Emerging biomarkers in aseptic loosening as molecular targets for bone repair and regeneration

Gema Vallés[1,2], Laura Saldaña[1,2],Eduardo García-Rey[2,3], Nuria Vilaboa[1,2]

[1]Grupo de Fisiopatología Ósea y Biomateriales, Instituto de Investigación Sanitaria del Hospital Universitario La Paz-IdiPAZ, Madrid, Spain
[2]Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina-CIBER-BBN, Spain
[3]Departamento de Cirugía Ortopédica y Traumatología. Hospital Universitario La Paz-IdiPAZ, Madrid, Spain

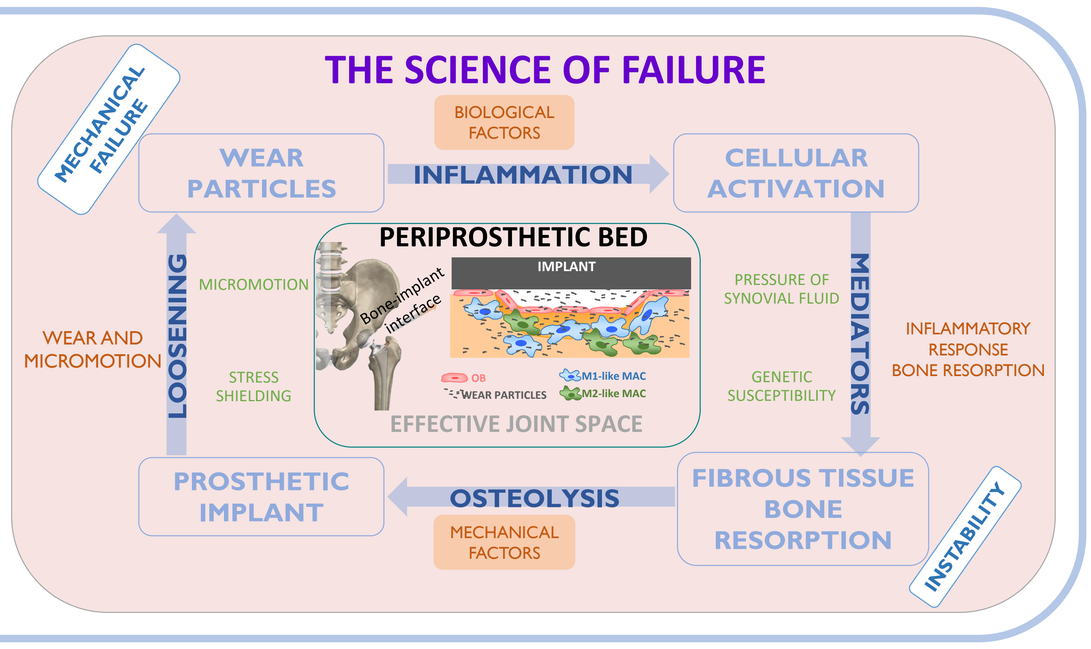
gema.valles@salud.madrid.org

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Introduction and Objective

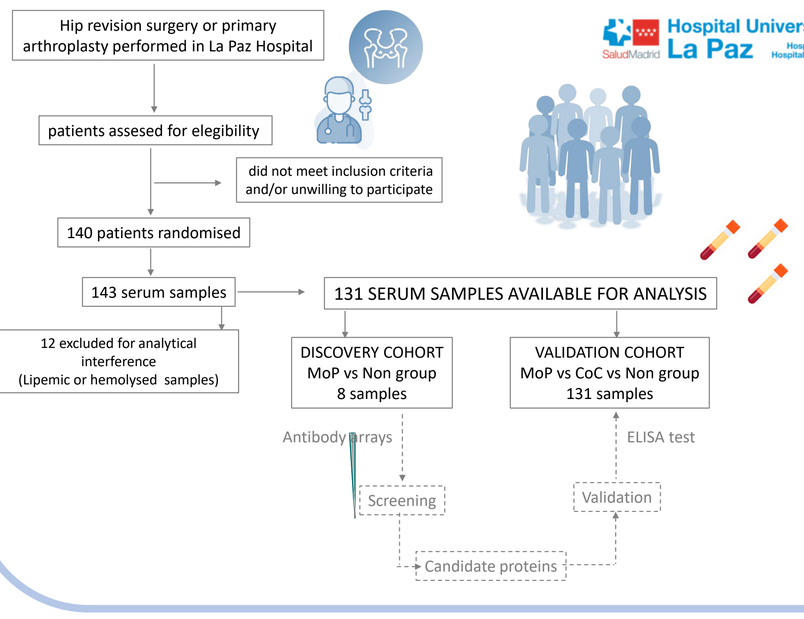
Aseptic loosening remains the leading cause of long-term failure in total joint arthroplasty and an important focus of research within bone regenerative medicine. This pathological process primarily results from the macrophage-mediated inflammatory response to wear particles, which leads to periprosthetic osteolysis, implant failure and eventually the need of a complex revision surgery. Biomarkers represent promising tools for early detection, monitoring disease progression, and evaluating responses to therapeutic interventions. However, reliable biomarkers for tracking aseptic loosening are still limited.

Our group aimed to identify serum biomarkers associated with aseptic loosening and to elucidate their potential mechanistic links to macrophage-mediated inflammatory responses.



Materials and Methods

STUDY WORKFLOW AND EXPERIMENTAL DESIGN



STUDY GROUPS AND PATEINT DEMOGRAPHICS

+ IMPLANT n= 97 samples

- IMPLANTED PATIENTS
- NON-REVISED: CONTRALATERAL HIP
- REVISED (NO INFECTION): AL, FX, LUX
- HIP BEARING SURFACE COMBINATIONS

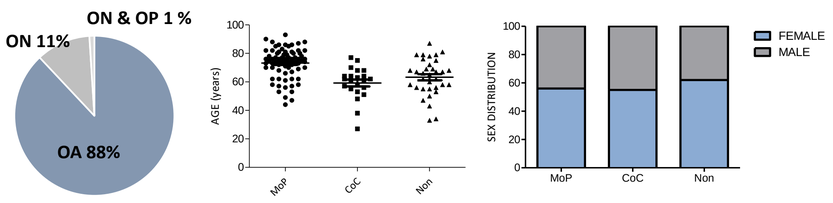
MoP GROUP n=75 — SERVICE TIME mean=10.2 years

CoC GROUP n=22 — SERVICE TIME mean=5.7 years

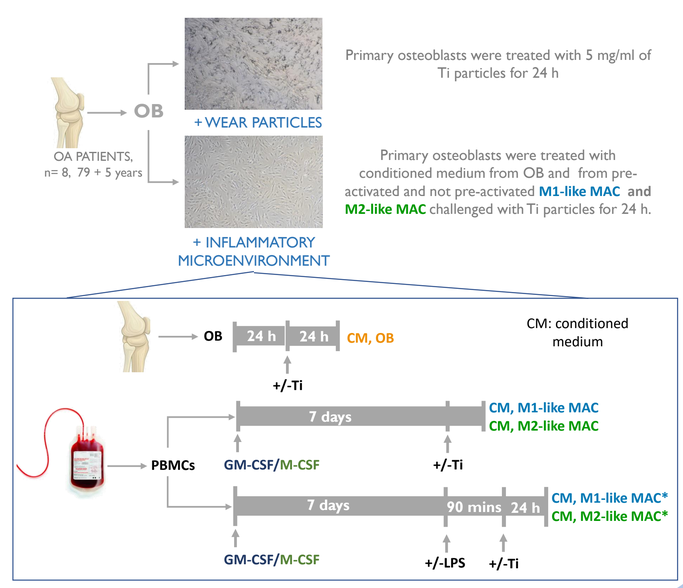
- IMPLANT n=34 samples

- 1st PRIMARY THA
- CONTROL GROUP

Non GROUP

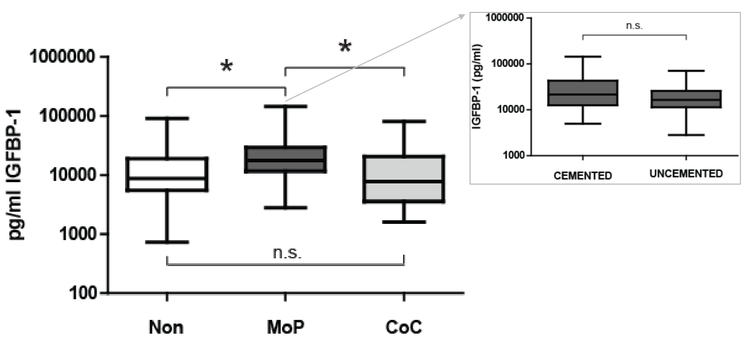


IN VITRO EXPERIMENTAL DESIGN AND MACROPHAGE POLARIZATION TIMELINES



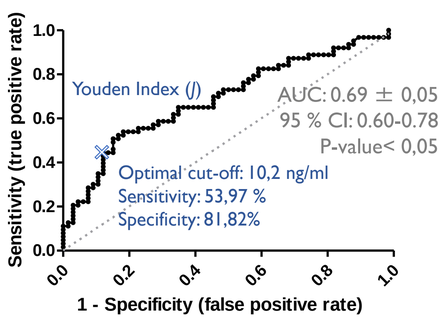
Results

SERUM IGFBP-1 LEVELS ACROSS STUDY GROUPS



Results are presented as box and whisker plots in which the centerlines show the median, boxes represent the range between the first and third quartile and whiskers illustrates the highest and lowest value. *p < 0.05; n.s. non statistically significant. The inset shows IGFBP-1 levels in cemented and uncemented MoP patients.

PREDICTIVE MODEL POWER OF IGFBP-1 FOR MoP IDENTIFICATION



Group	P-value	Odds ratio (OR)	95%CI
Non + CoC		1.0	Reference
MoP	<0.001	6.7	3.1-14.8

Receiver operating characteristic curve (ROC). Area under the curve (AUC) including the intervals at 95% of confidence level (CI), optimal cut-off value and associated data for sensitivity and specificity are shown.

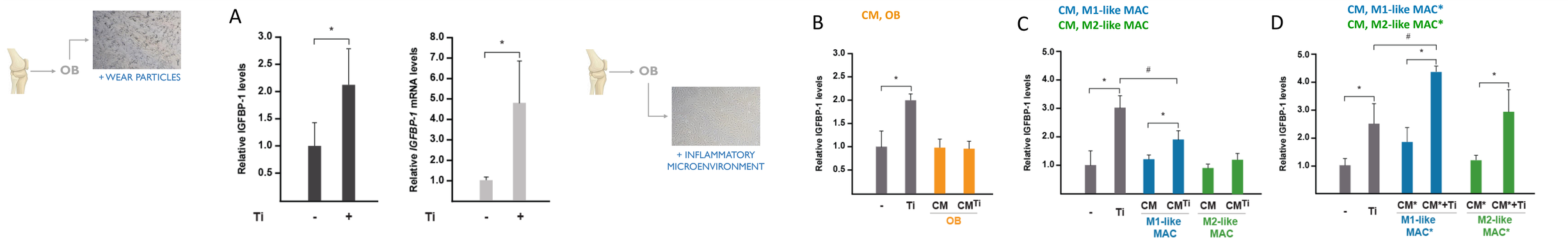
Logistic regression analysis showing the significant association between the MoP group and an OR of 6.7, supporting the diagnostic accuracy observed in the ROC analysis.

CLINICAL PROFILE AND RISK FACTOR DISTRIBUTION BY GROUP

Group	Age, years (Mean ± SD)	% patients with BMI> 30 kg/m2	% patients with Type 2 DM
Non	63 ± 13	32	18
MoP	73 ± 11*	25	16
CoC	59 ± 11	50	27

Analysis of age, body mass index, and diabetes type II status to identify potential variables that may influence IGFBP-1 levels. Data show that the MoP cohort is characterized by advanced age compared to Non and CoC, whereas metabolic indicators show no significant differences between groups.

IGFBP-1 PRODUCTION BY PRIMARY CULTURES OF HUMAN OSTEOBLAST (OB)



IGFBP-1 secretion and *IGFBP-1* mRNA levels in OB exposed (+) or not (-) to 5 mg/ml of Ti particles for 24 h. IGFBP-1 secretion in OB incubated for 24 h in conditioned medium from OB exposed (CM^{Ti}) or not (CM) to 5 mg/ml of Ti particles (B); in conditioned media from M1 and M2 macrophages exposed (CM^{Ti}) or not (CM) to 5 mg/ml of Ti particles (C); and in conditioned media from pre-activated M1 or M2 macrophages containing (CM*+Ti) or not (CM*) 5 mg/ml of Ti particles (D). Data are represented as mean ± SD and expressed as relative fold induction to levels in untreated OB, which were given the arbitrary value of 1. These levels corresponded to 6.36 pg IGFBP-1 in (A), 6.18 pg of IGFBP-1 in (B), 4.99 pg in (C) and 5.45 pg in (D) per μg of total proteins. *p < 0.05 as compared to OB not exposed to particles, and #p < 0.05 as compared to Ti-treated OB not incubated in CM.

Conclusion

IGFBP-1 levels are significantly elevated in patients undergoing total hip arthroplasty with MoP-bearing surfaces. This protein might serve as a reliable biomarker for aseptic loosening in patients implanted with this type of prosthesis

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DECLARATION OF INTEREST: Authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this research project.

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