Supplemental Material

Estimating nephron number from biopsies: impact on clinical studies

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Statistical analysis:

Reliability of needle and virtual biopsies:

The analysis was based on a 'replication reliability study' (Fleiss, The Design and Analysis of Clinical Experiments, 1986, Section 1.3) (1). These analyses help establish the reliability referring to the reproducibility of biopsy to estimate the whole kidney N_{glom}, and reveal the effect of measurement error on statistical power for comparing groups.

Needle Biopsy: Based on the statistical model of reliability (1), let T_i be the whole kidney N_{glom} measurement from person *i, i* = 1,…,N. This value is measured imperfectly by Y_{ij}, the j^{th} needle biopsy from kidney *i, i* = 1, …,n and *j* = 1,…,m. The N_{glom_NB} and whole kidney N_{glom} values are related by the model in Eq. 5:

$$Y_{ij} = \beta + T_i + \varepsilon_{ij} \qquad \text{Eq .5}$$

with $E(T_i) = \mu$, $Var(T_i) = \sigma_T^2$. The ε_{ij} are assumed independent with mean 0 and variance σ_e^2.

The accuracy of N_{glom_NB} estimated from needle biopsies compared to "gold standard" N_{glom} from CFE-MRI is based on the following model:

$$Y_{ij} - T_i = \beta + \varepsilon_{ij} \qquad \text{Eq. 6}$$

where T_i taken as a fixed and observed whole kidney N_{glom} for the i^{th} kidney. The bias in the needle biopsy-based N_{glom} measurement is β and the variance is σ_e^2. Estimates of the bias and variability parameters can be obtained in SAS 9.4 using PROC GLM or PROC MIXED.

Virtual Biopsy:

The statistical model for reliability of N_{glom_VB} is:

$$Y_{ijkl} = T_i + \beta_{j(i)} + \gamma_{k(ij)} + \varepsilon_{ijkl} \qquad \text{Eq. 7}$$

$$E(T_i) = \mu, \quad Var(T_i) = \sigma_T^2;\ E(\beta_{j(i)}) = \theta_j,\ Var(\beta_{j(i)}) = \sigma_s^2$$
$$E(\gamma_{k(ij)}) = 0,\ Var(\beta_{j(i)}) = \sigma_c^2;\ E(\varepsilon_{ijkl}) = 0,\ Var(\varepsilon_{ijkl}) = \sigma_e^2$$

Where *i* refers to kidney, *j(i)* refers to site within kidney, *k(ij)* refers to cluster and *l* is the measurement within a cluster in a site in a kidney. As above, this model can be fit in SAS 9.4 PROC GLM or PROC MIXED. Using PROC MIXED has some advantages in testing the assumption of this model. The 'group' and 'local' options in the 'repeated' and 'random' statements in SAS PROC MIXED allow for testing, for example, whether the variability due to sites within the kidney differs by site.

Linear regression plots:

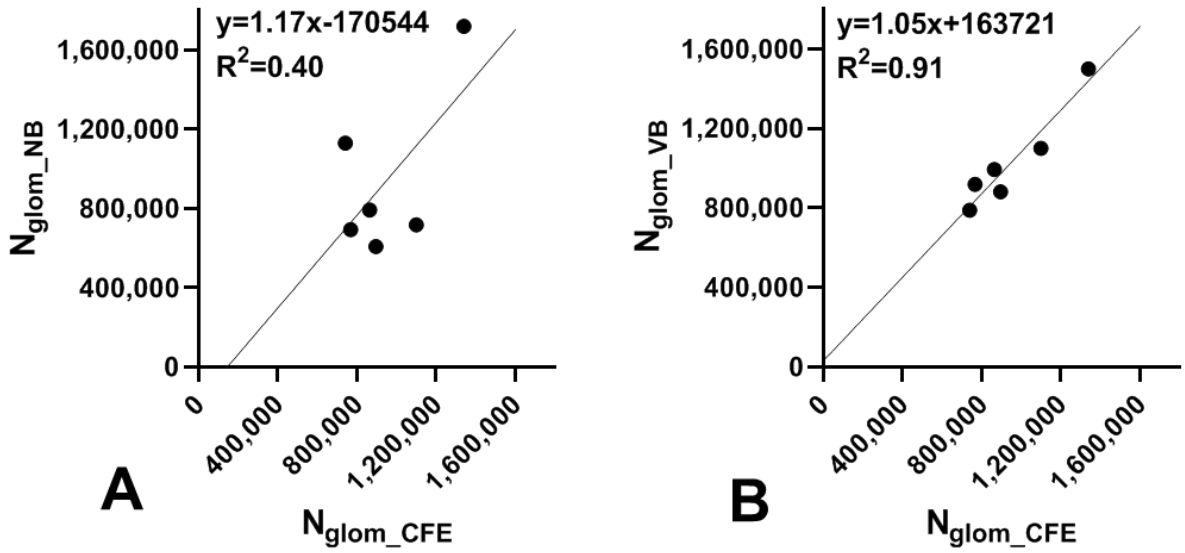

Figure 1S. Linear regression plots between (A) mean N_{glom} measured from needle biopsies (N_{glom_NB}) and Nglom measured by CFE-MRI (N_{glom_CFE}) or (B) mean N_{glom} measured from virtual biopsies (N_{glom_VB}) and N_{glom_CFE}.

References:

1. **Fleiss JL**. The Design and Analysis of Clinical Experiments. . In: *Biometrical Journa*lWiley, New York – Chichester – Brislane – Toronto – Singapore 1986, 432 S., 1986.