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Original Article

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Association of the Expression of Bone Morphogenetic Protein Subtypes in Recipient Epigastric Arteries and Long-Term Outcomes After Kidney Transplantation

Armin Atić[1], Marijana Gulin[2], Tvrtko Hudolin[3], Ivica Mokos[3], Željko Kaštelan[3], Marijana Ćorić[4], Nikolina Bašić-Jukić[1]

[1]Division of Nephrology, Arterial Hypertension, Dialysis and Transplantation, University Hospital Center Zagreb, Zagreb, Croatia
[2]Department of Nephrology, County Hospital Šibenik, Šibenik, Croatia
[3]Urology Clinic, University Hospital Center Zagreb, Zagreb, Croatia
[4]Department of Clinical Pathology and Cytology, University Hospital Center Zagreb, Zagreb, Croatia

ABSTRACT

Background: Bone morphogenetic proteins (BMPs) are growth factor proteins with various developmental and functional roles. They are associated with chronic kidney disease and vascular alterations such as atherosclerosis and calcification. In kidney transplantation, BMP 2 has been associated with delayed graft function, while downregulation of BMP 2, 4, and 6 in kidney grafts has been associated with interstitial fibrosis and atrophy. Rhis study was designed to investigate the associations of recipient artery BMP expression with long-term kidney allograft loss and mortality.
Methods: A prospective cohort study included 58 kidney transplant recipients from January 2012 to March 2013, monitored for up to 10 years. Bone morphogenetic protein expression in recipient epigastric arteries was evaluated using immunohistochemistry. Selected outcomes included death-censored graft loss (DCGL), death, and a composite endpoint (graft loss or death). Data were analyzed using t-tests, chi-squared tests, logistic regression, and Kaplan-Meier survival analysis.
Results: At 5 years, 88% of patients survived, with 81% maintaining graft function. BMP4m and BMP6m positivity were associated with 100% survival and graft function at both 5 and 10 years. At 10 years, 74% of patients survived, with 67% maintaining graft function. BMP4e staining was associated with better composite outcomes at 10 years. No significant associations were found between BMP expression and DCGL or death. Notably, older age at transplantation and lower creatinine clearance at 1 year post-transplant were linked to higher rates of adverse outcomes.
Conclusions: This study suggests that BMP expression does not correlate with long-term outcomes after kidney transplantations. Although BMP4 expression in the endothelium was associated with survival and graft function at 10 years post-transplant in this cohort, this correlation was lost when adjusting for other factors. Further research with larger cohorts is needed to validate these findings and explore the potential prognostic roles of BMPs in kidney transplantation.
Keywords: Bone morphogenetic protein, kidney transplantation, long-term outcomes, mortality

Corresponding author: Armin Atić ✉ aticarmin@gmail.com
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INTRODUCTION

Bone morphogenetic proteins (BMPs) are a group of growth factor proteins belonging to the transforming growth factor-β (TGF-β) superfamily.[1] They are involved in many processes in the development and maintenance of various organs, such as bone, cartilage, kidney, muscles, and blood vessels.[2] Important sources of BMP are vascular and endothelial cells, where they play a role in pathological processes such as vascular calcification, atherosclerosis, and calcification of the heart valves.[3-5]

Kidney transplantation is considered the optimal method of kidney replacement therapy (KRT) and offers better quality of life and survival when compared to dialysis.[6] Over the past 3 decades, short-term outcomes of transplantation have improved, a success mainly owed

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to the introduction of new immunosuppressive therapies, surgical proficiency, and follow-up.[7-8] Long-term outcomes, however, have remained the same and are at 5 years, 77% in Europe and 67% in the USA, and at 10 years, 56% in Europe and 43% in the USA.[8] Studies have identified many factors related to patients and graft survival. At the time of transplantation, they are divided into donor and recipient-related factors. Donor factors are organ quality, type of donor (living vs. deceased donor), donor criteria used (standard criteria vs. expanded criteria), and type of donor death (brain death donor vs. cardiac death donor). Recipient factors are numerous and include recipient age, native kidney disease, dialysis vintage, cardiovascular comorbidities, pretransplant diabetes, and immunological factors such as human leukocyte antibody (HLA) matching and anti-HLA immunization. Factors happening along the course of transplantation also affect long-term outcomes, and they include delayed graft function (DGF), chronic allograft dysfunction, graft function, proteinuria, opportunistic infections, and long-term effects of immunosuppresive drugs.[9-11]

Bone morphogenetic proteins are involved in atherosclerosis and calcification, processes central to factors associated with worse long-term transplantation outcomes such as cardiovascular comorbidities and chronic allograft dysfunction but also DGF. Decreased staining of endothelial cells of the recipient arteries for BMP 2 was found to be associated with DGF independently from other DGF risk factors such as cold ischemia time, hypertension, age, diabetes, and others; however, BMP 2 staining had no associations with 1-year survival.[12] A BMP 2 gene association study in a Korean cohort identified 2 single-nucleotide polymorphisms that are associated with acute rejection and graft dysfunction.[13] Other BMPs, namely BMPs 4, 6, and 7, were found to be downregulated in allografts with interstitial fibrosis and tubular atrophy.[14] Similarly, an increase in the urinary TGF-β/BMP 7 ratio, representing epithelial to mesenchymal transition, which is a pivotal component of fibrosis, has been shown to be positively correlated with creatinine values at 1 year post-transplant, possibly indicating patients with early kidney damage. In the same study, at 3 months, patients with a history of DGF had increased BMP 7—explained as a consequence of recovery from DGF and counteraction of the effects of TGF-β. However, no kidney biopsy was done in the study.[15]

Considering the associations of BMPs with various factors linked to worse long-term transplantation outcomes, this study was designed to investigate the associations of recipient artery BMP expression with long-term kidney allograft loss and mortality.

MAIN POINTS

- Bone morphogenetic proteins are a diverse group of proteins with developmental and regulatory roles in various human tissues.
- Changes in their expression have been associated with delayed graft function and increased interstitial fibrosis and atrophy.
- No studies have evaluated the recipient bone morphogenetic protein (BMP) expression and long-term outcomes after kidney transplantation.
- This study suggests no associations between BMP expression and long-term outcomes after kidney transplantations; however, BMP4 expression may be associated with better survival and graft function 10 years after transplantation.

MATERIAL AND METHODS

Patients and Clinical Data Collection

A prospective cohort study included all patients who received a kidney transplant at the institution from January 2012 to March 2013. All patients transplanted in the studied period who gave consent and agreed to the study protocol were included. Recipient medical history data collected included demographic data, cardiovascular risk factors, and kidney factors (primary disease, dialysis vintage, and type). Graft function was determined by creatinine clearance from a 24-hour urine sample at selected time points. During follow-up, patients were evaluated for the occurrence of predefined outcomes. The study is compliant with Ethical Standards and was approved by the University Hospital Center Zagreb Ethics Board (Approval number 02/21-LJH, Date: 30th January 2012). The study was conducted following the Declaration of Helsinki and Istanbul.

Sample Collection and Immunohistochemistry

The iliac fossa was accessed by the Gibson incision and the iliac vessels exposed. The full circumference of the epigastric artery was resected after ligation, as described in the previous paper.[12] Further processing was done in the Department of Clinical Pathology and Cytology. The samples were fixed in formalin and embedded in paraffin. Original slides were stained with hematoxylin and eosin and reviewed for the presence of arteries. Corresponding paraffin blocks were retrieved and additional slides were prepared from multiple, sequential 4-µm-thick sections. Anti-human Pro-BMP monoclonal antibodies (1:100) (R&D Systems) were used for immunohistochemical analysis. Paraffin sections (3-4 µm) of all specimens were deparaffinized in xylene and then rehydrated through graded alcohol. Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide for 10 minutes. PT link tanks (Dako, Glostrup, Denmark) were used for deparaffinization and heat-induced epitope retrieval (EnVision FLEX+ K8000, 3 in 1, Solution High pH; Dako). All slides were incubated for 20 minutes at 97°C and left in buffer (EnVision FLEX wash buffer; Dako). Staining was performed using an automated immunostainer (AutostainerLink48; Dako). The following protocol was used: slides were incubated for 10 minutes in an endogenous block (EnVision FLEX + K8000; Dako) and then incubated with the antibody for 30 minutes, after which the sections were incubated for 30 minutes in labeled polymer (EnVision FLEX+ K8000; Dako). Each individual stage was followed by buffer rinses (EnVision FLEX + K8000; Dako). Staining was visualized

using the chromogen 3,3′-diaminobenzidine for 10 minutes, counterstained with hematoxylin (EnVision FLEX+ K8000; Dako) for 10 minutes and manually covered.

Outcome Definitions

Selected outcomes were the following: 1. Death-censored graft loss (DCGL), defined as loss of graft function independent of patient death (i.e., patients who died with a functional kidney graft were not counted as graft loss); 2. death, defined as death from any cause irrespective of kidney graft function; 3. composite endpoint graft loss or death, defined as either loss of kidney graft function (i.e., switch to dialysis) or death.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS software, version 26.0 (IBM SPSS Corp.; Armonk, NY, USA). Continuous variables were tested for normality of distribution using the Kolmogorov–Smirnov test. Differences between 2 groups of normally distributed variables were tested using Student's *t*-test. Differences between categorical variables were tested using the chi-squared or Fisher's exact test. Logistic regression was used to test the associations between a categorical dependent variable and several independent variables. Survival analysis was performed using Kaplan–Meier analysis or log-rank tests for analyses in which no events occurred in one of the groups. All values were deemed statistically significant for a two-tailed $P < .05$.

RESULTS

Cohort Characteristics

During the studied period, 58 patients were included. There were 36 male patients (62%), with an average 49 years (SD 13.7). All the included patients were on KRT prior to transplantation. Hemodialysis was the KRT method in the majority of cases, accounting for 74% (43 patients). Regarding preexisting comorbidities, 84% (49) had hypertension, 7% (4) had diabetes, and hyperlipidemia was present in 38% (22). Additionally, 9% and 3% had prior cerebrovascular or coronary artery disease, respectively. During the studied period, 21% had DGF (12), and 10% had acute graft rejection, while the average graft function was 8.3 years (SD 2.9 years). All the continuous variables were normally distributed according to the Kolmogorov–Smirnov test.

BMP staining was performed for BMP 2, 4, 6, and 7, with counts of positive stains and the number of patients in whom certain staining was not performed presented in Table 1. Three patients were negative for all BMP subtypes, while 3 more were negative but had not had all types of staining done.

Five-Year Outcomes

At 5 years from the transplantation date, 51 patients have survived (87.9%), 47 with a functioning graft (81%). The selected end-point of DCGF was reached in 6 cases, and a composite end-point occurred in 11 cases. Among the groups, significant differences were found for older age and creatinine clearance at 1 year post-transplantation (Table 2). No significant differences were found for other patient-related factors, comorbidities, or post transplantation events such as DGF or acute rejection. For DCGL (N = 6) at 5 years, there were statistically significant differences for creatinine clearance at 1 year post-transplantation (59 vs 30, $P < .01$) and diabetes before transplantation ($P = .049$), while no other factor reached statistical significance. Comparing survivors to deceased participants, significant differences were found for age ($P = .034$) and creatinine clearance at 1 year post-transplant ($P = .003$).

Table 1. Bone Morphogenetic Protein Staining and Missing Data

BMP Type	N Positive/Negative	Missing Data
BMP 2m	7/33	18
BMP 2e	8/32	18
BMP 4m	4/53	1
BMP 4e	16/41	1
BMP 6m	1/57	0
BMP 6e	7/51	0
BMP 7m	40/11	7
BMP 7e	36/15	7

BMP, bone morphogenetic protein; e, indicates endothelial layer staining of recipient epigastric arteries; m, indicates staining of the intima media layer of recipient epigastric arteries.

Bone Morphogenetic Protein Expression and 5-Year Outcomes

No associations between all outcomes and BMP2 expression were found. For BMP4, all patients with positive BMP4m staining had survived with a functioning graft at 5 years (4 patients). BMP4e was positive in 1 patient with DCGL and positive in 15 without graft loss. Differences in patient characteristics and staining among groups for BMP4 staining did not reach statistical significance. The log rank test was not significant for BMP4m and composite outcome at 5 years ($P = .360$). All patients with any positive BMP6 staining had had a functioning graft and were alive at 5 years. Overall, BMP6m was positive in 1 patient and BMP6e in 7. No statistically significant differences were found. BMP7 positive staining was the most prevalent among all the tested BMPs, and BMP7m was positive in 40 of the 51 tested patients, 3 of whom had had DCGL, and all patients who had a negative BMP7m stain had a functioning allograft at 5 years. BMP7e was positive in 2 cases of DCGL and 34 without. For the composite outcome of graft loss and death, all patients who survived at 5 years had negative BMP7m staining, and only 1 had positive BMP7e staining, while 6 who had reached the endpoint had positive BMP7e. Survival analysis did not reach statistical significance for any BMP staining and selected outcomes. There were no significant associations between BMP staining and death at 5 years.

Table 2. Characteristics of Survivors with a Functioning Kidney Graft and Deceased Patients or Those Who Have Lost Graft Function at 5 Years Post Transplant

Value	No Event (n = 47)	Graft Loss or Death at 5 Years (n = 11)	*P*
Male sex, N	31	5	NS
Female sex, N	16	6	NS
Age at transplantation, years, (SD)	47 (13)	58 (10)	.019
Dialysis vintage, years (SD)	2.5 (2)	3.8 (2)	.07
Peritoneal dialysis, N	14	1	NS
Smoking, N	11	5	NS
Body mass index, (SD)	25 (4)	25 (3)	NS
Hypertension, N	39	10	NS
Diabetes, N	2	2	NS
Delayed graft function, N	9	3	NS
Acute rejection, N	4	2	NS
Creatinine clearance at 1 year post transplant, mL/min (SD)	60 (21)	36 (11)	<.01

Ten-Year Outcomes

Overall, 43 patients (74%) survived up to the 10-year follow-up, 39 with a functioning kidney allograft (67%). When comparing patients who were alive and had a functioning allograft with those who had reached the composite endpoint at 10 years, only age at the time of transplantation was significantly different (Table 3). Creatinine clearance at 1 year post-transplantation did not differ significantly among groups. For DCGL (N = 8), there were no differences among groups for age, sex, dialysis vintage, KRT type prior to transplantation, smoking, BMI, comorbidities at the time of transplantation, DGF, or acute rejection. When comparing survivors to deceased patients, significant differences were found for hyperlipidemia (*P* = .043, with Bonferroni correction), age at transplantation (*P* < .001), and creatinine clearance at 1 and 5 years post-transplant (*P* = .019 in both cases).

Ten-Year Outcomes and Recipient BMP Expression

Among patients who had reached the composite outcome at 10 years and the group that had not, there was a significant difference only for BMP4e staining (*P* = .011). In cases where BMP4m staining was positive, all the patients survived with a functioning graft. BMP6m staining showed the same result; however, there was only 1 patient with a positive BMP6m stain.

Table 3. Characteristics of Survivors with a Functioning Kidney Graft and Deceased Patients or Those Who Have Lost Graft Function at 10 Years Post Transplant

Value	No Event (n = 39)	Graft Loss or Death at 10 Years (n = 19)	*P*
Male sex, N	26	10	NS
Female sex, N	13	9	NS
Age at transplantation, years, (SD)	46 (13)	55 (13)	*P* = .017
Dialysis vintage, years (SD)	2.6 (2.1)	2.8 (2.2)	NS
Peritoneal dialysis, N	11	4	NS
Smoking, N	10	6	NS
Body mass index, (SD)	25 (4)	25 (4)	NS
Hypertension, N	32	17	NS
Diabetes, N	1	3	NS
Delayed graft function, N	9	3	NS
Acute rejection	3	3	NS
Creatinine clearance at 1 year post transplant, mL/min (SD)	60 (20)	51 (24)	NS
Creatinine clearance at 5 years post-transplant, mL/min (SD)	70 (22)	54 (19)	NS

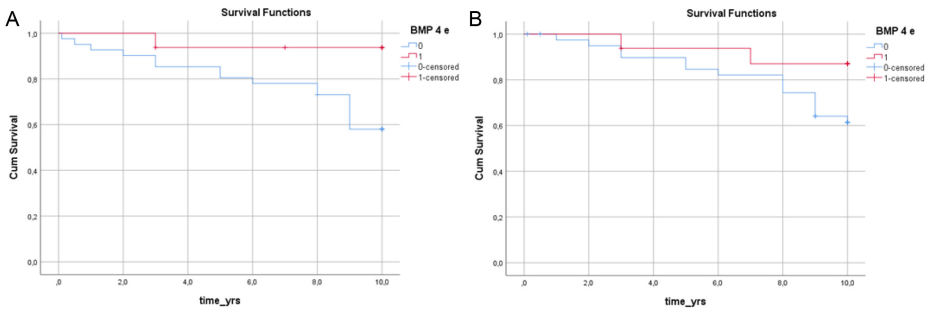

Figure 1. Left plot - Kaplan–Meier plot showing overall graft and patient survival difference for BMP4e positive staining; Right plot - Kaplan–Meier plot for BMP4e positive staining and survival (χ2 2.84, *P* .092).

Logistic regression has shown an association of BMP4e staining and the cumulative endpoint at 10 years (*P* = .029, 95% CI 0.11-0.78). Bivariate regression was not significant for other BMPs. A log-rank test has shown a statistically significant difference in survival distribution among the groups depending on BMP4e staining (χ^2 5.34, *P* = .021) (Figure 1), however, this association was lost in the multivariate regression model with hyperlipidemia, creatinine clearance at 5 years, and age (95% CI 0.68-56). To further investigate these findings, a Cox regression analysis was performed to examine the effects of BMP4e staining, age at transplantation, diabetes mellitus, coronary artery disease, gender, hyperlipidemia, creatinine clearance at 1 year, and DGF. The model's fit was evaluated with the −2 Log Likelihood value of 98.904 as confirmed with the non-significant omnibus test of coefficients Chi^2 (9) 14.248, *P* = .114, indicating a poor fit of the model. The hazard ratios indicated that BMP4e was not a significant predictor of survival (95% CI 0.64-50.8). None of the variables were significant for predicting survival at 10 years. For DCGL, there were no significant differences among groups. There were no significant differences for death across all BMP stains.

DISCUSSION

In this longitudinal study, 58 kidney transplant recipients were followed up to 10 years and investigated for differences in graft loss or death depending on BMP subtype expression on the recipient epigastric artery at the time of transplantation. At the 5- and 10-year marks 88% and 74% of patients survived, respectively, which is a higher proportion than the reported European average.[8]

No specific BMP staining was associated with a survival benefit at 5 years. However, for several BMPs, a survival analysis could not be done due to either low counts of positive stains or a complete lack of events. Patients who stained positive for BMP4m and BMP6 all reached the 5-year mark alive and with a functioning graft, and at the 10-year mark none of the deceased patients or those who lost graft function had BMP4m and BMP6m positive. Endothelial staining of BMP4 has shown a benefit for the composite outcome in Kaplan–Meier survival analysis, but not in DCGF or death.

BMP6 is known for its anti-inflammatory effects.[16] In animal and in vitro studies, BMP6 has been found to decrease inflammation, protect from oxidative damage in the retinal blood vessels, and decrease fibrosis in non-alcoholic fatty liver disease.[17-19] In studies on BMP6 null mice, tubulointerstitial damage and fibrosis were aggravated, indicating the importance of BMP6's anti-inflammatory functions in the cellular response to injury.[20] In areas of vascular calcification, BMPs 2, 4, and 6 have been demonstrated, and BMP2 and 4 are both upregulated in CKD related vascular calcification.[21,22] The effects of BMP4 in the vasculature are linked to endothelial dysfunction, calcification in vascular smooth muscle cells, and hypertension, all factors associated with chronic kidney disease.[23,24] Furthermore, in chronic kidney disease (CKD), plasma levels of BMP4 are elevated.[21] BMP2 has pro-inflammatory effects and drives calcification in the vasculature.[25] BMP7 has opposing effects to TGF-beta, a major driver of fibrotic changes in kidney tubules.[26] Urinary BMP7, as mentioned earlier, when decreased, could indicate kidney damage and progression towards fibrosis.[15] Although BMP4 is heavily linked to vascular calcification, this study did not find any detrimental effects of BMP4 expression and has even found a survival and graft function benefit of BMP4 expression in the endothelium at 10 years, but not at 5 years post-transplantation. Notably, in the studies that describe the role of BMP4, its upregulation was described in the tunica media of the aorta.[22] Interestingly, all patients that had BMP4 staining of the media layer survived with a functioning kidney allograft at 10 years. However, kidney transplantation resolves many of the driving forces behind the promotion of BMP4 and other pathways which promote vessel calcification. Notably, the uremic milieu is resolved, and the chronic inflammation of CKD is largely alleviated. It is possible that transplantation itself and the improvement of kidney function reverses or slows the processes associated with BMP and vascular dysfunction.

The only factor shared between 5- and 10-year outcomes was patient age at the time of transplantation. At 5 years post-transplantation, significant differences were found for diabetes at the time of transplantation and creatinine clearance at 1 year post-transplantation for DCGL. Older patients and those with worse graft function at 1 year were associated with higher rates

of death and DCGL at 5 years. Similarly, for death at 10 years, associations were found for age, creatinine clearance at 1 and 5 years post-transplant, and for hyperlipidemia.

The main limitations of this study are the relatively small sample size, particularly for some BMP subtypes. This may have particularly influenced the multivariate regression models. Other limitations include the lack of inclusion of post-transplant comorbidities, which may have influenced mortality, but also could have been related to BMP expression. Cause of death or the development of other major vascular events were not ascertained. Additionally, histological findings of the epigastric arteries may not be generalizable to other vascular beds.

This is the first reported study of BMP expression in the recipient arteries and long-term outcomes in kidney transplant recipients; however, this study is underpowered for all the studied BMP subtypes, particularly BMP6. Bone morphogenetic protein staining of recipient arteries appears not to have prognostic roles for death or graft loss in kidney transplantation, except for BMP4 staining in the endothelium, which has shown a survival and graft function benefit at 10 years. Larger prospective studies are needed to determine the relationship among these factors.

Data Availability Statement: The data that support the findings of this study are available upon request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University Hospital Center Zagreb (Date: 30.01.2012, Number: 02/21-LJH).

Informed Consent: Written informed consent was obtained from the participants who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.B.J., M.G., Ž.K.; Design – T.H., M.G., N.B.J.; Supervision – Ž.K., N.B.J.; Resources – T.H., I.M., M.Ć.; Materials – M.G., M.Ć.; Data Collection and/or Processing – A.A., M.G., I.M.; Analysis and/or Interpretation – M.Ć., A.A., M.G., N.B.J.; Literature Search – A.A., M.G., N.B.J.; Writing Manuscript – A.A., N.B.J.; Critical Review – N.B.J., T.H., Ž.K.

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