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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. Nevertheless, many publications are limited to single-center experiences, homogeny of procedural techniques that differ from other institutional practices, and variability of definitions of complications.[1] To date, there has been 2 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 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 the *KI Reports*, Hasegawa *et al*. report on the incidence of postprocedural 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 that encompasses >1000 hospitals and includes >90% of all tertiary hospitals in Japan. Available information within the database included demographics and anthropometric measurements, comorbidities, in-hospital prescriptions, procedures, and identification of complications using the International Classification of Diseases, Tenth Revision 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 practice 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 with shorter periods of observation.

In the study by Nangaku *et al*.,[5] the primary outcome was the occurrence of major bleeding complications as defined by red blood cell transfusion within 7 days, massive red blood cell transfusion (>1 l), or invasive hemostasis (transcatheter embolization or nephrectomy) after PRB in people with diabetes compared with individuals without diabetes. Major bleeding occurred in 678 patients (0.9%), 622 (0.8%) had red blood cell transfusion, 201 (0.3%) had massive transfusion, and 109 (0.1%) required invasive hemostasis, in essence, congruent outcomes with most studies.[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 (relative risk = 2.41 [95% CI 2.00–2.90] and relative risk = 1.57 [95% CI 1.18–2.10], respectively). Understandably, the authors could not account for all the coagulopathic complexities encountered in patients with diabetes and had suggested poor wound healing as one plausible mechanism for their results.

Bleeding after a native kidney biopsy differentiates largely into anatomical, procedural, and anticoagulable hazards. Anatomical 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

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include thrombocytopenia, anticoagulant or antithrombotic use, and hypertension. Anemia, although not necessarily an anticoagulable factor, influences transfusion rates postbiopsy. It is challenging to classify the presence of diabetes as either an anatomical 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 discussed previously. 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.[7]

The strengths of this study include the generalizability of the outcomes because 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, antithrombotic agents, and acute kidney injury. Because actual laboratory data were not available, surrogates were used instead. Admission International Classification of Diseases, Tenth Revision codes for chronic kidney disease and anemia were used to identify higher risk patients with elevated serum creatinine and lower preprocedural hemoglobin levels. As one would expect, failure to meticulously document International Classification of Diseases codes may alter the findings.

The limitations of this study are not unique to this work but are found 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 before and after PRB? Did the group with diabetes have a 2.4-fold increased 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 health care system follow strict universal blood management protocols to minimize transfusions? The authors conclude that the major bleeding associated with diabetes and patients using multiple agents or insulin leads to a worse prognosis. As expected, the diabetic cohort had a higher disease burden which was notable for patients with older age, more chronic kidney disease, antithrombotic use, and steroid use. The authors used multivariable regression to account for these independent variables and still found the dependent outcome (risk of bleeding). We wonder whether 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 evaluating bleeding risk in patients with PRB with native and kidney transplants found no difference in the group with diabetes.[4] They used multifactorial logistical regression modeling and identified aspirin use, low estimated glomerular filtration rate, anemia, higher preprocedure blood pressure, cirrhosis, and amyloidosis as risk factors.

The authors controlled antithrombotic use using International Classification of Diseases, Tenth Revision codes, but had hoped to have information on antiplatelet therapy. It is customary to hold antiplatelet 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.[8] The diabetic cohort seemed to have more comorbid conditions (older, chronic kidney disease, antithrombotics), and we presume a higher rate of monotherapy or dual antiplatelet therapy. We ponder whether the increased risk of bleeding in the population with diabetes was due to the continuation of antiplatelet therapy or a shorter time interval on 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 more accurately inform patients on the risk and benefits of kidney biopsy. We think that it is reasonable to anticipate a higher risk of bleeding in patients with more comorbidities, such as diabetes. Diabetic kidney disease is a highly variable clinical phenotype, and researchers have found that up to one-third of patients with diabetes have nondiabetic kidney disease but other pathologies.[9] Patient survival at 3 and 5 years on hemodialysis is an abysmal 57% and 42%, respectively.[S1] Therefore, we strongly support the practice of PRB in patients with diabetes 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.

DISCLOSURE

JJT reports providing consulting services for AstraZeneca. EDP reports providing consulting services and receiving speaker honoraria for Novartis, CareDx, Gador Argentina, Scienzia Uruguay, Verici, Transplant Genomics Inc., Veloxis, and Horizon. MM declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Reference.

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