Bone Markers in Charcot Neuroarthropathy

Dr. Brent Bernstein, DPM FACFAS, Dr. Brandy Grahn, DPM, Dr. Jill Stoltzfus, PhD

St. Luke's University Health Network, Allentown, Pa

Background

Effective medical therapy for charcot neuroarthropathy (CNA) has mostly been based on various biochemical markers utilized to gauge osteoclastic activity, and thereby gauge the progression of CNA [1,2-5]. Among these markers are deoxypyridinoline (DPD) crosslinks and bone specific alkaline phosphatase (BSAP). DPD crosslinks provide stabilization for Type I collagen, which is most commonly found in bone and when bone turnover is high, these crosslinks spill over into the urine. BSAP is found on the surface of osteoblastic cells and also serves as a marker of bone metabolism.

Bone turnover markers have also been used to monitor the effectiveness of bisphosphonate therapy in the treatment of CNA [1,2-5]. Bisphosphonates have been shown to successfully reduce the levels of these markers [2,14]. This reduction has led to the investigation of bisphosphonates as a potential medical therapy for CNA.

The assumption made here is that the levels of these bone markers correspond to the severity of the patient's disease. If this assumption is true, it would suggest that by decreasing the levels of these bone markers via bisphosphonate therapy, we are also taking CNA out of the acute phase. The purpose of this research is to compare levels of these bone markers in the acute and in the quiescent stages to determine if they accurately reflect the severity of CNA. We hypothesize that as the CNA progresses into the chronic or quiescent stages as measured via pedal temperature, the levels of these bone markers will decrease accordingly.

Methods

We retrospectively reviewed 41 patients diagnosed with Charcot neuroarthropathy in our clinic over a time frame of two years. Disease severity was determined via temperature differences between affected and unaffected limbs and was determined by a pedal temperature difference of of ≥ 2 degrees Celsius.

Pedal temperatures were taken at the medial and lateral ankle, midfoot, calcaneus, and the 1st metatarsal phalangeal joint. This was then compared to the contralateral side. Pedal temperature variations were then analyzed against DPD:CRT and BSAP levels. Separate Pearson product moment correlations were calculated comparing DPD:CRT and BSAP levels with pedal temperature in Charcot patients, with $p < .05$ denoting statistical significance and no adjustment for the multiple comparisons.

Results

The correlation between temperature and DPD:CRT was positive ($r = 0.16$, $p = 0.3$), while the temperature-BSAP correlation was negative ($r = -0.17$, $p = 0.3$); however, neither association was statistically significant. Pearson product-moment correlations are shown in figures 1 and 2.

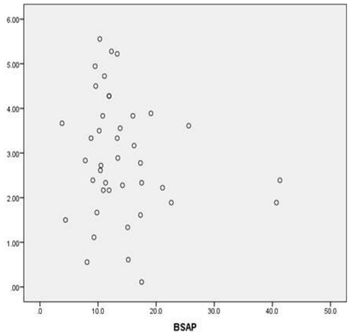

Figure 1: Pedal temperature (degrees Celsius) vs. BSAP (bone specific alkaline phosphatase) levels (mcg/L)

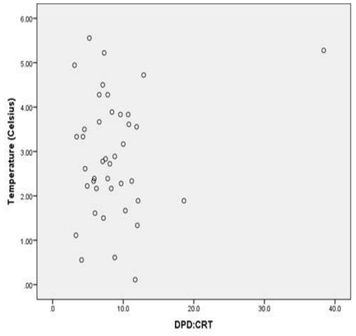

Figure 2.:Pedal temperature (degrees Celsius) vs. DPD:CRT (deoxypyridinoline crosslinks) levels (nmol/mmol)

Fig 5

Conclusions

Due to the questionable efficacy of bisphosphonates in the treatment of acute CNA, we cannot recommend their usage as their cost may not be worth their benefit. They have shown multiple benefits in regards to bone disease such as osteoporosis and Paget's disease; however, their side effects profile may outweigh their benefits in certain patients. For example, bisphosphonates have been shown to cause acute kidney injury, hepatitis, cardiovascular abnormalities, osteonecrosis (particularly of the jaw) and atypical femoral fractures.

To date, the study by Anderson et al. is the only paper that effectively links a reduction in bone markers to a reduction in temperature [6]. Contrary to Anderson et al., our study showed no significant link between CNA severity and the bone markers BSAP and DPD:CRT.

This study calls into question the utility of BSAP and DPD:CRT in the monitoring and staging of CNA. BSAP and DPD:CRT with pedal temperatures should not be used for clinical diagnosis or staging of CNA. Pedal temperatures in concert with clinical and radiographic findings have proven to be reliable for staging [7].

In conclusion, our data appears to uncouple common bone metabolic markers and severity of CNA. Limitations of this study is that it was retrospectively reviewed and limited in size and scope. Given the results of the present study, we recommend that the efficacy of any medical therapy (such as bisphosphonate therapy) for CNA be viewed skeptically if bone markers were utilized as a proxy for CNA staging. Moreover, we recommend caution when utilizing off-label medical therapies that have not been shown to correlate with reductions in cutaneous thermometric readings. This is particularly true when a medical therapy has been associated with significant known risks (bisphosphonates) and are being administered to a population with comorbidities. More research is needed to determine the efficacy and safety in the diabetic CNA patient population of off-label medications as our study was limited in size and scope.

References

1.Jude EB, Selby PL, Burgess J, et al: Bisphosphonates in the treatment of Charcot neuroarthropathy: a double-blind randomized controlled trial. Diabetologia 44:2032-2037, 2001.

2. Selby PL, Jude EB, Burgess J, et al: Bone turnover markers in acute Charcot neuroarthropathy. Diabetologia 41 (Suppl 1): A275, 1998.

3. Edelson GW: Identifying acute Charcot arthropathy through urinary cross-linked N-telopeptides. Diabetes 45 (Suppl 2): A108, 1996.

4. Selby PL: Bisphosphonate: a new treatment for diabetic Charcot neuroarthropathy. Diabet Med 11:14-20, 1994.

5. Gough A, Abraha H, Li F, et al: Measurement of markers of osteoclast and osteoblast activity in patients with acute and chronic diabetic Charcot neuroarthropathy. Diabet Med 14:527-531, 1997.

6. Anderson JJ, Woelffer KE, Holtzman JJ, et al: Bisphosphonates for the Treatment of Charcot Neuroarthropathy. J Foot Ankle Surg 43: 285–289, 2004.

7. Armstrong DG, Lavery LA: Monitoring healing of acute Charcot's arthropathy with infrared dermal thermometry. J Rehabil Res Dev 34: 317-321, 1997.

8.Varenna M, Bertoldo F, Di Monaco M, et al: Safety profile of drugs used in the treatment of osteoporosis: a systematical review of the literature. Reumatismo 65:143-66, 2013.

9.Armstrong DG, Lavery LA: Monitoring healing of acute Charcot's arthropathy with infrared dermal thermometry. J Rehabil Res Dev 34: 317-321, 1997.