PREDICTING LIVER FIBROSIS-RELATED SCREEN FAILURE RATES IN PATIENTS WITH RENAL IMPAIRMENT

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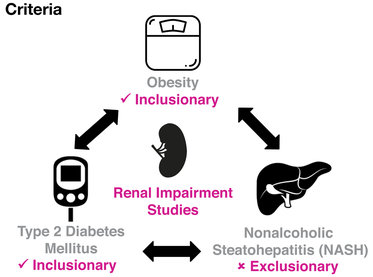
BACKGROUND

- Renal impairment (RI) pharmacokinetic (PK) studies are recommended for most investigational products that are 1) cleared by the kidney, 2) affect kidney function, or 3) intended for a patient population with comorbid kidney disease.
- Current inclusion criteria for RI PK studies include otherwise healthy patients with chronic kidney disease (CKD). While accommodations are made for patients with type 2 diabetes mellitus (T2DM) and obesity, other common comorbidities such as nonalcoholic fatty liver disease (NAFLD) and the more severe, nonalcoholic steatohepatitis (NASH) are typically exclusionary.
- NASH is strongly associated with T2DM and obesity, and since all three chronic metabolic diseases are on the rise [1], it is anticipated that many CKD patients may also have NASH-related liver fibrosis.

Figure 1. Chronic Metabolic Disease Triad in Relation to Renal Impairment Study Inclusion Criteria



OBJECTIVE

- The aim of the present study was to determine the predicted screen failure rate of CKD patients with signs of liver fibrosis in RI PK studies. Two prognostic, non-invasive composite biomarkers, FIB4 and APRI, commonly used for NASH screening were examined in a CKD population.

METHODS

- The dataset for this exploratory analysis was created using screening clinical laboratory results from Celerion's proprietary database.
- The degree of RI was determined by estimated glomerular filtration rate (eGFR) using the MDRD formula.
- The presence of liver fibrosis was determined with two non-invasive biomarkers; FIB4 or APRI formulas; cutoff values of FIB4 > 1.3 or APRI > 0.5 are predictive of NASH as previously described [2].

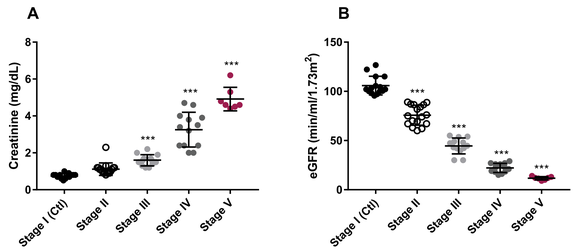
FIB4 index = (Age [years] x AST [U/L]) / (Platelet count [10^9/L] x √ALT [U/L])
APRI = (AST [U/L] / 40 U/L) / (Platelet count [10^9/L]

- Results are expressed as mean ± SD and were analyzed by one-way ANOVA followed by Dunnett's post-hoc test to determine statistically significant difference from the control group (Ctl; Stage I), where *p<0.05, **p<0.01, ***p<0.001. Associations among non-normally distributed variables were determined by Spearman correlation coefficient (R).

RESULTS

- Sixty-five subjects were included in this pilot study, and stratified based on CKD staging.

Figure 2. Creatinine and eGFR Values



- The majority of subjects were males (80%) and between 49-77 years old. Across all CKD stages, age, BMI and clinical values were similar to control subjects, expect for Stage III CKD patients which were older than controls.

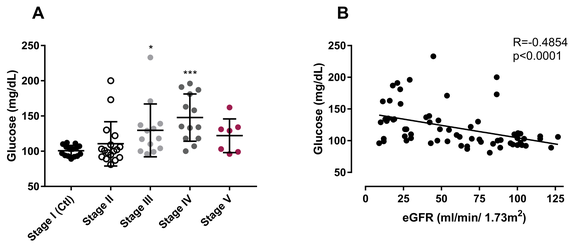
Table 1. CKD Patient Anthropometric and Clinical Data

Parameter	All	Stage I (Ctl)	Stage II	Stage III	Stage IV	Stage V
n	65	15	17	13	13	7
Male/Female	52/13	10/5	15/2	11/2	12/1	4/3
Age (years)	62.7±6.7	60.5±4.5	62.9±6.1	67.9±7.3*	61.6±6.6	59.0±7.6
BMI (kg/m^2)	29.2±3.5	30.3±1.8	27.8±2.7	27.8±3.4	29.2±4.5	31.0±4.4
ALT (U/L)	22.5±10.2	23.3±6.8	24.0±9.1	23.8±11.5	20.3±14.7	19.0±7.0
AST (U/L)	22.8±8.3	24.7±10.6	23.5±6.3	24.8±10.3	19.2±6.3	19.6±4.7
Platelet (10^9/L)	233.3±58.7	245.7±73.5	234.0±50.4	209.2±57.8	231.2±55.9	253.7±47.7

*p<0.05 vs Ctl group.

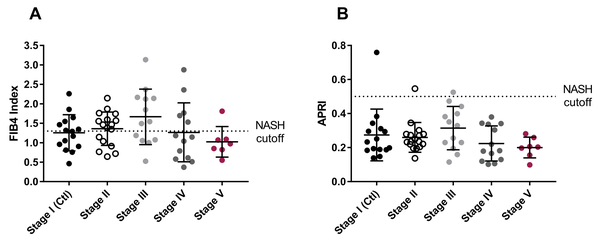
- Nearly one third of CKD patients had T2DM (34%). Fasting plasma glucose was increased in Stage II and Stage III CKD patients compared to the control group and glucose levels were significantly associated with eGRF.

Figure 3. Fasting Plasma Glucose Concentrations



- While mean FIB4 and APRI scores were similar among CKD patient and control subjects, more patients were above the NASH cutoff with the FIB4 versus the APRI biomarker. Seven control subjects and 25 CKD patients were predicted NASH-positive with FIB4 compared to one control subject and two CKD patients were predicted NASH-positive with APRI. By CKD stage, Stage II and Stage III patients demonstrated the highest rates of predicted NASH by FIB4 (65% and 62%, respectively) compared to controls (47%). For all CKD patients, half were predicted to display NASH.

Figure 4. CKD Patients Categorized by FIB4 and APRI Cutoffs



DISCUSSION

- While liver biopsy remains the reference standard for NASH diagnosis, composite biomarkers such as FIB4 show good sensitivity and specificity for predicting NASH [2].
- In the present study, 50% of all CKD patients and 47% of control subjects are predicted to have NASH-related fibrosis by FIB4 assessment. These rates are similar to other reports in CKD patients:
  - Transient elastography was examined in a cohort of CKD Stage III and IV patients. Hepatic steatosis was observed in 85.5% CKD patients and liver fat content negatively correlated with eGFR. In addition, 26.4% of CKD patients had liver stiffness (a marker of fibrosis) [3].
  - A large cross-sectional study determined 77% of CKD patients and 82% ESRD patients treated with hemodialysis displayed features of NAFLD by transient elastography [4].
  - Using the NAFLD fibrosis score (NFS), individuals at a high probability of fibrosis (NFS >0.676) had a 5.1-fold increased risk of having CKD [5].
  - Additionally, in a large NAFLD cohort, FIB4 >1.1 was a sensitive (69%) and specific (71%) marker for predicting CKD [6].
- Shared underlying mechanisms associated with both NASH and CKD include altered signaling of the renin-angiotensin system (RAS), upregulated inflammatory cytokines, increased oxidative stress, and insulin resistance [7].

CONCLUSION

- In the present study, we examined the potential for liver fibrosis and the NASH rate in a CKD population. Using a well-established NASH cutoff of FIB4 >1.3, we observed that 50% of CKD patients would screen-fail due to NASH-related exclusion criteria for a RI PK study.
- It is unclear whether the potential liver fibrosis seen in the RI population has any effect on drug metabolism; however, greater recruitment and increased screening efforts may be required to identify otherwise healthy CKD patients for RI PK studies, or flexible inclusion/exclusion criteria language regarding NASH in the study protocol is needed to overcome this challenge.

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