months (mean=21) during which time NMP22 levels and IC symptoms were measured.

**Results:** Three patients were acutely symptomatic (3+) and 2 were asymptomatic. The 2 asymptomatic patients had been taking oral calcium glycerophosphate (Prelief®, AkPharma Inc.) and the 3 symptomatic patients had not. All patients were given urine analysis, urine culture and sensitivity, urine cytology, radiographic studies, cystoscopy and bladder biopsies, in addition to the urine NMP22 Test. NMP22 values for the 3, 3+ patients were higher (mean=9.87) than the 2 asymptomatic patients who were taking Prelief® (mean=4.8). Subsequent administration of Prelief® to the 3, 3+ patients resulted in lower NMP22 values (mean=3.43), as well as the elimination of symptoms in all 3 of the 3+ patients. When 2 patients stopped and started Prelief® over succeeding months, NMP22 values and symptoms went up with discontinuation and down upon resumption. When one patient discontinued Prelief®, she became symptomatic and was started on pentosan polysulfate (Elmiron®, Ortho-McNeil). With Elmiron, NMP22 values increased and symptoms persisted. Re-addition and co-administration of Prelief® resulted in decreased NMP22 and elimination of all symptoms.

**Conclusions:** 1) NMP22 may be a useful marker for the cellular inflammation that causes symptoms in IC patients. 2) The use of Prelief®, either alone or as an adjunctive therapy, lowered NMP22 values, suggesting a decrease in cellular distress. 3) Prelief® also reduced subjective symptoms in all of the IC patients evaluated. The utility of Prelief® for the effective treatment of IC should therefore be confirmed in a full clinical trial.

## Purpose

### Purpose

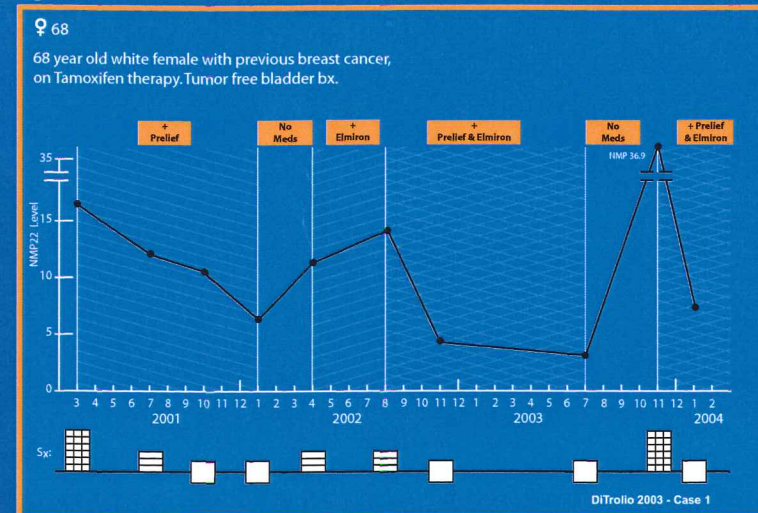
To prospectively measure urinary NMP22® levels in five (5) patients whose work-up has identified them as having Interstitial Cystitis. During a period from 2001-2004 these patients continued to have urinary NMP22 evaluated during medical management.

### Materials and Methods

#### Oral CGP and Epithelial Cells

This was a pilot study designed to establish whether NMP22, a widely utilized diagnostic test for bladder cancer might be a useful index to evaluate the efficacy of the treatment of Interstitial Cystitis (IC). The Matritech NMP22® Test Kit is an FDA-approved voided-urine tumor marker that detects nuclear matrix proteins (type 22) found in human epithelial cells. NMP proteins comprise part of the nuclear internal structure, and are associated with cellular functions such as DNA replication, RNA synthesis and hormone binding. To establish the relationship between NMP22 levels and IC symptoms, the subjects shown had these parameters recorded at each of the visits indicated. Subjects using Prelief® were asked to take 2 tablets twice daily. Subjective symptoms were evaluated using validated IC questionnaires.

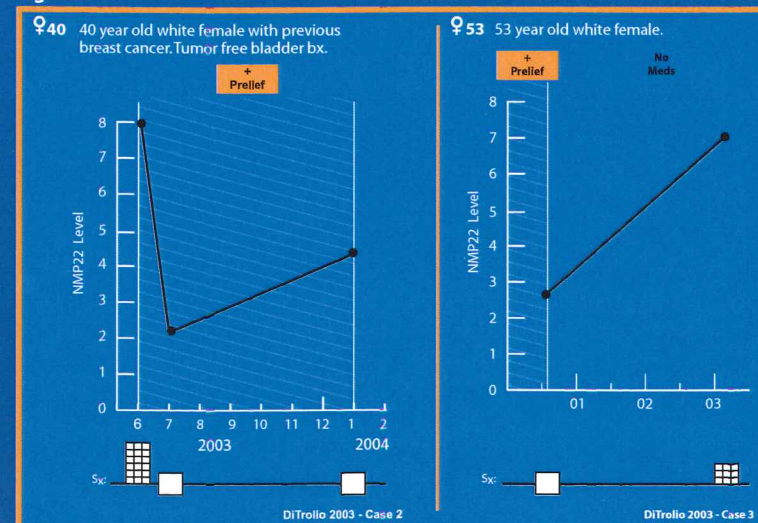
**Figure 1**



**Figure 1.** The effects of different treatment modalities on urinary NMP22 levels (shown on the left) and Interstitial Cystitis symptoms in a 68 yo female. The temporal relationship between treatment and reported symptoms (■ = acute, □ = none) are shown across the bottom. This patient was maintained for the indicated time with either Calcium Glycerophosphate (Prelief®, 2 tablets p.o., TID), Elmiron (100 mg p.o., TID), both in combination or no treatment. NMP22 levels and reported symptoms consistently decreased during Prelief® treatment and during treatment with Prelief® and Elmiron. NMP22 levels and symptom severity increased in the absence of medication or with Elmiron alone.

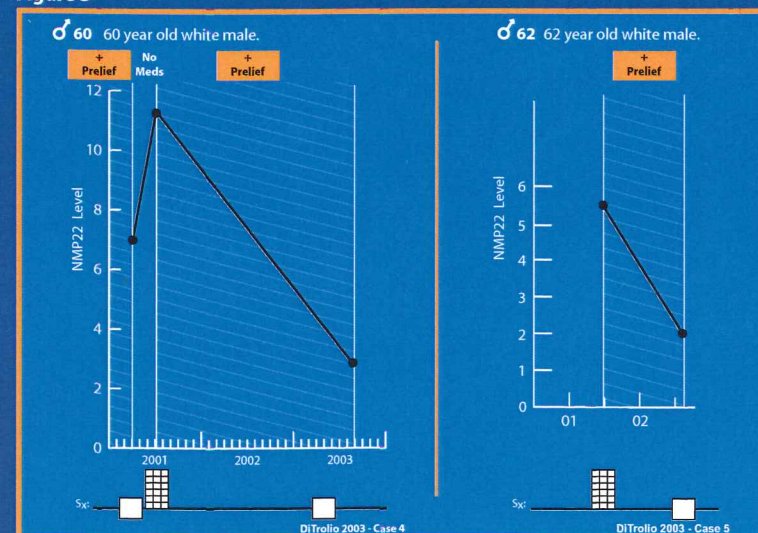
Sx: ■ Acute  
□ Moderate  
□ None

**Figure 2**



**Figure 2.** The effects of different treatment modalities on urinary NMP22 levels (shown on the left) and Interstitial Cystitis symptoms in a 40 yo female (Case 2) and a 53 yo female (Case 3). NMP22 levels and reported symptoms decreased or did not significantly increase during Prelief® treatment or did not significantly increase during Prelief® treatment (2 tablets p.o., TID) (Case 2) and increased following discontinuation of Prelief® (Case 3).

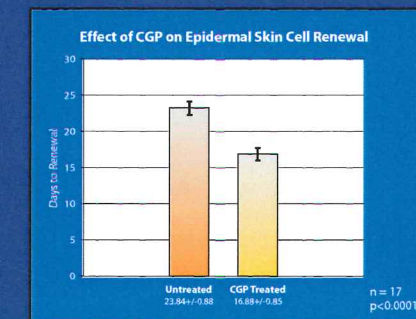
**Figure 3**



**Figure 3.** The effects of different treatment modalities on urinary NMP22 levels (shown on the left) and Interstitial Cystitis symptoms in a 60 yo male (Case 4) and a 62 yo male (Case 5). The temporal relationship between treatments and reported symptoms (■ = acute and □ = none) are shown across the bottom. NMP22 levels and reported symptoms decreased in both patients during Prelief® treatment (2 tablets p.o., TID).

## A SINGLE-BLIND, RANDOMIZED, CONTROLLED STUDY WITH TOPICAL CALCIUM GLYCEROPHOSPHATE IN PATIENTS WITH COMPROMISED EPIDERMAL CELL RENEWAL AND MODERATELY SEVERE DRY SKIN

Leyden, Wels and Grove, KGL Laboratories, 2003, pending publication



**Figure 4.** The effects of topically applied Calcium Glycerophosphate (Prelief®) on the rate of epidermal skin cell renewal were measured photometrically following staining of epidermal cells with a solution of 5% Dansyl Chloride. The disappearance of this fluorescent compound from the treated skin and untreated skin was measured every 2 days during the following 4 weeks. The application of Prelief®, twice daily for 3 weeks (CGP-treated, right bar) resulted in a significantly increased cell renewal rate when compared to untreated skin (left bar). This difference was statistically significant ( $p < 0.0001$ ,  $n = 17$ ), and represents an increased rate of epidermal cell renewal for all subjects tested. Mean renewal rate was 27%.

## Conclusions

### Conclusions

NMP22 is an excellent, FDA-approved test for bladder cancer detection, and changes in its levels mimic changes in the IC symptoms reported by this group of patients. The monitoring of NMP22 levels may therefore provide additional information regarding the efficacy of IC therapy. Quantitative urinary analysis of NMP22 may be useful to consistently assess physical improvement to correlate with symptomatic improvement in IC patients. These measurements may also allow for close observation of the status of bladder mucosa and help detect potential developing neoplasms.

The use of Prelief®, either alone, or as an adjunctive therapy with Elmiron, as shown in this pilot study, appears to be capable of ameliorating symptoms associated with Interstitial Cystitis. The ability of Prelief® to relieve symptoms of Interstitial Cystitis should therefore be evaluated in a prospective, placebo-controlled study.

### Speculation

The epidermal observations by Leyden and Grove are intriguing. A similar response is implied in the bladder of IC patients who are under Prelief® therapy when utilizing the NMP22 urinary marker to evaluate the state of epithelial distress. Other researchers have shown that patients with Interstitial Cystitis have an increased antiproliferative factor (APF), a sialoglycopeptide, produced by bladder epithelial cells. CGP (Prelief®) has been shown to effect epithelial cell growth, either by direct stimulation, or through another mechanism affecting cellular proliferation. In the present study we have documented beneficial effects of CGP in five (5) IC patients. We have measured and propose to correlate this benefit using NMP22 urinary marker, a measure of cellular distress. We propose therefore that the reduced NMP-22 levels in these subjects seen with CGP therapy is a result of a higher rate of bladder epithelial cell regeneration, a reduced rate of bladder cell destruction or a combination of both. The utility of using NMP-22 seems warranted by this study, and the specific nature of the effect of CGP is the subject of an ongoing investigation.