Are Markers of High Bone Turnover, Representing Poor Bone Quality, Associated with Pain After Total Knee Arthroplasty?

LSU Health NEW ORLEANS School of Medicine

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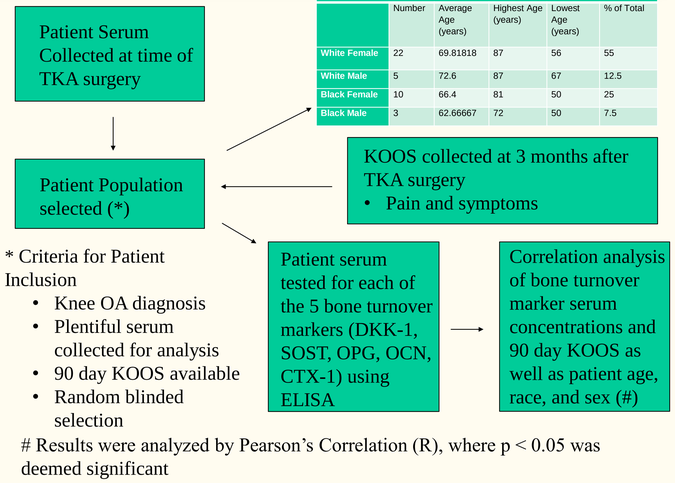
Introduction

- Osteoporosis, a disease characterized by decreased bone mass and overall poor bone quality, is drastically underdiagnosed in patients who undergo total knee arthroplasty (TKA) to treat knee osteoarthritis (OA) [1].
- There are numerous consequences for such an underdiagnosis, such as increased incidence of fracture, enhanced bone fragility, or even a change in the recommended surgical procedure [2,3].
- Currently, the American Academy of Orthopedic Surgeons (AAOS) offers no recommendation for measures of bone quality, such as bone mineral density (BMD) screenings which can be used to diagnose osteoporosis, on patients undergoing TKA [4].
- One way in which bone quality of patients can be examined is through measuring the levels of circulating proteins that indicate active bone turnover. Five bone turnover markers were investigated in this study: Dickkopf-related protein 1 (DKK-1), C-terminal telopeptide of Type 1 Collagen (CTX-1), Sclerostin (SOST), Osteoprotegerin (OPG), and Osteocalcin (OCN).
- We hypothesize that poorer outcomes in patients will be associated with markers of high bone turnover, or poor bone quality, such as low DKK-1, low SOST, high OCN, high CTX-1, and high OPG.

Variables Studied

- **DKK-1** is a secreted protein inhibitor of the Wnt/β-catenin signaling pathway and, thus, inhibits osteoblast differentiation and bone formation. Throughout the literature, it has been shown to be negatively correlated with the severity of OA and inflammation in patients [5].
- **CTX-1** is a protein product of the degradation of type 1 collagen during bone resorption by osteoclasts and is a common marker of bone resorption. It is a frequently used marker clinically and is often elevated in patients with progressive knee OA [6].
- **SOST** is another secreted protein antagonist of the Wnt/β-catenin signaling pathway and leads to a decrease in osteoblast differentiation and bone formation. Many studies have illustrated a negative correlation between SOST and the severity of OA in patients [7].
- **OPG** is a critical protein in bone homeostasis serving as a decoy receptor for RANKL. By binding RANKL, it prevents the activation of osteoclasts and leads to a decrease in bone resorption. Most studies have identified OPG levels as much higher in patients with OA as compared to healthy control patients [8].
- **OCN** is a major non-collagen protein of bone produced primarily by osteoblasts and is a marker of bone formation. One study illustrated a positive correlation between serum OCN levels and the severity of OA [9].

Methods



Patient Population (n=40)					
	Number	Average Age (years)	Highest Age (years)	Lowest Age (years)	% of Total
White Female	22	69.81818	87	56	55
White Male	5	72.6	87	67	12.5
Black Female	10	66.4	81	50	25
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* Criteria for Patient Inclusion
- Knee OA diagnosis
- Plentiful serum collected for analysis
- 90 day KOOS available
- Random blinded selection

Results were analyzed by Pearson's Correlation (R), where $p < 0.05$ was deemed significant

Results

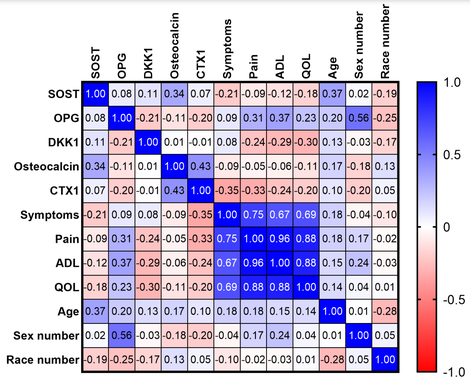


Figure 1: Pearson's Correlation analysis with R values showing negative or positive correlation. For sex, 1 is female and 2 is male. For race, 1 is white and 2 is black. Blue represents positive correlation, while red represents negative correlation.

Serum OPG concentration vs Patient Race and Sex

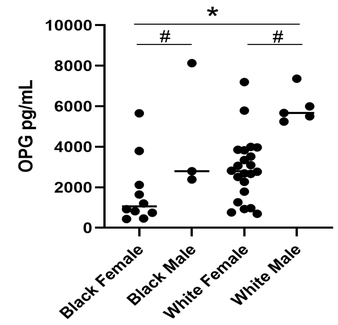


Figure 2: Serum concentrations of OPG were found to be significantly correlated with patient race and sex ($p < 0.05$). White males were shown to have much higher OPG levels, while black females had the lowest levels. **(* = $p < 0.05$ one-way ANOVA, # = $p < 0.05$ Tukey's post hoc test)**

Pain vs. Serum CTX-1 concentration (R = -0.33, p = 0.05)

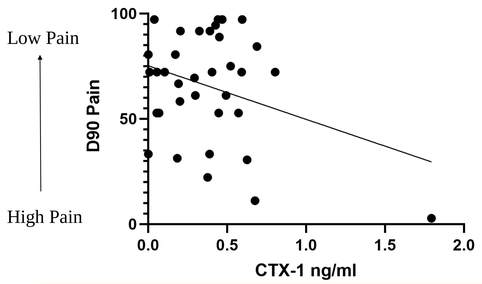
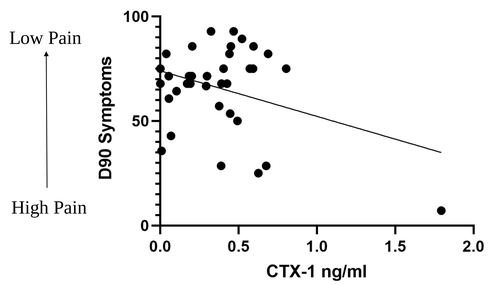


Figure 3: Higher serum CTX-1 was associated with poorer post-TKA outcomes and greater pain. Inverse correlation between the serum CTX-1 concentration and KOOS pain subscale scores collected at 90 days post-TKA (n=40).

Symptoms vs. Serum CTX-1 concentration (R = -0.35, p = 0.039)



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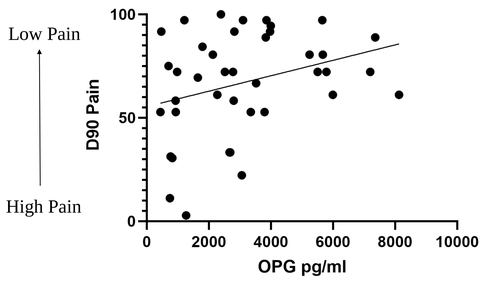

Figure 5: Lower serum OPG was associated with poorer post-TKA outcomes and greater pain. Positive correlation between serum OPG concentration and KOOS pain subscale scores collected at 90 days post-TKA (n=40)

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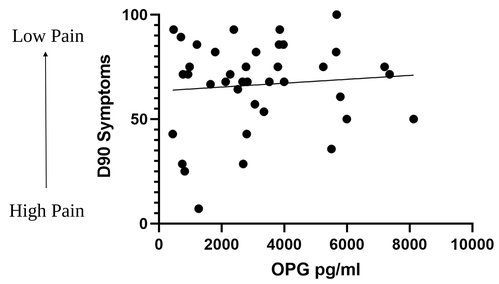

Figure 6: Serum OPG was not associated with post-TKA symptoms (n=40).

Conclusions

- Currently, serum measures of certain bone turnover markers (SOST, DKK-1, OCN) studied here are not a good predictor of pain and outcomes after TKA surgery.
- OPG and CTX-1, however, were found to significantly correlate with patient pain after TKA.
- Serum levels of OPG significantly correlate with patient race and sex, with white males more likely to have high levels and black females more likely to have low levels.

Limitations of Study and Future Directions

- Limited by the non-equal makeup of the sample population utilized
- Limited by the amount of serum available for each sample patient
- Limited by which patients within the patient population had serum samples as well as 90 day KOOS
- Limited by not normalizing patient BMI and other co-factors that may affect levels of serum markers

- Continue to increase sample size and power of study
- Expand study to also examine synovial fluid concentrations of each of the five bone turnover markers in patients and compare to serum levels of markers
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Patient Serum Collected at time of TKA surgery

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Patient Population selected (*)

KOOS collected at 3 months after TKA surgery
- Pain and symptoms

*Criteria for Patient Inclusion
- Knee OA diagnosis
- Plentiful serum collected for analysis
- 90 day KOOS available
- Random blinded selection

Patient serum tested for each of the 5 bone turnover markers (DKK-1, SOST, OPG, OCN, CTX-1) using ELISA

Correlation analysis of bone turnover marker serum concentrations and 90 day KOOS as well as patient age, race, and sex (#)

#Results were analyzed by Pearson's Correlation (R), where $p < 0.05$ was deemed significant

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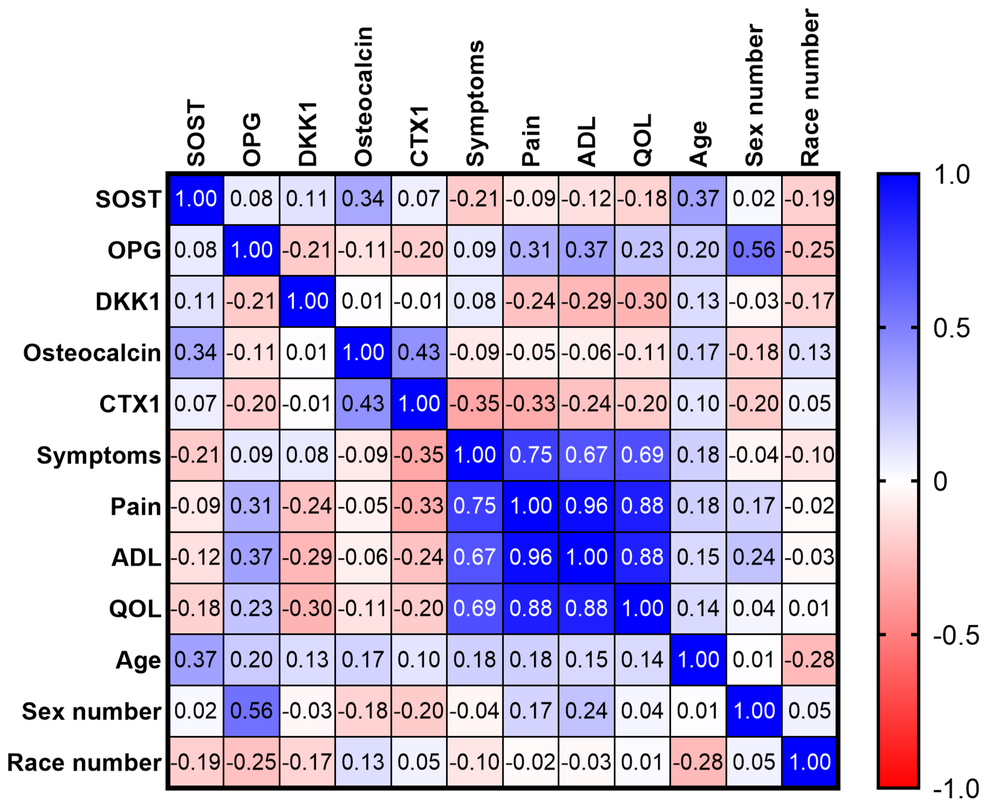

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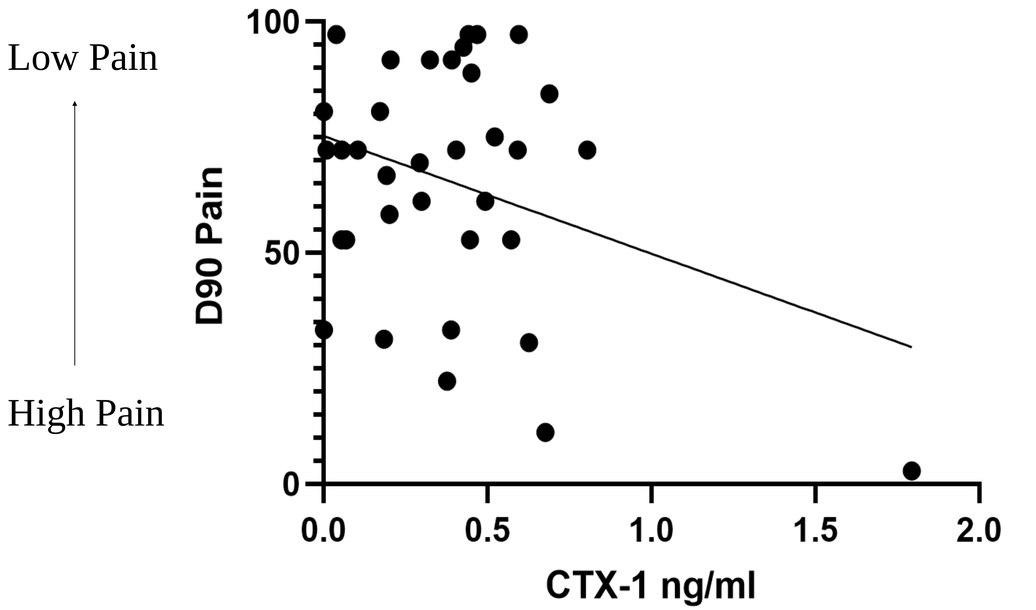

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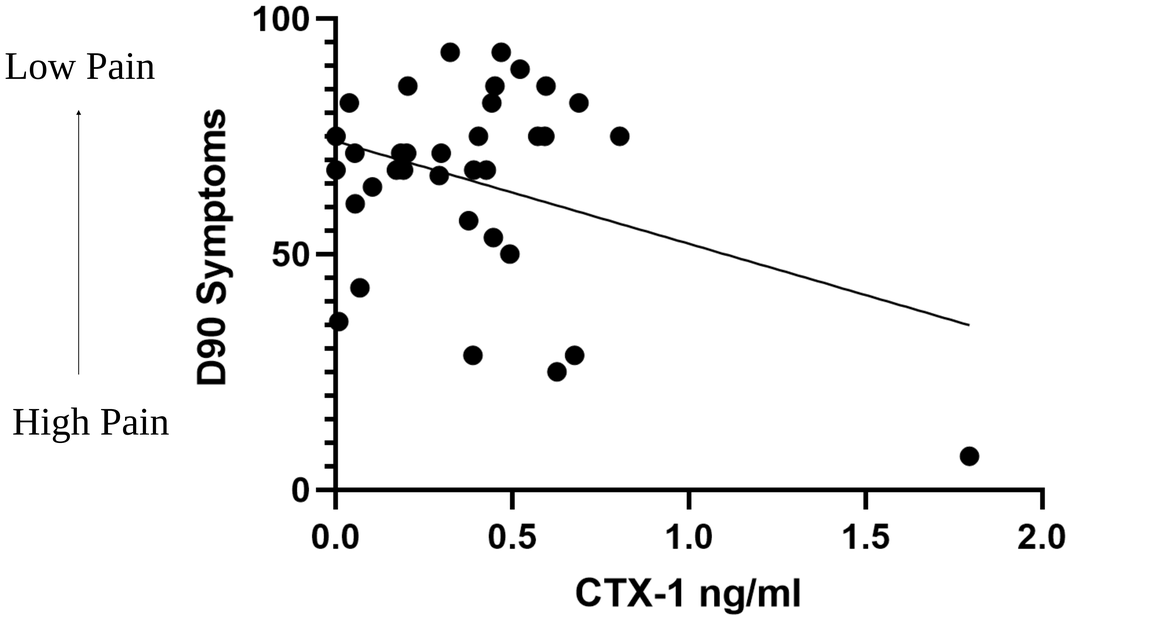

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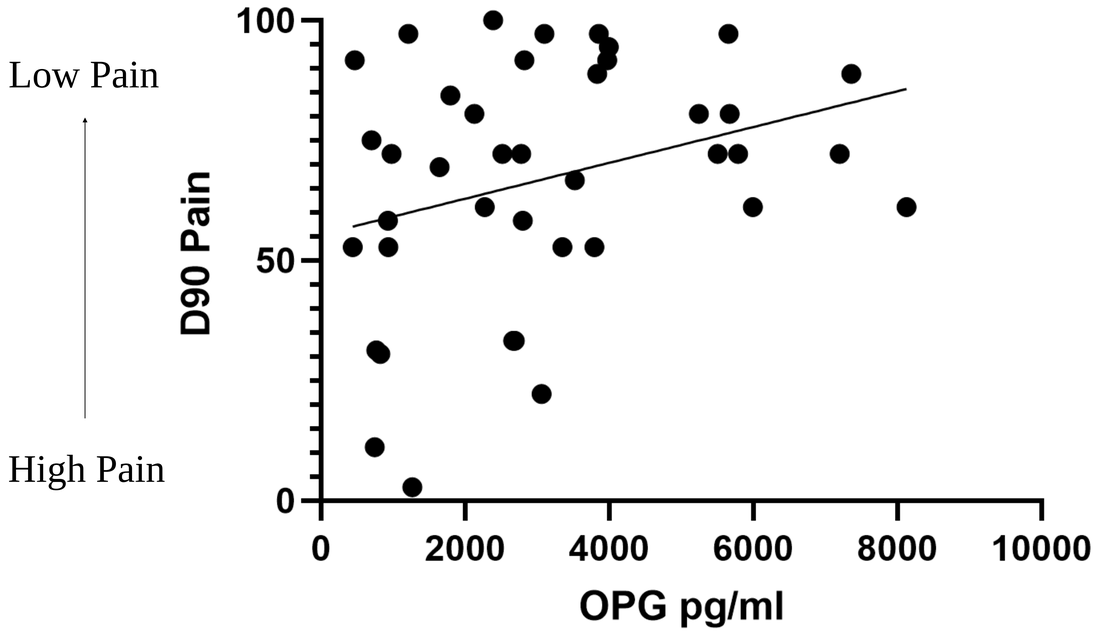

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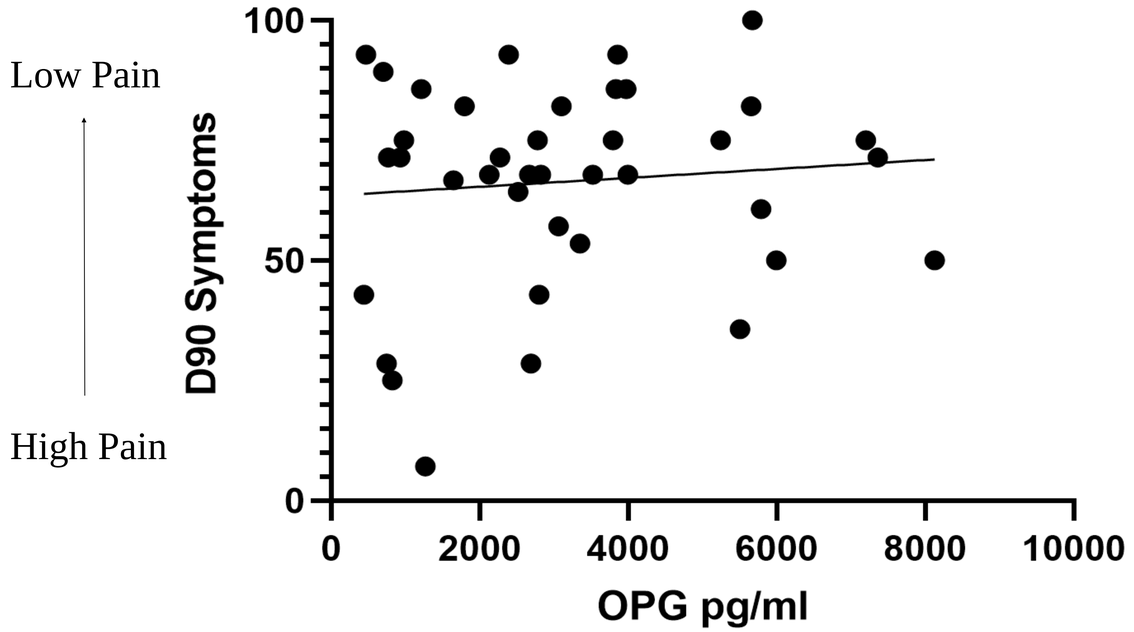

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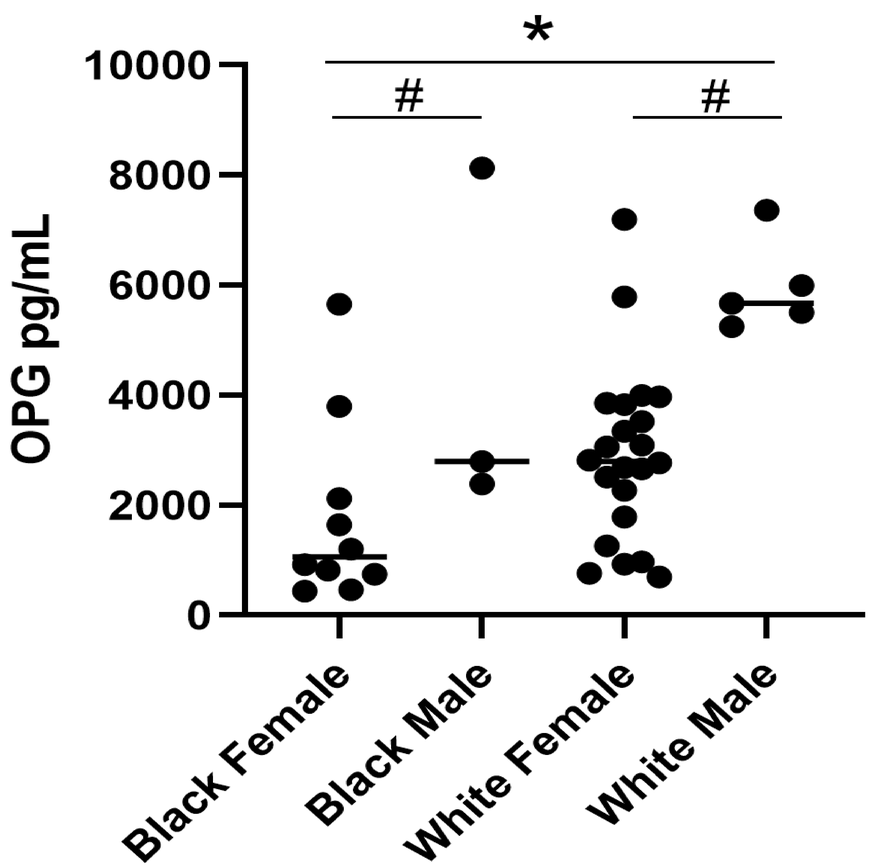

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