Title: Biopsying Diabetics...How Risky Is it?

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Despite automated biopsy devices and real-time imaging, hemorrhagic complications still occur with native kidney biopsies. Counseling patients on these known risks is imperative to achieving patient-centered care. Results from previously published retrospective registries have allowed clinicians to risk stratify patients, guide shared decision making, and provide better informed consent related to risks and benefits. However, many publications are limited to single center experiences, homogeneity of procedural techniques that differ from other institutional practices, and variability of definitions of complications.¹ To date, there has been two systematic reviews and meta-analysis of native percutaneous renal biopsy (PRB) that have attempted to address some of these issues.²,³ Interestingly, the nidus for the most recent review performed by the Kidney Precision Medicine Project (KPMP) investigators was to provide research participants accurate risk information as to the complications associated with PRB during the informed consent process.

In this edition of KI Reports, Hasegawa et al reports on the incidence of post procedural hemorrhagic complications in 76,302 patients who underwent native PRB in Japan. Patients were identified using procedural codes from the Diagnosis Procedure Combination database, a national inpatient Japanese registry which encompasses more than 1,000 hospitals and includes more than 90% of all tertiary hospitals in Japan. Available information within the database included demographics and anthropometric measurements, co-morbidities, in-hospital prescriptions, procedures, and identification of complications using ICD-10 codes. The authors enlighten its readers that most patients in Japan who undergo PRB are admitted to the hospital and undergo a 5 to 7 day observation period even in the absence of a complication, a practiced not replicated in the United States or other countries. Many groups advocate for PRB to be performed in the outpatient setting with an observational period as short as 4 hours or as long as 24 hours in most patients.⁴ Follow up periods of close observations for longer than the usual
practice are important to note as they may introduce some diagnostic bias and overestimation of events when compared to shorter periods of observation.

In the study by Nangaku\textsuperscript{5} et al, the primary outcome was the occurrence of major bleeding complications as defined by red blood cell (RBC) transfusion within 7 days, massive RBC transfusion (greater than 1 Liter), or invasive hemostasis (transcatheter embolization or nephrectomy) after PRB in diabetics compared to non-diabetics individuals. Major bleeding occurred in 678 (0.9%) patients, 622 (0.8%) had RBC transfusion, 201 (0.3%) had massive transfusion, and 109 (0.1%) required invasive hemostasis, in essence, congruent outcomes with most studies.\textsuperscript{6} Furthermore, in this registry study, the presence and the increased severity of diabetes were found to be significantly associated with greater relative risks of bleeding [RR = 2.41 (95% CI 2.00 to 2.90) and RR = 1.57 (95% CI 1.18 to 2.10), respectively]. Understandably, the authors could not account for all the coagulopathic complexities encountered in diabetic patients and had suggested poor wound healing as one plausible mechanism for their results.

Bleeding following a native kidney biopsy differentiates largely into anatomic, procedural, and anticoagulable hazards. Anatomic risk factors include small (< 8 cm), echogenic kidneys, with thin cortex in a thin individual, and highly inflamed and friable arterioles in active vasculitis. Procedural risk factors include decreasing needle gauge and increasing number of cores. Anticoagulable risk factors include thrombocytopenia, anticoagulant or antithrombotic use, and hypertension. Anemia, while not necessarily an anticoagulable factor, influences transfusion rates post biopsy. It is challenging to classify the presence of diabetes as either an anatomic or anticoagulable risk factor. Perhaps the presence of and increasing severity of diabetes correlated with bleeding in this study are surrogate markers of comorbid conditions and more traditionally established bleeding risk factors above. This is hypothesized in a Swedish renal biopsy registry which found that the presence of type 2 diabetes, but not type 1, is associated with a higher risk of bleeding from kidney biopsy.\textsuperscript{7}

The strengths of this study include the generalizability of the outcomes since this is a large sampling of a heterogeneous population from a national registry which include data from various hospitals case volumes. Authors used multivariable regression and sensitivity analysis of well described risk factors associated with bleeding such as age, body mass index, anti-thrombotic agents, and acute kidney injury. Since actual laboratory data was not available, surrogates were used instead. Admission ICD-10 codes for chronic kidney disease (CKD) and anemia were used to identify higher risk patients with elevated serum creatinine and lower pre-procedural hemoglobin levels. As one would expect, failure to meticulously document ICD codes may alter the findings.

The limitations of this study are not unique to this work but are seen in many retrospective registry studies. Therefore many questions remain. What is the clinical phenotype of those 77.6% of patients within the entire cohort with a main diagnosis as “Others”? Were they undergoing PRB for proteinuria, hematuria, or a kidney mass? What was the international normalized ratio, activated partial thromboplastin time, platelet count, and kidney imaging
characteristics (kidney size and echogenicity, cortex thickness) of those individuals who bleed? Was the blood pressure controlled prior to and after PRB? Did the diabetic group have a 2.4 fold increase risk of bleeding because of the well described higher rate of resistant hypertension in this cohort? Did the complications occur early or late in their 5 to 7 day observation period? Does the Japanese healthcare system follow strict universal blood management protocols to minimize transfusions? The authors conclude that the major bleeding associated with diabetes and patients using multiple-agent or insulin use leads to a worse prognosis. As expected, the diabetic cohort had a higher disease burden which was notable for patient older age, more chronic kidney disease, antithrombotic use and steroid use. The authors used multivariable regression to account for these independent variables and still demonstrated the dependent outcome (risk of bleeding). We wonder if the increased bleeding risks would have been attenuated if more laboratory and imaging information would have been available within the database to include in a more comprehensive model. Contrary to this study, a smaller, single center study assessing bleeding risk in native and kidney transplants PRB patients found no difference in the diabetics group.\textsuperscript{4} They used multifactorial logistical regression modeling and identified aspirin use, low eGFR, anemia, higher pre procedure blood pressure, cirrhosis, and amyloidosis as risk factors.

It is important to remark that the authors control for antithrombotic use which was identified through ICD-10 codes during the inpatient observation period, and had hoped to have information on anti-platelet therapy. It is customary to hold anti-platelet therapy for a minimum of 5 to 7 days before and after PRB to reduce the risk of bleeding, however not all studies support this practice.\textsuperscript{8} The diabetic cohort appeared to have more comorbid conditions (older, CKD, antithrombotics) and we presume a higher rate of monotherapy or dual anti-platelet therapy. We ponder if the increased risk of bleeding in the diabetic population was due to the continuation of anti-platelet therapy, or a shorter time interval around PRB and the timing of cessation and resumption of these agents.

We congratulate the authors on this work by adding to the available published literature. The large sample size and the heterogeneity of a national database supports the generalizability of the risk of PRB and will help clinicians better inform patients about the risk and benefits of kidney biopsy. We think that it is reasonable to anticipate a higher risk of bleeding in patients with more co-morbidities such as diabetes. Diabetic kidney disease is a highly variable clinical phenotype and researchers have shown that up to one third of diabetic patients have non-diabetic kidney disease but other pathologies.\textsuperscript{9} Patient survival at 3 and 5 years on hemodialysis is an abysmal 57% and 42% respectively.\textsuperscript{10} Therefore, we strongly support the practice of PRB in diabetic patients when a secondary diagnosis is suspected, and identification of that disease, would alter management with the hopes of reducing the progression to end stage kidney disease. As in all patients with or without diabetic kidney disease, we recommend aggressively managing modifiable risk factors to reduce the risk of bleeding.
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