KDIGO Controversies Conference on Autosomal Dominant Tubulointerstitial Kidney Disease

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Questions to be addressed

1. **Defining and naming the syndrome**

Unifying features:
- Autosomal dominant inheritance (or *de novo* mutation)
- Tubulointerstitial pathology
  (tubular atrophy, interstitial fibrosis, TBM abnormalities (?), absence of gross glomerular pathology)
- Slowly progressive CKD with ESRD usually after 30-40 yrs.
- Small kidney size
- Mild proteinuria at most
- Not regularly hypertensive
- Few if any extrarenal manifestations (cave: *HNF1B*)

Previous terminology:
- UAKD
- FJHN
- TIN
- MCKD I and II
- (Glomerulocystic kidney disease)

Proposal for new terminology
- Requirements:
  - Simple
  - Applicable prior (w/o) genetic testing
  - With possibility to stratify on the basis of genetic testing
  - With optional extension as additional defects may become identified
  - Not misleading (as MCKD, FJHN,…)

- Options:
  - Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD), Type …..
    Advantage: analogous to ADPKD (could also lead to mix-up)

2. **Diagnostic criteria and work-up**
   - Which signs and symptoms should raise the suspicion of the entity:

     Familial CKD with normal or small kidney size (in contrast to ADPKD), no signs of glomerular disease
     or

CKD of unclear origin in a single individual in the absence of signs of glomerular disease

- Which work-up is reasonable in cases with suspected diagnosis?
  e.g. Glucose tolerance test, liver function tests, uric acid (in relation to GFR), uric acid fractional excretion, abdominal ultrasound?

- Which signs and symptoms are needed to make the diagnosis:

  Familial CKD with normal/small kidneys (in contrast to ADPKD), no signs of glomerular disease
  or
  CKD of unclear origin in a single individual in the absence of signs of glomerular disease and
  Biopsy in at least one family member with tubulointerstitial pattern
  (NOTE: genetic testing not required for diagnosis)

3. Do biopsies require special work-up?
- Staining for *UMOD, MUC*, TBM aspect and constituents?
- EM?

4. Is urine analysis helpful to raise the suspicion or to make the diagnosis?
- *UMOD*?
- *MUC1*?
- Spot or collection?

5. Who should receive genetic testing?
- Patients who request certainty about diagnosis, prognosis and possible inheritance
- Special considerations for minors

6. How should genetic testing be performed?
- Genetic testing for the underlying disorders can be done sequentially or in parallel
- Clinical signs can guide the sequence of testing:
  hyperuricemia / early gout → *UMOD*
  anemia → *REN*
  Extrarenal pathology → *HNF1B*
  Glomerulocystic disease and proteinuria → *UMOD* and *HNF1B*
- Technical approach:
  …. (confirmation?)
- How is a pathogenic variant defined (i.e. how are irrelevant variants excluded?)

7. What is the optimal management?
- ACE-I or ARBs in the absence or presence of hypertension
- Uric acid lowering therapy; if yes, which agent?
- Diet and lifestyle?
- Avoidance of nephrotoxic agents

8. What is the optimal follow-up?
- Which tests should be performed and at which intervals?
  S-crea, eGFR, spot-urine

9. **Future research directions?**
- What is the prevalence of the syndrome and of the respective gene defects?
- What is the link between *UMOD* hyeruricemia and gout?
- Is uromodulin involved in non-*UMOD* disorders?
- Common pathway HNF1B - UMOD - REN - MUC1?
- Genotype - phenotype correlations?
- Value of urinary uromodulin and *MUC1*?