

# Impact of Cold Ischemia Time on Outcome of Deceased Kidney Transplantation

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Kidney transplantation is the preferred treatment for patients requiring the renal replacement therapy, and kidneys from deceased donors are a major source for it. Deceased-donor kidney transplants (DDKT) is usually accompanied with the immediate renal ischemic injury due to cold ischemia time (CIT) that often results in reduced deceased-donor allograft function and survival.<sup>1</sup> Prolonged CIT is also a considerable predictor of long-term graft loss.

Organ procurement at the national level often lengthens the CIT that is a risk factor for delay deceased-donor allograft function and early graft loss.<sup>2,3</sup> In addition, prolonged CIT is an important risk factor for the development of delayed graft function (DGF) and acute rejections that are significant determinants of short- and long-term graft survival.<sup>2,3</sup> Cold ischemia time is an unchanged parameter over the years, which is relevant to the kidneys from deceased donors, can lead to higher rates of the chronic allograft loss.<sup>4</sup> Salahudeen and coworkers studied 6465 kidney transplant patients using the United Network for Organ Sharing data and concluded that prolonged CIT is a strong risk factor for DGF and a significant predictor of short- and long-term graft loss in univariable and multivariable analyses.<sup>4</sup> Deceased-donor kidney allografts have shorter survival rates than those living-donor kidneys.<sup>5</sup> In a Mexican population, exposure of renal grafting to prolonged CIT is a risk factor for acute rejection.<sup>6</sup> Brain death and prolonged CIT, unique donor factors related to deceased donors, are major contributors to the poorer long-term outcome of DDKT.<sup>4</sup> Longer duration of CIT and DGF have also correlated with increased serum creatinine at 1 year after transplantation.<sup>7</sup> Moreover, Johnston and colleagues showed that

CIT has an important influence on the outcomes of extended-criteria donor transplantation.<sup>8</sup> Allografts exposed to prolonged cold preservation are mainly a cause of early kidney transplant dysfunction due to ischemic damage.<sup>9</sup> In a study on 6322 recipients from deceased donors, longer CIT was an independent risk factor for DGF and decreased graft survival in the Netherlands when adjusted for other potential risk factors.<sup>10</sup> In a series of 2525 DDKTs, the mean CIT was 17 hours and prolonged duration of CIT led to allograft kidney damage and contributed to a considerable reduction in both patient and graft survival rates.<sup>11</sup>

Kidney transplantation in Iran is mainly performed from living donors.<sup>12,13</sup> Although living-donor kidney transplantation offers better short- and long-term survival rates among the recipients compared to an allograft procured from a deceased donor,<sup>13</sup> deceased donation still offers an additional comparable source of allografts for patients requiring renal replacement therapy. Therefore, efforts have been made to extend the use of kidneys from deceased donors as an important source for transplantation, throughout the country.<sup>13</sup> Fortunately, DDKT has also increased from less than 1% of all kidney transplants in 2000 to 13% in 2006.<sup>12</sup>

Despite the fact that organ procurement from deceased donors in Iran is organized and managed centrally by the Ministry of Health,<sup>12</sup> sharing of deceased kidneys is now achieved at a local level and often shortens the CIT period. In a series of 180 Iranian kidney transplants, multivariable regression analysis failed to show the impact of CIT on the risk of developing DGF,<sup>14</sup> although CIT is a known risk factor for DGF and worsens transplant outcome.<sup>15</sup> It is partly due to reducing

prolonged CIT by regional distribution of organs in the Iranian organ procurement system. Furthermore, Mahdavi and colleagues<sup>16</sup> have also reported a good short-term outcome of DDKT from Mashhad, Iran. Since our organ procurement in Iran is local, CIT in the patients is short, which may be the key to better graft survival.

In the current issue of the *Iranian Journal of Kidney Disease*, Fattahi and colleagues<sup>17</sup> report a favorable short-term outcome for DDKT in their patients. It is of interest that the CIT was relatively short with the mean of  $190 \pm 50$  minutes (range, 1.5 to 4.7 hours).<sup>17</sup> Acute tubular necrosis was the only risk factor for worsening allograft outcome.<sup>17</sup> This study showed a marked improvement in the short-term graft and patient survivals of recipients using kidneys from deceased-donors.<sup>17</sup> They concluded that although DDKT has lately started in Iran, its annual number has steadily increased with promising results.

The adverse effect of CIT may be related to tubular cell death in the kidney.<sup>18</sup> Apoptosis is one of the major mechanisms leading to ischemic renal allograft injury during DDKT. Both human and animal studies indicate that apoptosis has been found to be a feature of the adverse effect of CIT.<sup>18</sup> Castaneda and coworkers<sup>19</sup> showed that human DDKT has considerably more apoptosis than living-donor kidney transplantation. The extent of apoptosis correlates with the duration of CIT and is associated with increased expression of B-cell lymphoma 2 protein within apoptotic cells.<sup>19</sup> Expression of genes involved in apoptosis is more pronounced in grafts from deceased donors. Prolonged CIT is associated with increased expressions of B-cell lymphoma 2 protein, tumor protein p53, and caspase-3. Caspase-3 and tumor protein p53 expressions are also significantly higher in kidneys with DGF.<sup>20</sup> It should be noted that caspase-3 is a major mediator of apoptotic cell death,<sup>18</sup> and a longer CIT is associated with elevation of caspase-3 activity.<sup>21</sup>

Solini and associates, in a recent study on fully major histocompatibility complex-mismatched rat model of kidney allotransplantation, demonstrated that longer CIT is associated with anticipation of proteinuria onset and graft function deterioration, more severe tubular atrophy, interstitial fibrosis, and glomerulosclerosis, and increased mortality rate. They concluded that longer CIT has an

important pathogenetic role in chronic allograft injury development by triggering acceleration of cellular and humoral reactions of chronic rejection.<sup>22</sup> In addition, prolonged CIT is associated with amplified arterial stiffness.<sup>23</sup>

In conclusion, prolonged CIT affects short- and long-term graft outcomes; thus, every effort should be made to minimize CIT in renal transplantation using deceased kidneys. Reducing prolonged CIT should be considered as a main target in regional distribution of organ in Iran for kidney transplantation, the key to better graft survival. Providing quicker access to the operating room may lead to further reduction CIT. Finally, limiting CIT may reduce the persistent high rate of long-term loss of deceased kidney allografts.

#### CONFLICT OF INTEREST

None declared.

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## Bone and Mineral Disorders After Kidney Transplantation

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Disturbances in bone and mineral metabolism are common in patients undergoing hemodialysis and often continue after successful kidney transplantation.<sup>1,2</sup> Vitamin D deficiency following kidney transplantation is a common problem and is usually due to a high prevalence of vitamin D deficiency at the time of transplantation, avoiding direct sun exposure because of the high risk of skin cancer due to immunosuppressive therapy, inadequate dietary calcium and vitamin D intakes, insufficient graft functioning, and side effects of drugs using after kidney transplantation.<sup>3-5</sup> In the current issue of the *Iranian Journal of Kidney Diseases*, Savaj and Ghods<sup>6</sup> revealed that vitamin D deficiency was a common complication among

kidney transplant patients (45%), which matches with the results reported by Stavroulopoulos and coworkers who found a 46% prevalence of hypovitaminosis D in long-term among kidney transplant recipients.<sup>7</sup> In one study, low 1,25-dihydroxyvitamin D3 levels persisted up to 18 months after kidney transplantation.<sup>1</sup> In a series of 61 kidney recipients, low levels of 1,25-dihydroxyvitamin D3 were reported in 48% of patients 6 months following kidney transplantation.<sup>8</sup> Querings and colleagues showed a significantly lower serum 25-hydroxyvitamin D3 levels in kidney transplant recipients when compared to a control group.<sup>9</sup> In addition, vitamin D deficiency was more likely to occur in recipients with higher