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Growth differentiation factor 15 is decreased by kidney transplantation

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ABSTRACT

Background: Growth differentiation factor 15 (GDF15) is markedly increased in end-stage kidney disease and has been related to increased mortality in patients on dialysis. We hypothesized that kidney transplantation would decrease both GDF15 and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and that GDF-15 decrease relates to post-kidney transplantation allograft function.

Methods: End-stage kidney disease patients on dialysis awaiting a living donor kidney transplantation (n = 39), and those expected to be on the deceased donor waitlist for at least 12 months (n = 43) were enrolled at three transplant centers. Serum GDF15 and NT-proBNP were measured at 0, 3, and 12 months post-kidney transplantation or post-enrollment. Change in serum GDF15 and NT-proBNP concentrations, and their relation to estimated glomerular filtration rate (eGFR) were assessed by non-parametric tests and regression analyses.

Results: Median baseline GDF15 was 4744 pg/ml and 5451 pg/ml for the kidney transplantation and dialysis groups, respectively ($p = 0.09$). Kidney transplantation resulted in a significant decrease in GDF15 (month 12 median 1631 pg/ml, $p < 0.0001$ vs. baseline), whereas there was no change for the dialysis group (month 12 median 5658 pg/ml, $p = 0.31$). Post-kidney transplantation NT-proBNP highly correlated with GDF15 ($\rho = 0.64$, $p < 0.0001$). GDF15 inversely correlated with post-transplant eGFR for the kidney transplantation group ($\rho = -0.42$, $p = 0.0081$). Month 12 NT-proBNP explained 15.8% and 40.1% of the variance in month 12 GDF15 in the dialysis and kidney transplantation groups, respectively. The relationship of GDF15 with eGFR was no longer significant when NT-proBNP was included in the models.

Conclusions: Kidney transplantation significantly decreases serum GDF15 concentrations. The post-kidney transplantation association of GDF15 with NT-proBNP is consistent with a gradient of post- kidney transplantation cardiovascular risk.

1. Introduction

Growth differentiation factor 15 (GDF15) (also known as macrophage inhibitory cytokine-1 (MIC-1), placental BMP (PLAB), placental transforming growth factor-beta (PTGFB), nonsteroidal anti-inflammatory drug-activated gene (NAG-1) and prostate-derived factor (PDF)) [1] is associated with a variety of cardiovascular pathologies, including vascular endothelial dysfunction, and atherosclerotic plaque burden, as well as left ventricular hypertrophy and systolic dysfunction [2]. Increased GDF15 concentrations also associated with an increased risk for incident chronic kidney disease and a more rapid decline in kidney function [3,4]. Higher circulating serum GDF15 concentrations link to mortality in hemodialysis and chronic kidney disease patients [5–8] and anemia in kidney transplantation patients [9]. GDF15 is also involved in the regulation of nausea and appetite, which are important clinical considerations in end-stage kidney disease [10,11]. Other putative functions identified for GDF15 include reducing platelet activation [12], suppression of neutrophil and macrophage function, and inhibition of erythropoiesis [1]. The effect on platelets would be consistent with the risk for bleeding for participants in the ARISTOTLE trial

Abbreviations: eGFR, Estimated glomerular filtration rate; GDF15, Growth differentiation factor 15; NT-proBNP, N-terminal pro B-type natriuretic peptide

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of apixaban, where a serum GDF15 concentration > 2000 pg/ml was predictive of a 5-fold increased risk for bleeds and death [13]. In sum, GDF15 is a promising emergent cardiovascular biomarker.

Progressive chronic kidney disease entails increased cardiovascular risk [14]. The understanding of the complexity of the relationship between kidney and heart function, cardiorenal syndrome, has been identified as a priority by the American Heart Association [15]. The cardiovascular risk extends to the dialysis phase of chronic kidney disease, leading to intense cardiovascular screening in kidney transplant candidates [16]. Cardiovascular risk declines after kidney transplantation [17] but the mechanisms behind this improvement remain mostly unknown. Cardiovascular risk may be partly related to chronic intravascular volume expansion, which is an important clinical consideration both before and after kidney transplantation. Kidney transplantation results in improved left ventricular hemodynamics, as well as reduced serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) [18]. NT-proBNP associates with both left ventricular mass and systolic function in chronic kidney disease [19]. The trajectory of GDF15 concentration and its relation to restored kidney function after kidney transplantation and NT-proBNP remain unknown. Therefore, we hypothesized that the elevated concentration of GDF15 that has been reported in end-stage kidney disease would be reduced by kidney transplantation in concert with reduced NT-proBNP concentrations and increased estimated glomerular filtration rate (eGFR), serving to indicate an improved post- kidney transplantation cardiovascular risk profile based on improved intravascular volume regulation.

2. Materials and methods

2.1. Study protocol

A description of the recruitment and selection of participants to the kidney transplantation and dialysis groups has recently been published [18]. The target population was adult end-stage renal disease patients who were expected to receive kidney transplantation within six months of enrollment. The inclusion criteria included low immunological risk for acute rejection and suitability for minimal steroid-based immunosuppressive drug regimen. Exclusion criteria were 1) patients with end-stage renal disease on hemodialysis who in the opinion of the investigator were unlikely to receive a kidney transplantation; 2) patients < 18 years of age and patients > 75 years of age; 3) patients with uncontrolled hypertension (defined as systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg); 4) patients with acute coronary syndrome or coronary revascularization within the past 6 months; 5) severe heart failure, defined as New York Heart Association functional class IV, chronic atrial fibrillation, or presence of a pacemaker or implantable cardiac defibrillator. The control group was kidney transplantation -waitlisted end-stage renal disease patients on dialysis who were not expected to receive kidney transplantation for at least 24 months.

No patients were lost to follow up, and there were no deaths during the study period. Of 39 transplant subjects, 34 received a live donor kidney transplantation, and 5 received a deceased donor kidney transplantation.

Estimated GFR was calculated as described by Levey et al. [19]. The study was approved by the Research Ethics Board at St. Michael's Hospital (REB 10–239) and by the ethics boards at the collaborating sites. All participants provided written informed consent. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. Blood collection

Blood was collected at baseline, month 3, and month 12. The baseline samples were collected before or on the day of the transplant before the procedure. Month 12 samples were collected as close to the 12-month post-kidney transplant time point as possible. Month 12 samples for the participants who remained on dialysis were collected at or near the time of the 12-month MRI. Serum samples were used for the measurement of GDF15 and NT-proBNP.

2.3. Measurement of GDF15 and NT-proBNP

GDF15 was assayed with the Quantikine ELISA for human GDF15 from R&D Systems, Inc. (Minneapolis, MN, USA) with a between-run CV of 7% for quality control pools with values of 291 ± 20.2 and 209 ± 14.8 pg/ml. This assay has been reported to have an acceptable correlation with the Roche Elecsys assay for concentrations above the Roche assay lower limit of 400 pg/ml [20]. NT-proBNP was determined with the routine clinical assay on the Roche Cobas 6000 601e (Mississauga, ON, Canada).

2.4. Statistical analysis

The sample size of 42 participants per group was based on the power to detect changes in left ventricular mass by cardiac magnetic resonance imaging [18]. Between-group comparisons were made by unpaired Student's *t*-Test, Wilcoxon rank-sum, Fisher's exact test, or chi-square analysis as appropriate. A two-tailed P-value of < 0.05 was considered significant for all analyses. Stepwise linear regression with forward selection was used to determine percent variance. SAS version 9.4 (Cary, NC, USA) was the statistical software used for these analyses. Friedman's nonparametric test for paired groups and graphs were done using GraphPad Prism 8.0 (San Diego, CA, USA).

3. Results

The kidney transplantation group included 34 participants who received a live donor kidney and five who received a deceased donor kidney (total n = 39). The dialysis group consisted of 43 participants. Table 1 provides selected characteristics of the study population that have been described elsewhere [18].

At 12 months, the eGFR in the kidney transplantation group was

Table 1
Demographic and baseline characteristics of patients in the Transplant Group (N = 39) and Dialysis Group (N = 43).

	Transplant (N = 39)	Dialysis (N = 43)
Age (y)	46.5 ± 12.4	55.5 ± 11
Gender (M/F)	27/12	31/12
Race		
Caucasian	23	11
Black	4	5
East Asian	3	11
South Asian	3	16
Others	5	9
Cause of end-stage kidney disease		
Diabetes	9	18
Hypertension	1	6
Glomerulonephritis	7	14
Polycystic kidneys	10	2
Others/unknown	8	4
Dialysis modality		
Hemodialysis	27	31
Peritoneal dialysis	12	12
Waist-Hip ratio	0.93 ± 0.09	0.94 ± 0.07
Body mass index (kg/m^2)	26 ± 4.6	26.8 ± 4.9
Systolic blood pressure (mmHg)	129.4 ± 18.1	129.9 ± 28.9
Diastolic blood pressure (mmHg)	81.2 ± 11.9	77.6 ± 12.9
Number of anti-hypertensive medications	2.3 ± 1.7	2.2 ± 1.6

Values are mean ± standard deviation.

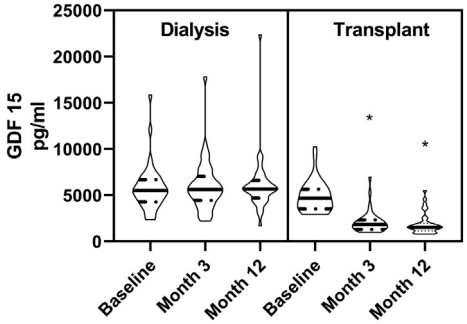

Fig. 1. Violin plots of the concentration of GDF-15 at baseline, month 3, and month 12 in for participants remaining on dialysis (n = 42) versus those receiving a renal transplant (n = 37). The solid line is the median, and dashed lines are the 25th and 75th percentiles. The frequency distribution is shown with high smoothing fit of the data. * Indicates differences between the two groups with $p < 0.0001$ for Wilcoxon rank sum analysis.

58.1 ± 15.6 ml/min/1.73m^2 (range 8.8–93). Kidney transplantation reduced serum parathyroid hormone ($p < 0.001$) and phosphate ($p < 0.0001$) and increased serum albumin concentration ($p = 0.003$), compared to the dialysis group. Hemoglobin, which was not different between groups at baseline, was increased in the kidney transplantation group at 12 months (135 ± 19.6 g/L) compared to the dialysis group (116 ± 12.4 g/L, $p = 0.0008$). Blood pressure did not change significantly post-kidney transplantation, although the number of antihypertensive medications used diminished and averaged 1.46 ± 1 (range 0–3) for the kidney transplantation group, compared to 2.05 ± 1.5 (range 0–6) for the dialysis group at month 12 ($p = 0.10$).

The serum concentration of GDF15 at baseline, month 3, and month 12 is illustrated in Fig. 1. GDF15 was not different between the groups at baseline, before transplantation, with median (25th – 75th percentile) values of 4684 (3639–5784) and 5509 (4283–6683) pg/ml, for the transplant and dialysis groups, respectively ($p = 0.07$). GDF15 was significantly lower in the kidney transplantation group compared to the dialysis group at 3 months post-transplant with a median of 1867 (1346–2520) compared to 5630 (4485–6944) ($p < 0.0001$) and at 12 months post-transplant with a median of 1560 (1182–2073) versus 5569 (4720–6616) ($p < 0.0001$). Within the kidney transplantation group, month 3 and month 12 GDF15 were significantly lower than baseline ($p < 0.0001$, Dunn's multiple comparison test).

The correlation between GDF15 and NT-proBNP at baseline and month 12 was not significant for the dialysis cohort ($\rho = 0.29$, $p = 0.06$ and $\rho = 0.30$, $p = 0.05$, respectively). The correlation was also not significant for kidney transplantation group at baseline ($\rho = 0.27$, $p = 0.1$); however, it was highly significant at month 12 ($\rho = 0.64$, $p < 0.0001$).

Baseline and month 12 serum GDF15 concentrations for the dialysis group correlated with age at onset of dialysis ($\rho = 0.38$, $p = 0.012$; $\rho = 0.47$, $p = 0.0015$, respectively). Baseline GDF15 in the kidney transplantation group also correlated with age at onset of dialysis, but this did not reach statistical significance ($\rho = 0.32$, $p = 0.062$). Month 12 GDF15 did not correlate with the age at onset of dialysis ($\rho = 0.25$, $p = 0.13$). There was a significant correlation between age at baseline, before kidney transplantation, and baseline GDF15 ($\rho = 0.46$, $p < 0.0001$) when analyzing the combined groups (n = 81). There was a significant negative correlation between month 12 eGFR and GDF15 concentration ($\rho = -0.42$, $p = 0.0081$) in subjects with kidney transplantation; these subjects also had a non-significant correlation of eGFR with NT-pro-BNP ($\rho = -0.29$, $p = 0.079$).

Linear regression analysis of the month 12 log-transformed values for GDF15 as the dependent variable, identified log NT-pro-BNP as explaining 15.3% (in the dialysis group) and 44.2% (in the kidney transplantation group) of GDF15 variance ($p = 0.006$, 0.0002, respectively), whereas age of dialysis onset contributed 15.8% of the variance in dialysis patients ($p = 0.003$) but was insignificant in the kidney transplantation group. The eGFR explained an additional 4.7% of the variance ($p = 0.085$) for the kidney transplantation group. Therefore, significant variance in GDF15 was explained mostly by NT-proBNP.

The change in actual weight between baseline and month 12 in the kidney transplantation group was 3.09 ± 8.1 kg (range -19.7 kg–22.5 kg) compared with 0.55 ± 4.3 kg (range -11.3–14.7 kg) for the dialysis group ($p = 0.04$). There was no correlation between change in either GDF15 or NT-proBNP and weight change in the dialysis group ($\rho = 0.14$, $p = 0.4$, $\rho = 0.17$, $p = 0.31$, respectively). Similarly, there was no correlation between change in GDF15 or change in NT-proBNP and weight change in the kidney transplantation group ($\rho = 0.18$, $p = 0.27$, $\rho = 0.09$, $p = 0.62$, respectively). Similar results were obtained when body mass index and change in body mass index were analyzed (data not shown).

GDF15 and hemoglobin were not correlated at baseline or month 12 for the dialysis group and not correlated at baseline for the kidney transplantation group. However, there was an inverse correlation between GDF15 and hemoglobin at month 12 for the kidney transplantation group ($\rho = -0.43$, $p = 0.0057$), which is similar to that reported by Malyszko et al. [9].

4. Discussion

The current study demonstrates for the first time the impact of improved kidney function through kidney transplantation on serum GDF15 concentrations and the relationship between GDF15 and NT-proBNP both pre- and post-kidney transplantation. We anticipated that GDF15 would be high in participants on dialysis and that kidney transplantation would reduce GDF15 in concert with reduced myocardial stretch, indicated by NT-proBNP, and improved kidney function, indicated by eGFR. The primary question addressed was the magnitude of the effect and the extent of correlation of these two factors pre- and post-kidney transplantation. GDF15 decreased post-kidney transplantation to the extent that three-quarters of kidney transplantation recipients had concentrations below 2000 pg/ml, above which there was a 5-fold increased risk for death in the ARISTOTLE trial [13]. GDF15 concentration correlated with eGFR post-transplant in the present study; however, this relationship was superseded by its correlation with NT-proBNP.

Breit et al. [5] observed that GDF15 ≥ 7500 pg/ml predicts mortality for patients on dialysis. Our cohort had 73 of 81 subjects with GDF15 < 7500 pg/ml at baseline. Johnen et al. [21] reported that GDF15 correlated with BMI in patients on dialysis. We did not detect a statistically significant relationship between GDF15 and BMI, but using the estimated correlation of 0.189 from the study of Johnen et al., the present study would have only 20% power to detect this correlation.

Many physiological and pathological processes involve GDF15. The placenta produces GDF15 as a normal phase of pregnancy [1]. GDF15 also plays a role in wound healing and feedback regulation of erythropoiesis. A large body of work demonstrates the predictive value of GDF15 in acute coronary syndrome [2]. Higher GDF15 concentrations positively associated with a worse prognosis in acute heart failure independent of NT-proBNP [22]. Cancer can result in high circulating GDF15, presumably due to expression by the tumor. GDF15 may be a factor in suppressing macrophage function as a paracrine effect and with appetite suppression and cachexia, for example, as seen in cancer [1,10,11,21].

The stress of impaired kidney function could also contribute to renal GDF15 production [23]. The human kidney produces GDF15, and the concentration of GDF15 mRNA is inversely correlated with eGFR [3]. Thus, the kidney may contribute directly, as a source of GDF15, and indirectly, through cardiac stress, to increase GDF15 concentrations. Since GDF15 did not correlate with weight either pre- or post-kidney transplantation, more detailed studies will be required to test for a relationship between GDF15 and appetite in patients pre- and post-kidney

transplantation. Thus, the present study is consistent with the literature in finding extreme elevations of GDF15 in chronic kidney disease and establishes that the magnitude of the decrease in GDF15 would be consistent with beneficial effects of lowering GDF15.

The current observational study did not permit matching of participants between the cohorts for expected confounders such as age and time on dialysis that may influence GDF15 concentrations. The range of GDF15 concentrations varied post-kidney transplantation, and so a suitably powered observational trial may be needed to demonstrate a graded relationship of cardiovascular end-points with concentrations of GDF15 and NT-proBNP. Furthermore, GDF15 acting via the GFRAL receptor, may play a role in cachexia, nausea, and vomiting [24–27], all of which are likely to resolve after kidney transplantation, raising in turn the possibility that GDF15 plays a regulatory role in both volume and lean body mass homeostasis, although we were unable to demonstrate the latter in this study. Another limitation in our current understanding of GDF15 is that no data is available about the production rates and or the contribution of the kidney to the clearance of GDF15.

Apple et al. [28] reported that the tertiles of NT-proBNP predicted mortality in patients with end-stage kidney disease. As noted by Breit et al. [5], it is possible that observational study cohorts exclude patients with severe heart failure due to survivor bias. To address this issue, for future cohort studies, it may be necessary to include pre-dialysis patients. Overall, the concentration of NT-proBNP in the context of chronic kidney disease, i.e., cardiorenal syndrome, is predictive of cardiovascular mortality [15], but generalization of specific cut-points for clinical action requires the study of larger cohorts that represent the full spectrum of patients with chronic kidney disease. However, it is reasonable to speculate that the stronger correlation of GDF15 with NT-proBNP compared to eGFR indicates that myocardial stretch is a more proximal mechanism for GDF15-associated cardiovascular morbidity and mortality than kidney dysfunction-related uremia per se.

In summary, the present study demonstrates that kidney transplantation induces beneficial intravascular volume alterations informed by changes in the serum GDF15 concentration. While GDF15 may contribute to cardiovascular risk in dialysis patients, its uniform elevation in the dialysis population suggests that measurement would not improve the classification of risk. However, the range of response of GDF15 in kidney transplantation patients provides a strong rationale to prospectively study its measurement post-kidney transplantation to evaluate cardiovascular risk stratification in populations with restored kidney function, such as kidney transplantation recipients.

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Declaration of Competing Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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