Higher blood urea nitrogen is associated with increased risk of incident diabetes mellitus

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Experimental evidence suggests that higher levels of urea may increase insulin resistance and suppress insulin secretion. However, whether higher levels of blood urea nitrogen (BUN) are associated with increased risk of incident diabetes mellitus in humans is not known. To study this, we built a national cohort of 1,337,452 United States Veterans without diabetes to characterize the association of BUN and risk of incident diabetes. Over a median follow-up of 4.93 years, there were 172,913 cases of incident diabetes. In joint risk models of estimated glomerular filtration rate (eGFR) and BUN. there was no association between eGFR and the risk of incident diabetes in those with a BUN of 25 mg/dl or less. However, the risk was significantly increased in those with a BUN over 25 mg/dl at all eGFR levels, even in those with an eGFR of 60 ml/min/1.73m^2 or more (hazard ratio 1.27; confidence interval 1.24-1.31). The risk of incident diabetes was highest in those with BUN over 25 mg/dL and an eGFR under 15 ml/min/1.73m^2 (1.68; 1.51-1.87). Spline analyses of the relationship between BUN and risk of incident diabetes showed that risk was progressively higher as BUN increased. In models where eGFR was included as a continuous covariate, compared to a BUN of 25 mg/dl or less, a BUN over 25 mg/dl was associated with increased risk of incident diabetes (1.23; 1.21-1.25). Every 10 ml/min/1.73m^2 decrease in eGFR was not associated with risk of incident diabetes (1.00; 1.00-1.01). Two-stage residual inclusion analyses showed that, independent of the impact of eGFR, every 10 mg/dL increase in BUN concentration was associated with increased risk of incident diabetes (1.15; 1.14-1.16). Thus, higher levels of BUN are associated with increased risk of incident diabetes mellitus.

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Chronic kidney disease (CKD) is characterized by disturbances in glucose and insulin homeostasis.[1] In a cohort of 4680 participants without diabetes mellitus in the Cardiovascular Health Study, Pham *et al.*[2] reported that a decreased estimated glomerular filtration rate (eGFR) is associated with increased insulin resistance; however, over a median follow-up of 12 years, participants with a decreased eGFR did not have an increased risk of incident diabetes mellitus. It was noted that the majority of cohort participants had mild CKD, and the number of participants with an eGFR <45 ml/min per 1.73 m^2 was small ($N = 282$), which may not have allowed a more nuanced characterization of the risk of diabetes mellitus in those with a very low eGFR. In an elegant subsequent study of 59 participants with nondiabetic CKD (mean eGFR, 37.6 ml/min per 1.73 m^2) and 39 healthy controls, de Boer *et al.* reported that those with CKD had lower insulin sensitivity, reduced insulin clearance, and inadequate augmentation of insulin secretion.[3,4] The investigators suggested that the combination of insulin resistance and an inability to adequately augment insulin secretion led to the observation of a higher prevalence of glucose intolerance in moderate to severe CKD.

Experimental evidence identifies urea as a putative culprit of reduced insulin sensitivity and defective insulin secretion.[5,6] Studies by D'Apolito *et al.*[5] suggest that cultured adipocytes treated with urea (at disease-relevant concentrations) exhibited decreased insulin sensitivity. In a mouse model of surgically induced kidney failure, uremic mice displayed insulin resistance and glucose intolerance, and urea infusion produced the same degree of insulin resistance in normal mice.[5] Recent seminal observations by Koppe *et al.*[6] and Thomas *et al.*[7] suggest that defective insulin secretion in CKD is mechanistically caused by elevated levels of circulating urea, a condition that becomes manifest in advanced stages of CKD.

The disturbances of glucose and insulin homeostasis in CKD are complex and represent 2 opposing forces at play.

On the one hand, CKD decreases insulin sensitivity (and increases insulin resistance) and, in advanced stages, results in beta-cell dysfunction and defective insulin secretion.[8] On the other hand, CKD leads to decreased insulin clearance, thus prolonging its half-life.[1,9] The balance of these 2 opposing forces shapes the state of glucose metabolism and ultimately the risk of diabetes mellitus in any individual patient. We hypothesized that as CKD progresses and blood urea nitrogen (BUN) increases, both reduced insulin sensitivity and defective insulin secretion become more pronounced and result in a state of clinically evident diabetes mellitus and that, congruent with the experimental evidence of urea suppressing insulin sensitivity and insulin secretion, higher levels of BUN are associated with an increased risk of incident diabetes mellitus. Taking a big data approach, we used the US Department of Veterans Affairs (VA) databases to build a national cohort of 1,337,452 US veterans without diabetes mellitus and followed them over time to characterize the association of BUN and the risk of incident diabetes mellitus.

RESULTS

There were 1,337,452 cohort participants followed for a median of 4.93 years (interquartile range, 4.93–4.93). Table 1 details the demographic and health characteristics of the overall cohort by BUN category (≤25 and >25 mg/dl) at time of cohort entry (T_0). Supplementary Table S1 describes baseline characteristics by eGFR category. Overall, cohort participants were mostly of white race and male sex (Table 1). Cohort participants had an average first eGFR and first BUN level of 75.55 ± 19.94 ml/min per 1.72 m^2 and 16.78 ± 7.04 mg/dl, respectively (Table 1). There were 172,913 (12.93%) incident cases of diabetes in the overall cohort. In inverse probability weighting analyses (which account for the uneven probability of experiencing competing risk in BUN categories) (weighted N = 1,340,998), there were 210,873 (15.73%) cases of incident diabetes: 23,649 (19.85%) in those with a BUN level >25 mg/dl and 187,224 (15.32%) in those with a BUN level ≤25 mg/dl (Table 1). The 5-year diabetes-free survival probability by time-updated eGFR category and time-updated BUN category are presented in Figures 1 and 2, respectively.

Association between time-updated eGFR and the risk of incident diabetes mellitus

In Cox survival models adjusted for age, race, sex, and time-varying variables including body mass index (BMI), serum carbon dioxide, albuminuria, frequency of outpatient encounters, frequency of hospitalizations, and relevant comorbidities and health characteristics, compared with those with an eGFR ≥60 ml/min per 1.73 m^2, there was a gradual increase in the risk of incident diabetes mellitus with a decreasing eGFR (Table 2). Risk was pronounced in those with an eGFR <30 and ≥15 ml/min per 1.73 m^2 and those with an eGFR <15 ml/min per 1.73 m^2 with a hazard ratio (HR) of 1.17, 95% confidence interval (CI) 1.12–1.22, and an HR of 1.64, 95% CI 1.48–1.82, respectively (Table 2). Spline analysis of the relationship between the eGFR and the risk of incident diabetes mellitus suggested an exponential relationship in which risk progressively increased as eGFR decreased (Figure 3).

Association between time-updated BUN and the risk of incident diabetes mellitus

Using a big data approach, we tested the question of whether elevated levels of urea are associated with an increased risk of incident diabetes mellitus. In a joint risk model (of eGFR and BUN), we examined the risk of incident diabetes by BUN and eGFR category (Table 3). In cohort participants with low BUN (≤25 mg/dl), there was no significant relationship between the eGFR and the risk of incident diabetes in any eGFR category. In cohort participants with BUN >25 mg/dl, the risk of incident diabetes was significantly increased at all eGFR levels, even in those with an eGFR ≥60 ml/min per 1.73 m^2 (HR, 1.27; 95% CI 1.24–1.31) (Table 3). The risk of incident diabetes was highest in those with BUN >25 mg/dl and an eGFR <15 ml/min per 1.73 m^2 (HR, 1.68; 95% CI 1.51–1.87) (Table 3). A joint risk model with BUN categorized in quintiles yielded consistent findings (Supplementary Table S2). A spline analysis of the relationship between BUN and the risk of incident diabetes showed that the risk of incident diabetes was progressively higher as BUN increased (Figure 4).

In models in which eGFR was included as a continuous covariate, compared with BUN ≤25 mg/dl, BUN >25 mg/dl was associated with an increased risk of incident diabetes mellitus (HR, 1.23; 95% CI 1.21–1.25). In the same model, every 10-ml/min per 1.73 m^2 increase in the eGFR was not associated with the risk of incident diabetes mellitus (HR, 1.00; 95% CI 1.00–1.01). Spline analysis, which included both the eGFR and BUN, showed that although the risk of incident diabetes mellitus increased with increased BUN concentrations, the risk was decreased with decreased eGFR (Figure 5). Because the eGFR and BUN are inherently correlated, we applied a 2-stage residual inclusion method to account for this correlation and evaluate the independent impact of BUN on the risk of incident diabetes.[10] Results showed that, after accounting for the effect of eGFR and its correlation with BUN, every 10 mg/dl increase in BUN concentration was associated with a significant increase in the risk of incident diabetes mellitus (HR, 1.15; 95% CI 1.14–1.16). However, independent of the impact of BUN, every 10 ml/min per 1.73 m^2 increase of eGFR yielded no significant change in the risk of diabetes mellitus (HR, 1.01; 95% CI 1.01–1.01).

Formal interaction analyses were undertaken and showed that increasing age attenuated the association of BUN and the risk of incident diabetes (P value for interaction <0.001). BUN >25 mg/dl was more strongly associated with an increased risk of diabetes among cohort participants who were younger than the median age of the overall cohort (65.1 years