Expression of BMP-2 in vascular endothelial cells of recipient may predict delayed graft function after renal transplantation

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Introduction

Delayed graft function is an independent risk factor for decreased short and long-term graft survival. It is associated with increased incidence of acute rejections and prolonged hospitalizations. For these reasons, the prediction and prevention of DGF may improve outcomes of renal transplantation. BMP-2 is involved in both endothelial function and immunological events. We investigated expression of BMP-2 in the epigastric artery of renal transplant recipients and its correlation with delayed graft function and posttransplant outcomes.

Results

In patients with DGF, hospitalization was more than two times longer compared to the patients with IGF (median 28 days, interquartile range 18-33 days *vs.* 12 days, 9-16 days, respectively; P<0.001). Patients with DGF had worse graft function at one year after transplantation (Table 1). BMP2 staining was recorded in the cytoplasm of endothelial cells of epigastric arteries. Statistically significant difference was recorded for BMP-2e expression between groups (P= 0.006). In DGF patients 93% had no expression of BMP-2 in endothelial cells, compared to 45% in IGF group (P = 0.001). BMP2 staining was recorded in the cytoplasm of muscular cells within the media layer of epigastric arteries. Although statistically significant difference in BMP-2 muscular cells expression between DGF and IGF was not found (P=0.553), patients with DGF tend to have lower expression (Figures 2 and 3).

	IGF (N = 64) (No, %)	DGF (N = 15) (No, %)
Death	2 (3)	0
Graft loss	1 (2)	2 (13)
Acute rejection	6 (9)	2 (13)
Serum creatinine at 1 y	155.7±38.6	201.1±51.0*
≥200 µmol/L	10 (16)	4 (31)
150-199 µmol/L	24 (39)	6 (46)
100-149 µmol/L	23 (38)	3 (23)
<100 µmol/L	4 (7)	0

Table 1. Selected outcomes in patients with immediate (IGF) and delayed graft function (DGF). Results are presented as number (%) or arithmetic mean ± standard deviation. *Statistically significant difference between groups (student's *t*-test, P<0.001)

Conclusion

This study provides the first evidence that histologic materials obtained from recipient may have prognostic value after renal transplantation. We have shown that increased BMP-2 expression in endothelial, but not in muscular cells of media layer of the epigastric artery of recipient, may predict development of DGF, as well as graft function at 1 year after transplantation.

Patients and methods

Seventy-nine patients undergoing renal transplantation from which epigastric artery samples were taken at the time of surgery, were included in this study. Patients were grouped based on presence or absence of parameters for delayed graft function, defined as need for dialysis more than 7 days after transplantation. Control group included 16 non-diabetic patients, nephrectomized due to localized renal cancer (T1, N0, M0), with serum creatinine within the normal range.
After ligation of the epigastric artery, full circumference was resected, and further processed. Anti – human Pro-BMP-2 monoclonal antibody (1:100) was used. Immunoreactivity in cells was accessed by grading (0 - 3) and the results were expressed as percentage of positive cells (negative < 10 %, 10-49 % reactive cells – grade 1, 50-74% reactive cells – grade 2, and more than 75 % reactive cells – grade – 3).
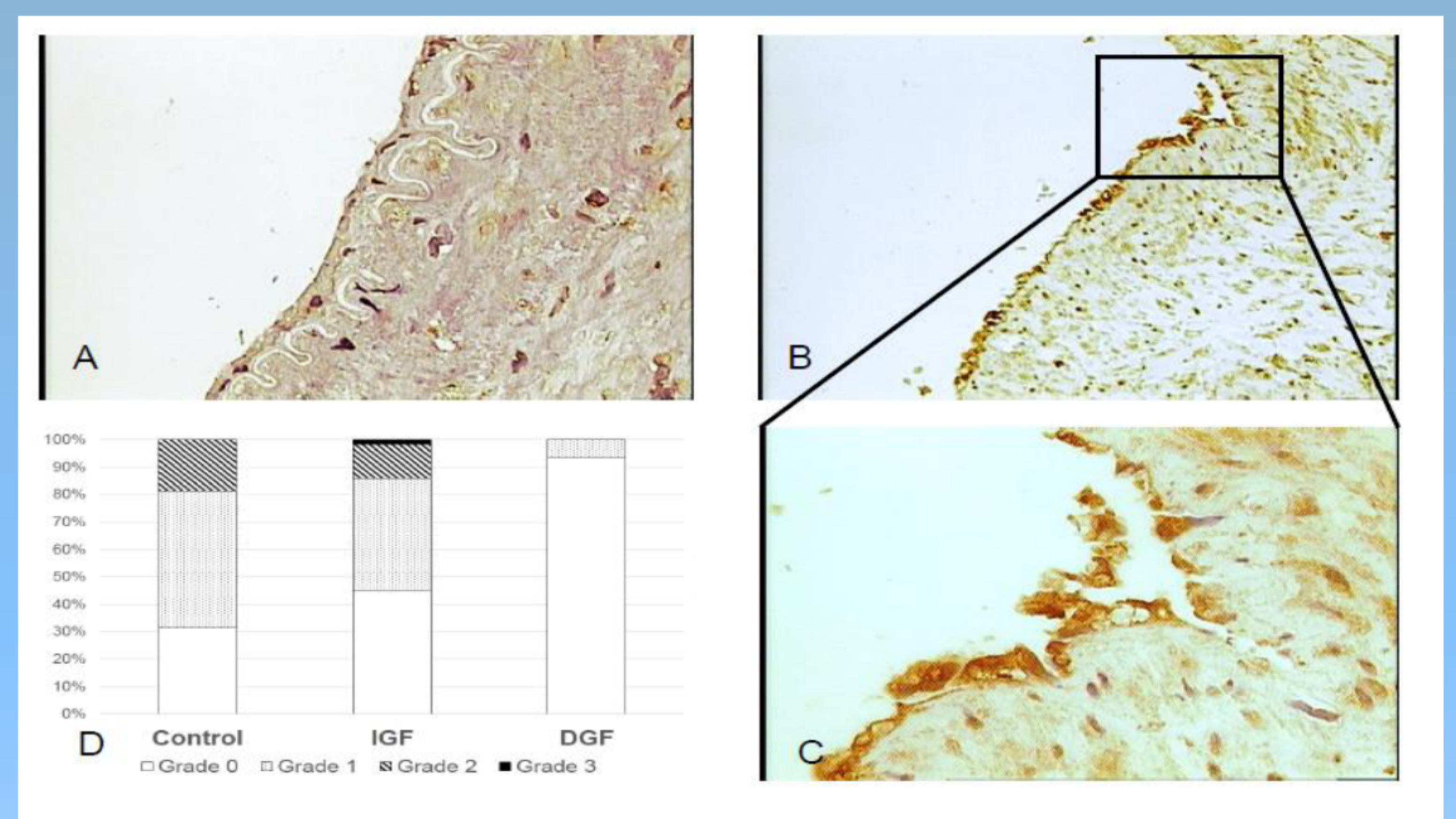

Figure 1. BMP-2 staining in endothelial cells of epigastric artery. A. Section of a epigastric artery showing no staining for BMP. B. Immunohistochemical staining for BMP-2 demonstrates strong cytoplasmatic immunoreactivity in endothelial cells (X20). C. Enlargement x 63 D. Distribution of BMP-2 expression in endothelial cells of epigastric arteries. IGF-immediate graft function, DGF-delayed graft function. *Statistically significant difference between groups for each grade of BMP-2e expression (Pearson's χ^2 test, P < 0.05).
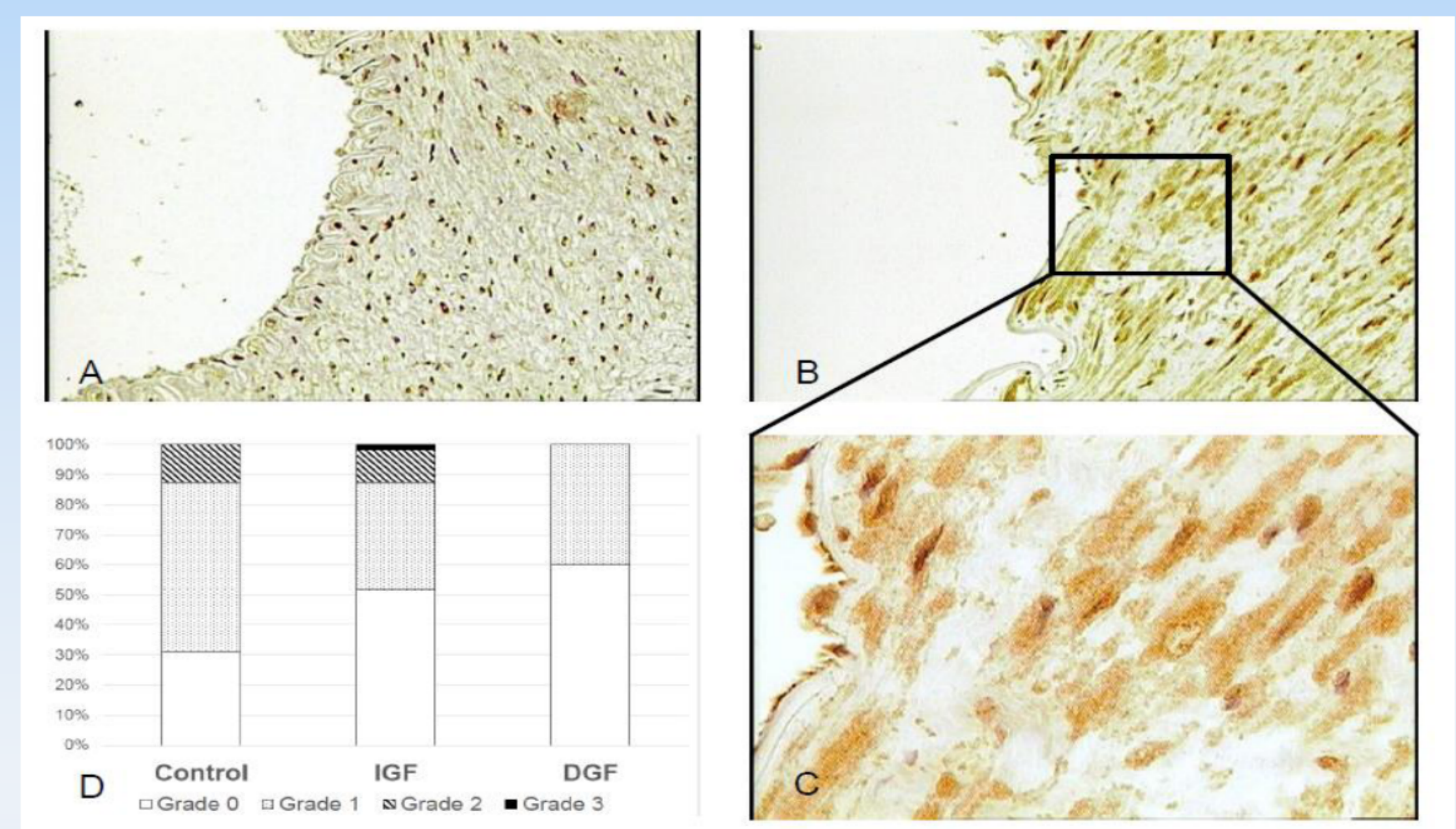

Figure 2. BMP-2 staining in media of epigastric artery. A. Negative immunohistochemical reaction for BMP-2 in the media of the arterial wall. B. Strong cytoplasmic and nuclear immunoreactivity for BMP-22 within the medial smooth muscle cells (X20). C. Enlargement x 63. D. Distribution of BMP-2 expression in the media of epigastric arteries. IGF-immediate graft function, DGF-delayed graft function. There was no statistically significant difference between two groups.