Abstract

With an increased incidence of living-donor kidney transplants, in response to increasing unmet needs for renal transplant, a clear understanding of determinants of posttransplant outcomes is essential. The importance of delayed graft function in deceased-donor kidney transplant is now part of conventional medical wisdom, due to the large amount of evidence focused on this aspect. However, the same is not true for living-donor kidney transplant, partly due to lack of evidence on this crucial clinical question and partly due to lack of awareness about this issue. The current review aims to highlight the importance of delayed graft function as a crucial determinant of outcomes in living-donor kidney transplant. An exhaustive search of online medical databases was performed with appropriate search criteria to collect evidence about delayed graft function after living-donor kidney transplant, with a special focus on studies from the Middle East. Data on incidence, impact, risk factors, and possible prevention modalities of delayed graft function in patients undergoing living-donor kidney transplant are presented. A key finding of this review is that contemporary incidence rates reported from the Middle East are comparatively higher than those reported from outside the region. Although in absolute terms the incidence is lower than deceased-donor kidney transplant, the effects of delayed graft function on graft rejection and graft and patient survival are sufficiently large to warrant the formulation of specific treatment protocols. Key to formulating prevention and treatment strategies is identifying discrete risk factors for delayed graft function. Although this evidence is scant, an overview has been provided. Further studies examining different aspects of delayed graft function incidence after living-donor kidney transplant are urgently needed to address a so far little known clinical question.

Key words: Graft survival, Incidence, Patient outcome assessment, Review

Introduction

Kidney transplant: incidence rates and causes

The need for kidney transplant has seen a sharp increase, with 112,707 individuals in the United States listed for transplant as of January 14, 2011.1 Between 2006 and 2011, there were an annual average of 10,052 deceased-donor and 6,153 living-donor kidney-only transplants in the United States.1 In contrast, in the Middle East, living-donor transplants are more common than deceased-donor kidney transplants. Of all kidney transplants performed in 2013, an estimated 83% in Saudi Arabia, 80% in Turkey, 76% in Kuwait, and 56% in Iran were from living donors.2

Kidney transplant becomes necessary due to end-stage renal disease (ESRD), which develops from a variety of causes ranging from common ones like type 2 diabetes mellitus, hypertension, and glomerulonephritis to rare causes like pinworm infections.3 Thus, kidney transplant is essentially a life-extending intervention (with a 1-year posttransplant mortality risk reduction of > 80%) in a wide variety of patients with complex clinical histories.4
Advantages of living-donor kidney transplant
Although deceased-donor kidney transplants are numerically more common than living-donor kidney transplants, the latter offer several advantages to both patients and the health care system. Living-donor kidney transplant, especially between related individuals, is likely to provide a more closely matched organ for the recipient than a deceased-donor transplant. Even altruistic, unrelated living kidney donations help in diverting existing resources to more important patient needs. Furthermore, issues surrounding kidneys from deceased donors are not likely encountered with living kidney transplants, including the proper clinical recognition of “death” (brain or cardiac), availability of clinical teams for prompt graft retrieval, and ethical issues posed by cultural sensitivities.

Delayed graft function
Definition
Although kidney transplants deliver life-saving care to patients, it is of concern that over the past 2 decades there have been no real improvements in long-term graft survival, after either living- or deceased-donor transplants. A key modulator of graft survival is delayed graft function (DGF), which is defined as the failure of the transplanted kidney to function properly in the early phase after transplant due to ischemia-reperfusion and immunological injury. “Failure” after transplant has been conventionally interpreted as the requirement of dialysis in the first week after kidney transplant; however, this approach is subjective due to variations in criteria in prescribing dialysis across institutions. Alternative criteria that have recently been used include temporally defined changes in serum creatinine levels, rate of reduction in serum creatinine levels, and urine output after transplant. However, no single criterion has been found to be superior to others in predicting outcomes after transplant; therefore, in the absence of a criterion standard, the requirement of dialysis in the first week after transplant is the most commonly used one due to its simplicity.

Incidence and impact
Despite the plurality of diagnostic criteria, the reported incidence of DGF with kidney transplant remains high irrespective of the criterion used. Between 1998 and 2011, the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients annual data report estimates an average annual rate of DGF of 21.88% for deceased-donor kidney transplants and 3.5% for living-donor kidney transplants in the United States. Similar comprehensive data from Middle Eastern countries are currently lacking; however, the rate of DGF with deceased-donor kidney transplant has been reported to be 18.6% to 20.0% in Saudi Arabia, whereas the rate with living-donor kidney transplant has been reported to be 6.3% to 18.8% in Iran. Table 1 summarizes the rates of DGF incidence in living-donor transplants reported in studies from the Middle East.

The perceived “low” rate of DGF in living-donor kidney transplant should be seen in the context of the nature of its effect after transplant. Delayed graft function may progress into more severe post-transplant events, resulting in increased morbidity rate, prolonged patient hospitalization, and increased health care costs, eventually playing an important role in both acute and chronic graft rejection. This makes the early detection and prevention of DGF incidence a major target for both physicians and healthcare systems.

Rationale of the current review
Delayed graft function is an important modulator of outcomes after living- or deceased-donor kidney transplant. While the enumeration of its incidence suggests that it occurs less often after living-donor kidney transplant, its impact is severe enough to warrant close monitoring and timely management. Specifically, in the context of living-donor kidney transplant, any negative outcomes after transplant

<table>
<thead>
<tr>
<th>Author (Year)</th>
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<tr>
<td>Montazeri et al (2011)</td>
<td>Iran</td>
<td>Double-blind randomized clinical trial in 60 transplant cases</td>
<td>14.3</td>
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<tr>
<td>Senel et al (1998)</td>
<td>Turkey</td>
<td>Observational study of 158 patients</td>
<td>8.8</td>
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<tr>
<td>Rostami et al (2013)</td>
<td>Iran</td>
<td>Randomized clinical trial with 40 adult patients with stage 4-5 chronic kidney disease</td>
<td>2.5</td>
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<tr>
<td>Kamali et al (2012)</td>
<td>Iran</td>
<td>Retrospective cohort study of 360 consecutive transplant recipients</td>
<td>6.3-18.8</td>
</tr>
<tr>
<td>Tutal et al (2012)</td>
<td>Turkey</td>
<td>Retrospective study of 80 patients</td>
<td>12.5</td>
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<tr>
<td>Ounissi et al (2013)</td>
<td>Tunisia</td>
<td>Retrospective study of 554 patients</td>
<td>6.82</td>
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not only directly affect the recipient but also may cause emotional and psychological distress in the donors. This may further act as a disincentive to people considering related or unrelated kidney donations.

Although there is sufficient data cataloguing the impact of DGF in patients undergoing deceased-donor kidney transplant, the same is not true for living-donor kidney transplants. However, available evidence clearly points to the importance of DGF as a determinant of outcomes after living-donor kidney transplant. The current review is an effort to provide an overview of the available evidence related to the incidence, effects, risk factors, and treatment of DGF in living-donor kidney transplants. We first focus on describing the effects and risk factors of DGF in these patients followed by its treatment. The review aims to initiate discussion about the importance of DGF in living-donor kidney transplant and to provide a summated view of currently available evidence. Together, these can work to be the basis of both formulating treatment protocols for DGF and indicating areas for further study, with particular emphasis on the Middle Eastern region.

**Methodology**

An extensive search was performed in databases of medical and scientific literature including, but not limited to, PubMed, CrossRef, EMBASE, and Cochrane Library, with search terms kidney transplant, delayed graft function, living donor, graft function, graft survival, graft rejection, survival rate, and other terms related to our research topic. The search identified previous randomized control trials, prospective observational studies, and retrospective case series, reflecting a balance between predesigned, coordinated studies, and real-world clinical data. Studies that showed significance in terms of sample size, location, and clinical importance were qualitatively graded before inclusion in our review. The review was aimed at presenting wide-ranging discussions on the current topic; hence, no specific data synthesis was carried out.

**Effects of delayed graft function on outcomes of living-donor kidney transplant**

Delayed graft function has a major effect on health outcomes of patients undergoing living-donor kidney transplant. For patients undergoing deceased-donor kidney transplant, these effects have been well reported, and consequently, avoiding DGF has been a focus area of treatment. Large-scale studies on DGF in living-donor kidney transplant are clearly lacking; however, the currently available studies indicate the negative effects of DGF in living-donor kidney transplant patients.

**Acute rejection, patient survival, and graft survival**

Acute rejection is a commonly seen negative outcome with DGF and is in turn associated with lower survival rates in patients experiencing DGF. Senel and associates\(^\text{17}\) reported that, of the 158 patients, more patients with DGF experienced acute rejection episodes within 1 year of transplant than did patients without DGF (43% vs 30%; \(P\) = not significant). Furthermore, the 5-year graft survival rate consequent to an acute rejection episode was lower in patients who had shown DGF than that in patients who experienced acute rejection but did not show DGF (61% vs 74%; \(P < .002\)).\(^\text{17}\) The 1-year patient and graft survival rates and 5-year patient survival rates for the DGF group were lower than those shown in patients without DGF but statistically non-significant. However, the relatively smaller number of patients who developed DGF reduced the power of the analysis and could have obscured significant cause-effect relationships. In an observational study of 93 living-donor transplant recipients, Kwon and associates\(^\text{22}\) reported the relative risk of DGF for occurrence of acute rejection to be 3.35 (\(P = .00001\)), which was reflected in the incidences of acute rejection in the DGF group (70.6%) and the non-DGF group (21.1%). The group also showed that acute rejection after DGF affected long-term graft survival, with 5-year survival rate of 100% for patients with DGF but no acute rejection, 63.6% for patients with DGF and acute rejection, 98% for patients with no DGF and no acute rejection, and 91.7% for patients with no DGF and acute rejection.\(^\text{22}\)

The negative effects of DGF in live-donor transplant recipients have also been reported in independent studies. In an observational study of 570 patients, Zeraati and associates\(^\text{8}\) showed that graft survival was worse in patients who had DGF than in those who had slow graft function or early graft function, with 6-month and 3-year graft survival rates of 74% and 93% for DGF, 96% and 70% for slow graft function, and 88% and 90% for early graft function (\(P < .001\), but no statistically
significant difference between slow graft function and early graft function). The rate of resumption of graft function does not affect long-term survival as much as a delay in function.\(^8\) In a retrospective study of graft survival that excluded patient deaths (\(n = 472\) transplant recipients), Hellinger and associates\(^23\) reported that the difference in death-censored survival rates between patients with DGF and normal graft function resulted in an adjusted hazard ratio of 6.340 (95% confidence interval [CI], 1.832-21.938; \(P = .004\)). Low graft survival in transplant recipients (\(n = 11,698\) solitary kidney transplant recipients from live and deceased donors between 2002 and 2011 from the Scientific Registry of Transplant Recipients) with DGF resulted in 35% increased likelihood of repeat transplant (adjusted odds ratio [OR] of 1.35, 95% CI, 1.18-1.54; \(P < .0001\)).\(^24\) Understanding the reason for the persistently close relation between graft survival and DGF warrants further study and a need to formulate further modalities for the optimal treatment of DGF after transplant.

In patients with DGF after living-donor kidney transplant, low graft survival and graft rejection result in higher than usual risk of death, with a degree of association shown between death and DGF.\(^25\) In a study of 44,630 adult living-donor kidney recipients (first transplants only), Narayanan and associates\(^26\) showed that the hazard ratio for the effect of DGF on risk of death with graft function decreased over time but remained significantly higher even 1 year after transplant (0-1 mo: 7.10 [95% CI, 3.48-14.46]; 1-3 mo: 3.21 [95% CI, 1.72-5.98]; 3-12 mo: 2.20 [95% CI, 1.38-3.52]; > 12 mo: 1.60 [95% CI, 1.29-1.98]). Hazard ratios for death with graft function in patients with DGF are most marked for cardiovascular disease and stroke and infection or sepsis-related deaths. The increased risk of death translates into higher actual number of patient deaths; in a retrospective study of 385 transplants from Iran, significantly more deaths occurred in patients with than without DGF, at both 1 year (7.5% vs 1.5%; \(P = .0001\)) and 5 years (14.9% vs 2.8%; \(P = .001\)) after transplant.\(^27\) In a retrospective study of 310 transplant recipients, 10-year graft survival rate was significantly lower in patients with slow graft function group and acute rejection than in patients with immediate graft function and acute rejection (64.9% vs 78.9%; \(P < .05\)).\(^28\)

### Risk factors for delayed graft function in living-donor kidney transplant

Delayed graft function may also indicate underlying causes. Therefore, in addition to the timely treatment of DGF after transplant, recognizing patients who are at higher risk of DGF for suitable interventions is also warranted. In patients undergoing kidney transplant, it may be more prudent to identify high-risk individuals for focused treatment than to institute new protocols for pre-empting DGF risk in all patients, thereby increasing treatment complexity. Several risk factors, both demographic and clinical, have been indicated to be associated with the risk for DGF incidence after living-donor kidney transplant.

#### Age and sex

Donor age and sex are common demographic factors whose association with DGF after transplant has been well discussed in the literature. The association between donor age and chronic graft dysfunction is already known\(^29\); however, donor age is also associated with initial DGF.\(^30\) In a multivariate analysis performed on data from 211 patients who had undergone living-donor kidney transplant, age was one of the 2 significant parameters to predict recipient glomerular filtration rate (GFR) after transplant (\(P = .025\)). When incorporated into a predictive model for posttransplant GFR, donor age along with the other predictive factor (kidney volume) was highly accurate in predicting observed recipient GFR.\(^31\) In a retrospective observational study of 310 patients, recipients and donors of transplants that resulted in slow graft function were older than those of transplants that resulted in early graft function (\(P < .05\) for each group).\(^28\) In another retrospective study (\(n = 117\)), grafts from donors \(\geq 60\) years old have been shown to have a numerically higher, though not significant, incidence of DGF than grafts from donors younger than 60 years old (4.3% vs 2.1%; \(P > .05\)).\(^32\) However, the evidence must be seen in the context of the relatively small number of patients (\(n = 23\)) who were older than 60 years of age in this analysis. Thus, although the higher incidence of DGF with increased age has been shown, the role of age in determining DGF incidence must be investigated further.

Donor age as a potential determinant of DGF is also available from other evidence in patients with living-donor kidney transplant. Although telomere length, a marker for biologic age of a tissue, in itself
is not associated with DGF risk after transplant, recipient age and incidence of DGF have been reported to be associated with the risk of developing transplant renal artery stenosis. Thus, available evidence points to the important role of age in living-donor kidney transplant, but clear indications of its significance requires further study.

Previous studies have also remarked on the high proportion of women who experience DGF after transplant; however, a clear indication of such a trend through a large-scale study designed for a multivariate analysis has not been obtained. In a study by Senel and associates, eleven of the 14 patients who developed DGF after living-donor kidney transplant were women. In patients undergoing living-donor kidney transplant, gender-related differences in renal mass supply and metabolic demand are well known and may possibly hold the clue for explaining the higher incidence of DGF in women. However, the association between gender and incidence of DGF is unclear and needs further elucidation.

**Body mass index**

Other demographic characteristics that have been investigated for possible association with the incidence of DGF are body weight and body mass index (BMI). An analysis of epidemiologic data from the Scientific Registry of Transplant Recipients indicated that, in patients who had undergone kidney transplant, an incrementally higher risk of DGF was associated with patients who were overweight or obese before transplant. Higher donor BMI was also associated with slower recovery of graft function in living-donor kidney transplant recipients. Similarly, higher recipient BMI is known to affect graft function in terms of higher incidence of DGF. The key to understanding such an effect of BMI on graft function after transplant may lie in treating it as an issue of the relationship between renal allograft weight to BMI and GFR. Amante and associates suggested that grafting a relatively smaller living-donor kidney into a heavy recipient may be a risk factor for allograft failure and that a minimum renal allograft weight-to-recipient body weight ratio of 8.2 or more predicted a good GFR after transplant. In a retrospective observational study of 310 patients, the donor-to-recipient BMI ratio was lower in the patient group with slow graft function than in the group with immediate graft function.

**Inflammatory markers**

The resumption of renal function in grafts after transplant depends on its integration with the host with minimal immunologic challenge. Consequently, inflammatory markers serve as useful tools in evaluating the risk of DGF after transplant. Incidence of DGF is significantly associated with levels of urinary inflammatory biomarker, namely, neutrophil gelatinase-associated lipocalin on posttransplant day 1 and interleukin-18 on posttransplant day 3. Higher immunogenicity of kidneys from older donors versus young donors resulted in functional deterioration after living-donor kidney transplant. Markers of higher immunologic response, such as elevated preoperative neutrophil-to-leukocyte ratio in recipients, potentially increase the risk of DGF incidence, especially in patients who receive grafts from living donors.

**Type 2 diabetes mellitus**

Type 2 diabetes mellitus is a common underlying cause of end-stage renal disease and is known to be associated with a long-term negative effect on renal function and thus can be expected to have a long-term effect on graft function. Studies have shown that type 2 diabetes mellitus is a major determinant of DGF soon after living-donor kidney transplant. More patients with DGF have type 2 diabetes mellitus as a cause of their renal disease than those with good early graft function (45% vs 16%, in a retrospective study 470 patients). Risk of poor early graft function is significantly higher in recipients with renal disease from type 2 diabetes mellitus than those with other causes (OR of 2.44, 95% CI, 1.39-4.29; \( P = .0019 \)). In a retrospective study of 25,523 transplant pairs, univariate analysis showed that recipients with type 2 diabetes mellitus of living-donor grafts have increased risk of DGF (OR of 1.32, 95% CI, 1.23-1.42; \( P < .01 \)).
Ischemia time
Cold ischemia time after graft retrieval and warm ischemia time before transplant are important risk factors for DGF in living-donor kidney transplant. In a retrospective cohort study of 231565 recipients who underwent renal transplant between January 1990 and September 2005, Simpkins and associates\textsuperscript{50} reported that the probability of DGF increases with longer duration of cold ischemia time. The adjusted probabilities of DGF were 4.9% with cold ischemia duration of 2 to 4 hours (95% CI, 4.3%-5.8%), 8.3% with 4 to 6 hours (95% CI, 6.1%-11.2%), and 9.2% with 6 to 8 hours (95% CI, 4.1%-19.1%). Patients whose grafts had undergone 4 to 6 hours of cold ischemia were significantly more likely to experience DGF than those with the 0 to 2 hours of cold ischemia ($P < .001$).\textsuperscript{50} Longer duration of cold ischemia is also associated with acute rejection and death-censored renal graft rejection after DGF. Each hour of cold ischemia was reported to aggravate the risk of acute rejection by 4% in a retrospective cohort of 611 transplant patients.\textsuperscript{51}

Helleginger and associates\textsuperscript{52} demonstrated that prolonged warm ischemic time is a significant risk factor for poor early graft function in 472 transplant patients, where the adjusted OR was 4.252 (95% CI, 1.914-9.447). Furthermore, laparoscopic procurement, overweight recipient, right donor kidney, and multiple renal arteries are shown to be significantly associated with prolonged warm ischemic time by multivariate analysis.\textsuperscript{52} In a study that included 469 patients, Brennan and associates\textsuperscript{48} reported that the mean warm ischemia time was higher in patients with slow graft function or DGF versus patients with early graft function.

Vascular anastomosis time
Few data exist on the exact nature of the effects of vascular anastomosis time on DGF after living-donor kidney transplant. In a retrospective cohort of 298 deceased-donor kidney transplants, anastomosis time was independently associated with DGF (OR of 1.037 /min, 95% CI, 1.016-1.057; $P = .001$). A 3.5-fold higher risk of DGF (OR of 3.5, 95% CI, 1.6-7.3; $P = .001$) was seen for an anastomosis time greater than 29 minutes.\textsuperscript{53} Although there is no direct evidence indicating an association between DGF after living-donor kidney transplant and anastomosis time, multiple allografts with more than 2 arteries have been reported to be associated with increased DGF and renal artery stenosis.\textsuperscript{15}

Relatedness, human leukocyte antigen matching, and ABO compatibility
The relatedness between donor and recipient is known to affect the survival of a wide variety of graft types. Related living-donor kidney transplants are known to have a higher rate of early graft function and lower rate of slow graft function than unrelated living-donor transplants.\textsuperscript{28} In a retrospective analysis of 322 living-donor kidney transplants, the mean estimated GFR was lower in unrelated than in related living kidney donors (49 ± 14 vs 59 ± 29 mL/min/1.73 m²; $P = .032$).\textsuperscript{54} Acute rejection-free survival ($P = .018$) and graft survival ($P = .025$) have been reported to be lower for unrelated living-donor transplants than for related living-donor transplants in a retrospective study of 779 kidney transplant recipients.\textsuperscript{55} In addition, the mean estimated GFR was lower for unrelated kidney transplants than for related kidney transplants. Unrelated living-donor kidney transplants also showed higher rates of total human leukocyte antigen (HLA) and HLA-DR mismatches.

Human leukocyte antigen and blood type incompatibility are barriers of considerable importance that hinder live donation. Simulation modeling has demonstrated that, of the patients who enter the system annually, between 2500 and 4000 have an antibody-mediated incompatibility with their solitary living donor.\textsuperscript{50} In living-donor kidney transplant, the additive effects of anti-HLA antibodies have been estimated to explain up to a 27% decrease in the mean estimated GFR.\textsuperscript{56} Brennan and associates demonstrated that greater than 3 HLA mismatches were associated with a trend for poor early graft function (OR of 1.65; $P = .067$). The study showed a significant association between transplants with greater than 3 HLA mismatches (OR of 2.16, 95% CI, 1.41-3.29; $P = .0004$) or those involving an unrelated donor-recipient pair (OR of 1.95, 95% CI, 1.29-2.96; $P = .0016$) with an approximately two times higher likelihood to experience rejection.\textsuperscript{48}

Another important antibody-based determinant of DGF is ABO blood group incompatibility. The cumulative incidence of graft loss is higher among ABO incompatible recipients (5.9%, 10.4%, 17.4%, and 27.1% at 1, 3, 5, and 10 years) than ABO compatible matched controls (2.9%, 6.4%, 11.0%, and 23.9%) ($P = .001$).\textsuperscript{57} A statistically significant association was seen between higher HLA and ABO compatibility on one hand and immediate graft function on the other
in a retrospective review of 442 renal transplant patients.\textsuperscript{58} Thus, judicious selection of donor-recipient pairs and optimizing the need for graft with donor-recipient compatibility is an important step in reducing the negative effect associated with DGF.

**Other risk factors**

Several other risk factors for DGF after living-donor kidney transplant have been reported in the literature. Ozdemir and associates\textsuperscript{59} reported that the risk for DGF is greater when pretransplant systolic blood pressure level is less than 120 mm Hg.\textsuperscript{59} Chang and associates indicated that DGF or slow graft function after transplant is independently correlated with higher donor phosphorus levels.\textsuperscript{60} Clinical issues like the duration between radiologic renal observation and transplant also modulate the risk of DGF incidence. Tutal and associates reported that DGF was observed in a greater number of patients undergoing early transplant (≤ 20 d; n = 42) than late transplant (≥ 20 d; n = 38) after renal angiography (22.0% vs 2.6%; \(P = .009\)).\textsuperscript{20} Important interventional issues that affect the risk of DGF incidence are the mode of donor nephrectomy and the duration of warm ischemic time in living-donor transplant. A Cochrane database review showed that open donor nephrectomy is associated with a higher risk of DGF than laparoscopic donor nephrectomy (relative risk of 1.09, 95% CI, 0.52-2.30).\textsuperscript{61}

Interestingly, results of kidney transplant between unrelated individuals in Western countries indicate that immunologic factors such as HLA matching, ABO incompatibility,\textsuperscript{62} and longer cold ischemia time using advanced technology such as hypothermic machine perfusion\textsuperscript{63} have minimal effect on DGF. Therefore, further studies are certainly warranted to investigate the effect of these factors on DGF from a Middle Eastern perspective to ensure high success rate in terms of graft function. In addition, it is also important to identify differences in treatment practices between countries where DGF is a rare occurrence and those where it is more common. Table 2 summarizes the studies reporting the risk factors associated with the incidence of DGF in living-donor kidney transplants.\textsuperscript{11,17,31,32,33,38,41,44,46,48,52,54,58,64,65}

**Treating risks associated with DGF**

Given the paucity of data about the effects of and the risk factors for DGF in living-donor kidney transplant, studies that focus on treating these risk factors are also limited. However, given the effects of DGF after living-donor kidney transplant, strategies to minimize or prevent the risk of DGF are needed. In kidney transplant, careful matching of donor and recipient characteristics has been suggested to have an effect on DGF after transplant. Because living-donor transplants are not dictated by the exigencies of immediate organ availability, these transplants are better suited for donor-recipient matching. Age- and gender-matched donor-recipient pairs are less likely to display DGF after transplant.\textsuperscript{11} Another important factor that facilitates the reduction of DGF risk is matching patients with respect to graft volume in relation to recipient body weight. Transplants with higher graft weight-to-donor body weight ratio (> 4.5) show better graft function after living-donor kidney transplant than those with lower ratios (< 3.0).\textsuperscript{66}

In addition to screening donors and recipients to establish the right match, clinical interventions can also help to reduce DGF risk after living-donor kidney transplant. Few interventional approaches have been tested in randomized control trials to minimize the risk of DGF after living-donor kidney transplant. In a randomized controlled study from the Middle East that compared graft outcome of laparoscopic donor nephrectomy with open donor nephrectomy, laparoscopic donor nephrectomy was not only associated with greater donor satisfaction and less morbidity\textsuperscript{67} but also with a 5% (89.5% vs 84.3%) better graft survival in a 5-year follow-up.\textsuperscript{68} Similar results were observed in other studies where laparoscopic donor nephrectomy was associated with better 5-year death-censored graft survival,\textsuperscript{69} reduction in parenteral morphine requirement (\(P = .001\)), shorter hospital stay (\(P = .001\)), and earlier return to employment (\(P = .004\)) favoring laparoscopic donor nephrectomy.\textsuperscript{70} Warm ischemic time is a determinant of DGF after living-donor kidney transplant, and it is sought to be counteracted using both — donor interventions like donor hyperoxia and recipient interventions like ischemic preconditioning. Modest improvements in DGF incidence rates have been reported in trials that used donor hyperoxia to address DGF.\textsuperscript{16,19} Similarly, ischemic preconditioning has been shown to be useful in managing DGF in deceased-donor kidney transplant, but the results have not been replicated in living-donor kidney transplants. In a randomized control trial, Chen and associates reported that patients who undergo living-
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<th>Indicative Statistical Index</th>
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<tr>
<td>Age</td>
<td>Srithongkul et al</td>
<td>211 living-donor kidney transplant recipients without delayed or slow graft function</td>
<td>Correlation coefficient = 0.5; P = .025</td>
<td>Correlation between donor age and GFR after transplant</td>
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<td>Lan et al (2012)52</td>
<td>Older donor group (age ≥ 60 y, n = 23) and younger donor group (age &lt; 60 y, n = 94)</td>
<td>Delayed graft function of older group 4.3% vs younger group 2.1%; P &gt; .05</td>
<td>Small size of older donor group limited interpretation of statistical significance</td>
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<td>Sapir-Pichhadze et al (2013)54</td>
<td>Scientific Registry of Transplant Recipients (2000-2009, n = 49,589)</td>
<td>1.87-fold increase in adjusted odds of DGF in oldest vs youngest groups</td>
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<td>Abreu et al (2004)51</td>
<td>100 consecutive laparoscopic living-donor nephrectomies</td>
<td>Female vs male transplant and higher need for dialysis: P = .005 Failure to achieve serum creatinine level &gt; 2.5 mg/dL by postoperative day 5: P = .007</td>
<td>No multivariate analysis performed; risk for different definitions of DGF obtained</td>
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<td></td>
<td>Senel et al (1998)57</td>
<td>158 consecutive related living-donor kidney transplant recipients</td>
<td>DGF group: most donors were female (1/14); sex difference significant in DGF group: P &lt; .02</td>
<td>No test of significance for association between sex and DGF incidence</td>
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<td>Donor BMI</td>
<td>Heimbach et al (2005)66</td>
<td>553 consecutive hand-assisted laparoscopic living-donor kidney donations</td>
<td>No differences in renal function based on donor BMI</td>
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<td>Recipient BMI</td>
<td>Abreu et al (2004)51</td>
<td>100 consecutive laparoscopic living-donor nephrectomies</td>
<td>Mean BMI associated with higher need for dialysis: P = .08 Failure to achieve serum creatinine level &gt; 2.5 mg/dL by postoperative day 5: P = .05</td>
<td>No multivariate analysis performed; risk for different definitions of DGF obtained</td>
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<td>Graft volume-to-recipient weight</td>
<td>Akoglu et al (2013)58</td>
<td>69 living donors</td>
<td>Recipient GFR positively correlated with volume-to-weight ratio (r = 0.49, P &lt; .001)</td>
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<td></td>
<td>Lee et al (2011)51</td>
<td>94 living-donor kidney transplants</td>
<td>Graft volume-to-recipient body surface ratio correlated with GFR at 1 and 6 mo (r = 0.416, P &lt; .001 and r = 0.361, P &lt; .001)</td>
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<td>Inflammatory markers</td>
<td>Salamzadeh et al (2012)64</td>
<td>Observational cohort study of patients undergoing living-donor renal transplant</td>
<td>DGF incidence associated with NGAL level of NGAL 1st day, level of IL-18 on the 3rd day Multivariat logistic regression analysis: differences between the 1st and 3rd day of urinary NGAL levels significant</td>
<td>Sample of both living and deceased donors; greater association in living donors</td>
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<td></td>
<td>Halazon et al (2013)46</td>
<td>398 kidney transplant recipients; 88 living donors</td>
<td>Multivariate analysis: neutrophil-to-lymphocyte ratio (HR = 10.673, 95% CI, 6.151-18.518; P &lt; .0001), greater effect in living donors</td>
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<tr>
<td>Type 2 diabetes mellitus</td>
<td>Brennan et al (2004)46</td>
<td>469 living-donor kidney transplants</td>
<td>Diabetic cause (OR of 2.22; P = .021) independently associated with poor EGF</td>
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<tr>
<td>Warm ischemia time</td>
<td>Hellegering et al (2012)52</td>
<td>472 consecutive living-donor kidney transplants</td>
<td>Prolonged warm ischemia time associated with poor EGF (OR of 4.252, 95% CI, 1.914-9.447)</td>
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<td></td>
<td>Brennan et al (2004)46</td>
<td>469 living-donor kidney transplants</td>
<td>Warm ischemia time (OR of 1.05/min increment; P = .0025) associated with poor EGF</td>
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<td>Donor-recipient relatedness</td>
<td>Ahmed et al (2008)54</td>
<td>322 living-donor kidney transplants</td>
<td>GFR lower: unrelated vs related (49 ± 1.4 versus 59 ± 2.9 mL/min/1.73 m²; P = .032)</td>
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<td>HLA mismatch</td>
<td>Brennan et al (2004)46</td>
<td>469 living-donor kidney transplants</td>
<td>&gt; 3 HLA mismatches (OR of 2.16, 95% CI, 1.41–3.29; P = .0004)</td>
<td>&gt; 3 HLA mismatches have &gt; 2 times higher likelihood of rejection</td>
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<tr>
<td>ABO incompatibility</td>
<td>Sierko et al (2003)58</td>
<td>Retrospective review of 442 renal transplants</td>
<td>Significant association between HLA and ABO compatibility and renal function</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index; CI, confidence interval; DGF, delayed graft function; EGF, early graft function; GFR, glomerular filtration rate; HLA, human leukocyte antigen; HR, hazard ratio; IL-18, interleukin 18; NGAL, neutrophil gelatinase-associated lipocalin; OR, odds ratio
donor renal transplant fail to show improvement in early renal function after remote ischemic preconditioning. Furthermore, no deleterious effect of warm ischemia time of up to 17 minutes has been found on graft survival, although DGF due to other reasons can decrease graft survival, seen more with open donor nephrectomy possibly by renal artery spasm, which may occur more often with open donor nephrectomies.

Immunologic factors play a crucial role in determining graft function after transplant; therefore, immunomodulation has been used extensively to improve renal function posttransplant. Immunosuppression with thymoglobulin has shown promise in studies of patients undergoing living-donor kidney transplant. Thymoglobulin has been shown to have zero incidence of DGF in 214 living-donor transplant recipients in one single-center retrospective study. Follow-up treatment with other immunomodulatory agents such as tacrolimus for maintenance of immunosuppression has also yielded positive results. Currently, a variety of agents targeting different risk factors of DGF after renal transplant are being tested in phase I and phase II trials. Important interventions currently under investigation include vasodilators (calcium channel blockers, adenosine A1 receptor antagonists) and anti-inflammatory agents (recombinant P-selectin glycoprotein ligand IgG fusion protein, recombinant human annexin B, C-X-C chemokine receptor inhibitors). However, their specific application in living-donor kidney transplant cases is hindered by lack of studies in that context.

Conclusions

This review of the literature shows that a high burden of DGF has been reported by studies from the Middle East. The magnitude of DGF incidence in the region is higher than ranges reported from other parts of the world, resulting in a substantial clinical effect.

Conventionally, the perception that DGF is predominantly associated with deceased-donor kidney transplant has hindered focused studies on DGF in living-donor kidney transplant. There is a considerable, if only numerically lower, burden of DGF incidence in living-donor kidney transplant recipients. However, there is a perceptible lack of evidence from large well-conducted studies from the Middle East about the epidemiologic, clinical, and pathologic aspects of DGF in living-donor kidney transplant.

Available evidence clearly shows that DGF is associated with significantly higher rates of acute rejection and patient mortality and lower rates of graft survival. Risk factors for DGF in living-donor kidney transplant recipients have not yet been clearly identified, but this is an area of active research. Age, sex, body mass index, graft volume in relation to recipient body weight, and inflammatory markers are some of the important risk factors for DGF incidence in living-donor transplant. The identification of urinary inflammatory markers as risk factors for DGF incidence has greatly enhanced the ability to respond with necessary treatment. However, the exact nature of association of these risk factors with DGF has rarely been reported in recipients of living-donor kidney transplant.

Careful matching of donor with recipient, appropriate interventional approaches, and novel pharmacologic agents for living-donor kidney transplant recipients will enhance the health care professional’s ability to effectively take care of the risk of DGF. Further studies on the risk of DGF will allow appropriate strategies to be formulated to minimize its risk and optimize the benefits of living-donor kidney transplant. Minimizing the risks associated with negative outcomes after living-donor kidney transplant will not only improve the outcomes of recipients but will also act as an incentive for altruistic living donation of kidneys.

References


