Clinical Kidney Journal

Clinical Kidney Journal, 2024, vol. 17, no. 3, sfad242

https://doi.org/10.1093/ckj/sfad242
Advance Access Publication Date: 12 March 2024
Editorial Comment

EDITORIAL COMMENT

Continuous surveillance for kidney transplant rejection: ready for clinical trials?

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There is a clear medical need for the continuous, cheap and reliable monitoring of the alloimmune response in kidney transplants. The test characteristics and limitations of currently available plasma and urine biomarkers and/or sequential surveillance biopsies have been recently discussed in a controversies format in the September 2023 issue of *Kidney International* [1, 2]. The complexity of alloimmune events can be appreciated by the continuous refinement of the Banff criteria for allograft pathology, especially for antibody mediated rejection (AMR), which requires kidney biopsies [3]. Although this procedure is usually performed in an outpatient setting and can be considered the golden diagnostic standard, it is invasive and cannot be repeated too often without a clear indication. Thus, an online monitoring device/tool that may guide the clinician's propensity to take a biopsy even before the established eGFR marker serum creatinine is rising would therefore be highly appreciated.

The rate of acute T-cell mediated rejection (TCMR) is nowadays below 10% in most transplant centers and occurs usually in the first months after engraftment but is also a risk factor for subsequent TCMRs and premature graft loss in the modern era [4]. Exceptions are cases where patients are non-adhering to their maintenance immunosuppressive medication at later timepoints after transplantation. A hallmark of TCMR is inflammation, defined as the infiltration of immune cells into the transplant kidney. As the first of the five well described cardinal symptoms/signs of inflammation (calor, dolor, rubor, tumor, and functio laesa) is heat, and inflamed sites exhibit an increased blood flow, it is appealing to use an online temperature probe at the surface of the transplant kidney as surveillance 'immunometer'. This is exactly what the researchers from Chicago recently investigated in a rat model of allogenic (MHC mismatched) and isogenic (MHC identical) kidney transplantation (Fig. 1) [5]. A minuscule thermo sensor was placed on the surface of the transplanted kidneys. A small transmitter unit was placed in the cavum peritonei of the rats. The readouts of the sensor were continuous temperature in °C as proxy for the severity of inflammation and thermal conductivity in W/mK as proxy for blood flow. Thermal conductivity can be defined as the rate at which heat is transferred by conduction through tissue, i.e. increased blood flow leads to an increase in conductivity.

Short-term variability of kidney temperature by about ±1°C was observed in all animals and could be attributed to motion activity of the animal. The investigators were able to show a disruption of the circadian cycle in the rejecting allotransplant model and a rise in kidney temperature by more than 1°C from an average of 37.5°C but with individual variability in the allograft setting that preceded an increase in serum creatinine by 2 to 3 weeks. In the experiments where the tacrolimus-based immunosuppression was discontinued, the kidney temperature increased 3 days before a rise in creatinine, respectively (Fig. 2). Thermal conductivity was not changed in the transplant experiments, but six days after unilateral nephrectomy it almost doubled from 0.33 to 0.64 W/mK in the remaining kidney, which fits well with the increased blood flow to the now single kidney. For comparison, water has a thermal conductivity of 0.5 W/mK, an insulation material $<$0.06 W/mK and an excellent thermal conductor such as silicon nitride $>$100 W/mK.

Late-stage graft rejection at around six days after withdrawal of immunosuppression led to a kidney temperature drop by about 3°C on median. This likely reflects fibrosis/scarring around the thermal probe area and the lack of food and water intake of the sick animal.

Based on these exiting data, the authors concluded that this biophysical approach may be useful for real-time monitoring

Received: 15.9.2023; Editorial decision: 16.9.2023

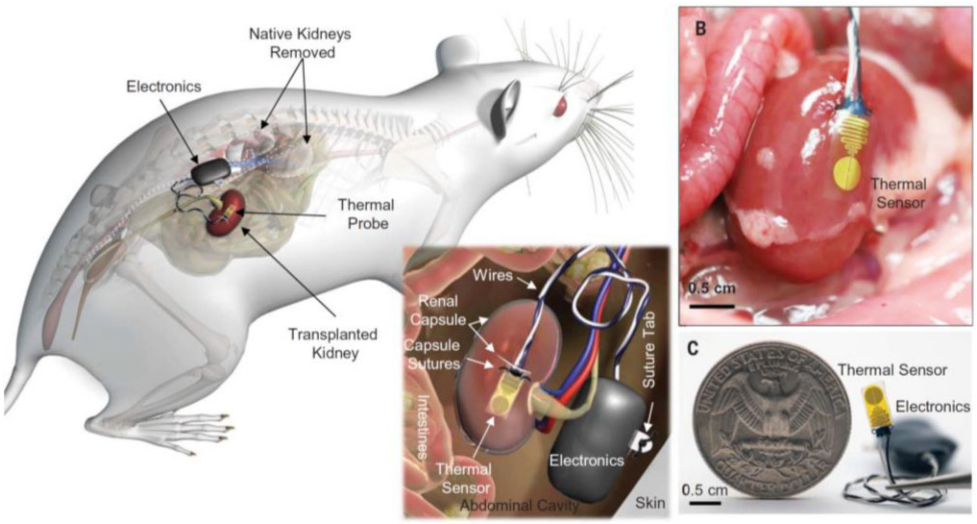

Figure 1: Schematic drawing of the implantation site and size comparisons of the kidney thermo-sensor and transducer in a rat kidney allograft model. Reprinted with permission from Madhvapathy *et al.* [5].

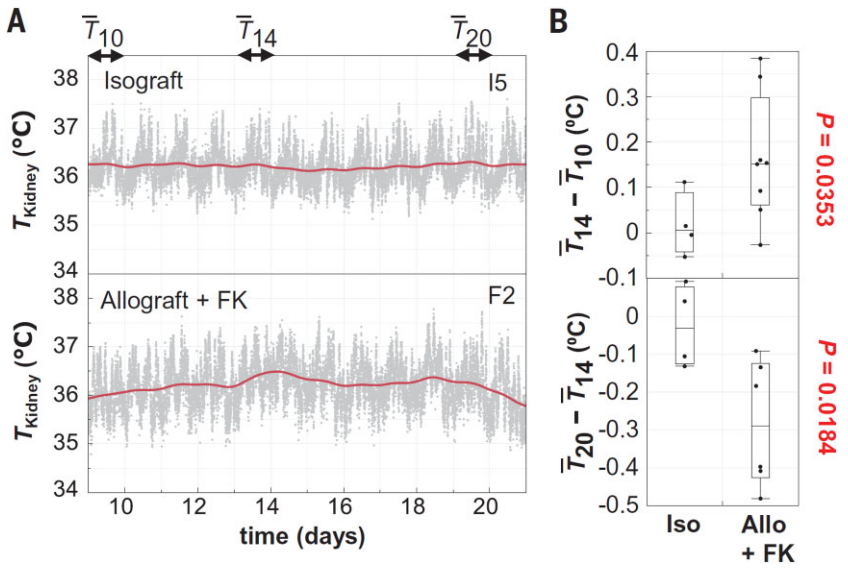

Figure 2: Temperature course after iso- and allogenic rat kidney transplantation. Allograft recipients received tacrolimus (FK) as immunosuppressive therapy and rejected after three weeks (<21 days). Abnormal temperature variation was observed throughout the follow-up of the allograft recipients. The temperature sensor uncovered ultradian rhythms, disruption of the circadian cycle, and a rise in kidney temperature as early as day 14, which precedes a rise in serum creatinine by two weeks. The end-stage rejection stage at three weeks is renal fibrosis, which caused a drop in kidney allograft temperature (reproduced with permission from Madhvapathy SR *et al.*, *Science* **381**, 1105, 2023).

and early detection of subclinical acute kidney transplant rejection, i.e. before a rise in serum creatinine occurs.

The described approach of real-time monitoring of kidney allograft inflammation/rejection has many advantages. It is cheap, robust, provides a continuous quantitative readout and after initial implantation is non-invasive. From that point it is an optimal surveillance tool for kidney inflammation. There are clearly some limitations as acute TCMR accounts only for a small fraction of intrinsic allograft pathologies and subsequent graft loss [6]. It remains to be determined if other prevalent causes and processes of initial subclinical graft dysfunction such as AMR, urinary tract infections, polyomavirus-associated nephropathy, calcineurin inhibitor toxicity, and recurrent disease provide sufficient signals via the thermo-sensor to increase the pre-test probability for a biopsy. Even if that would not be the case, such a sensor would add valuable information to the current discontinuous surveillance practice by sequential determination of *de novo* or preformed donor specific anti-HLA antibodies (DSAs), urinary dipstick test and albumin to creatinine ratio (ACR) complemented by the measurement of blood levels of immunosuppressants and a preemptive strategy against BK and cytomegalovirus infection. The greater concern is that sporadic and temporal increases of the kidney temperature, for example due to physical activity, which is not caused by an inflammation

process in the kidney may lead to concerns and uncertainty of the patient and eventually an unnecessary biopsy or even blind immunosuppressive overtreatment.

A useful indication could be the continuous real-time measurement of blood flow by the thermo-conductivity read out in kidneys with acute renal graft failure and delayed graft function. In the paper the readout of k_{kidney}—the thermo-conductivity—in the first two days after transplantation is only provided for a single animal. What the authors showed, however, in supplemental figure 20 is that k_{kidney} could initially not discriminate isofrom allografts and single native kidneys but dropped over time in three of the five allotransplants consistent with severe fibrosis around the thermo sensor. It is of note that the response rate of the thermos-sensor was also slower in these cases but the temperature measurement sensitivity itself was not affected by this reaction to a foreign body.

Clearly further studies in larger animal models over much longer time periods are required before a first human trial over many years can be considered. It is of special note that the immunology and the clinical course of the MHC mismatched rat kidney allograft model is not directly applicable to the human setting with its more mature adaptive immune system. Despite that fact, the graft loss rate in the first year and thereafter is below 4% in recent eras and thus the average graft half-life has increased to around a decade [7]. This impressive success could be achieved by sophisticated allo-risk stratification after high resolution HLA genotyping or whole exome sequencing of donor and recipient and personalized use of potent induction and maintenance triple immunosuppression [8]. Even patients that develop dnDSAs and exhibit signs of AMR in the biopsy can nowadays be much better treated than before [9].

Implantation of mechanical or bioelectrical devices such as vagus nerve stimulator (VNS) or cardiac pacemakers has been performed in humans for long time and the incidence rate of infections even in immunosuppressed transplant patients is usually below 2% [10]. In addition, the device is a sensor and not a pacer and thus a technical failure such as an exit site block would be without clinical consequences. Therefore, I do not consider this a major hurdle for the introduction into clinical medicine once the test characteristics and utility of a thermo kidney probe have been evaluated for the different allograft pathologies described above. Furthermore, the use of this device vs the current standard of allograft monitoring needs to be compared in an appropriately designed trial with a clinically accepted unambiguous and quantitative outcome measure. A potential surrogate outcome could be the iBox score because it incorporates parameters such as DSAs and ACR along the course of the transplant and thus exhibits a more precise prediction of graft loss than other tools that include, correctly, only pretransplant donors and baseline recipient values. Furthermore, it was validated with data from a large randomized clinical intervention trial [11].

In conclusion, this study is highly innovative and the results are clear and appealing and thus it has the potential to be a trend-setter to encourage further transplant studies in larger animals. There may, however, be a longer road with some obstacles before clinical trials can start.

CONFLICT OF INTEREST STATEMENT

None declared.

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Received: 15.9.2023; Editorial decision: 16.9.2023