

Chapter 2

Urea

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Abstract Urea is generated by the urea cycle enzymes, which are mainly in the liver but are also ubiquitously expressed at low levels in other tissues. The metabolic process is altered in several conditions such as by diets, hormones, and diseases. Urea is then eliminated through fluids, especially urine. Blood urea nitrogen (BUN) has been utilized to evaluate renal function for decades. New roles for urea in the urinary system, circulation system, respiratory system, digestive system, nervous system, etc., were reported lately, which suggests clinical significance of urea.

Keywords Urea · Urea cycle · BUN

Generation of Urea

Urea is a polar, highly water soluble, and charge-neutral molecule, with an oxygen and two nitrogen atoms serving as hydrogen bond acceptors, and two amino functions providing a total of four hydrogen bonds for donation (Fig. 2.1). A solution

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Fig. 2.1 The molecular structure of urea. The molecular formula is $\text{CO}(\text{NH}_2)_2$; the molecular mass is 60.06 g/mol

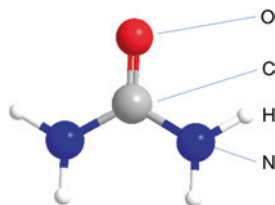
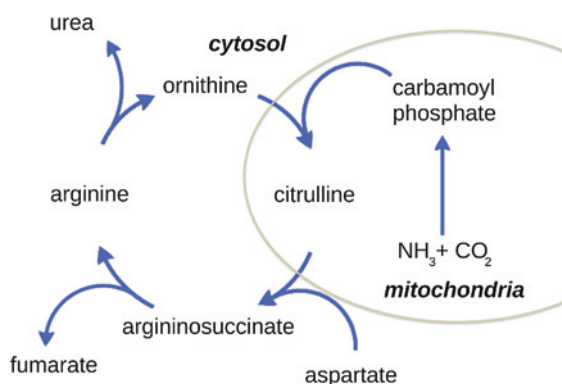


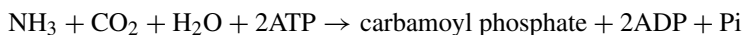
Fig. 2.2 The urea cycle. The process happens around the membrane of mitochondria



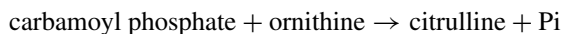
of urea is colorless, odorless, and neither acidic nor alkaline. In 1932, Hans Krebs and Kurt Henseleit discovered the biosynthesis pathway of urea in mammalian liver in vitro, and this pathway was subsequently named as the urea cycle (also known as the ornithine cycle) [95]. The urea cycle is as necessary to life as is the Krebs cycle (also known as the TCA cycle). The generation of urea serves a key role in protein catabolism in mammals.

The urea cycle consists of five enzymatically controlled reactions: The first two steps happen in the mitochondria and the rest happen in the cytosol (Fig. 2.2). This ammonia disposal mechanism, i.e., the urea cycle, was expounded by a series of studies [71, 75, 108, 136, 143, 144, 145, 146, 147, 148, 153, 154, 163, 166].

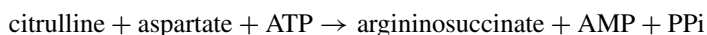
Step 1: Location: mitochondria; catalyzed by carbamoyl phosphate synthetase I (CPS-1); rate-limiting step



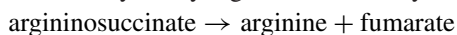
Step 2: Location: mitochondria; catalyzed by ornithine transcarbamoylase (OTC)



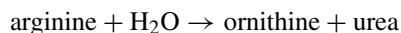
Step 3: Location: cytosol; catalyzed by argininosuccinate synthetase (ASS); rate-limiting step



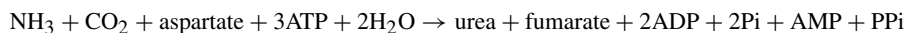
Step 4: Location: cytosol; catalyzed by argininosuccinate lyase (ASL)



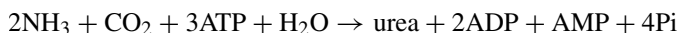
Step 5: Location: cytosol; catalyzed by arginase I (ARG-1)



Therefore, the overall equation of the urea cycle is:



Or it sums up as:



Apart from the above five enzymes, several other proteins participate in efficient functioning of the pathway in vivo, including glutaminase, glutamate dehydrogenase, N-acetylglutamate synthetase, mitochondrial aspartate/glutamate transporter, and mitochondrial ornithine/citrulline transporter [17, 28, 43, 83, 93, 126, 130, 202]. The complete urea cycle also exists in enterocytes in mammals [45], whereas the three cytoplasmic enzymes are found in a variety of other tissues such as stratum corneum [118], brain [36], mammary gland [149], kidney [149], submaxillary salivary gland [149], epididymis [149], eye [142], and endothelium [211]. (Fig. 2.3). The physiology of the incomplete urea cycle in these organs is to synthesize products, such as polyamines and NO, which catalyzed the conversion of arginine to ornithine.

In ureotelic animals such as mammals, the physiological significance of the urea cycle in liver is to convert the cytotoxic ammonia to much less toxic urea, even though the synthesis has a net energy cost [48, 117, 156]. Urea is not able to be further metabolized by mammalian tissues but urea markedly inhibits ureagenesis itself as negative feedback regulation [50]. Though it converts a basic substance to a neutral one, the urea cycle is not involved in the regulation of acid–base homeostasis because it cannot be regulated by acid or base load [21, 25, 26]. In conditions where the urea cycle in liver fails, such as in cirrhosis [125, 195], the accumulation of ammonia that causes hepatic encephalopathy is fatal [40, 191]. Body nitrogen balance is controlled via regulation of the generation of urea [217].

Protein in the diet can raise urea synthesis through upregulation of urea cycle enzymes to 300 % above what is present at the onset of a fast [160]. Under conditions of varying dietary protein quality, the liver level of free amino acids may limit the rate of the urea synthesis, primarily without a change of enzyme activities [72]. Infusion of glucose-alone elicits a significant reduction in ureagenesis [67, 69]. Xylitol inhibits urea synthesis and alanine metabolism [68]. In rats fed with a high-fat diet, ARG-1 is downregulated, which may lead to a lower rate of urea generation [122]. Defects in the urea cycle enzyme systems may be present in rats fed with a zinc-deficient diet, which is linked to deficiency of OTC [141].

Urea biosynthesis is susceptible to regulation by hormones. Insulin decreases the capacity for urea synthesis [69]. In insulin-dependent diabetes mellitus, the generation of urea in rat liver is elevated through upregulation of CPS-1 and OTC, causing negative nitrogen balance [88]. When cultured hepatocytes are supplemented with amino acids, high insulin preconditioning downregulates urea synthesis by means of downregulating CPS-1, OTC, ASS, and ARG-1 [98]. Additional dexamethasone induces the expression of CPS-1, ASS, ASL, and

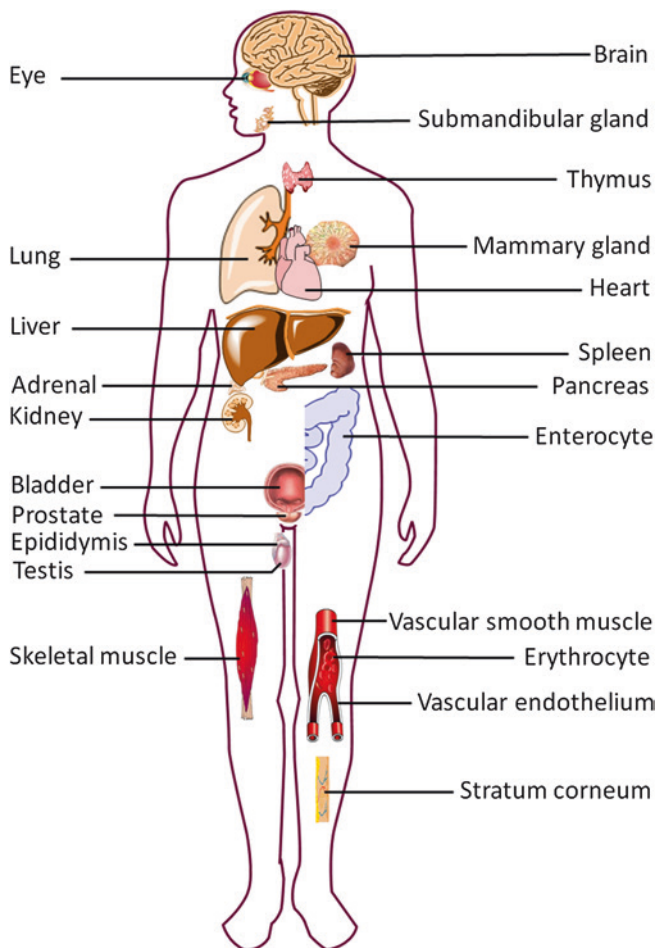


Fig. 2.3 The organs generating urea. The organs generating urea include liver, brain, eye, submandibular gland, thymus, lung, mammary gland, heart, spleen, adrenal, pancreas, kidney, intestine, bladder, prostate, testis, epididymis, skeletal muscle, vessel, erythrocyte, and skin

ARG-1 in cultured fetal hepatocytes, which can be inhibited by insulin treatment [80]. Contrarily, glucagon infusion independently accelerates the rate of urea generation in both humans and rodents [4, 67, 196]. The urea synthesis rate is markedly reduced in patients with chronic pancreatitis whose glucagon secretion is impaired [66]. The effect of glucagon administration on the urea cycle relies on upregulating CPS-1, ASL, and ARG-1 in cultured fetal hepatocytes [79, 81]. Hyperinsulinemic-induced hypoglycemia patients, whose glucagon concentration is doubled, have a markedly high rate of urea biosynthesis [64]. Adrenergic agonists (phenylephrine and norepinephrine) stimulate the generation of urea, as compared to untreated hepatocytes in vitro [91]. Both exogenous and endogenous glucocorticoids can upregulate hepatic urea synthesis [62, 79, 80, 161, 206, 207],

which can be reversed by a glucocorticoid receptor blocker [73]. Growth hormone and insulin-like growth factor I can either singly or in combination decrease urea biosynthesis by downregulating all five enzymes [62, 63, 206]. Patients infused with somatostatin display higher rate of the urea synthesis [74].

The generation of urea is also affected in other conditions. Iron overload in liver can be found in patients with hemochromatosis, alcoholic liver disease, and chronic viral hepatitis, or secondary to repeated blood transfusions. Based on a proteomic analysis, elevated CPS-1, OTC, and ARG-1 levels were found in iron-overloaded patients, which may lead to higher rate of the urea synthesis [137]. Liver cirrhosis decreases the level of urea cycle enzymes [191], resulting in low efficacy of urea synthesis [195]. Release of endotoxin lipopolysaccharide (LPS) during infection in cirrhosis can separately impair the urea synthesis process by decreasing urea cycle enzymes as well [125]. Thus, the reduced capacity to detoxify ammonia may be the reason why infection exacerbates hepatic encephalopathy in patients with cirrhosis [40]. The levels of all five urea cycle enzymes are significantly lower in hepatoma, which is considered as the next step of cirrhosis [27].

Moreover, the rate of urea synthesis is also elevated in other cachectic tumor-bearing rats, which implies negative nitrogen balance in cancer cachexia [41]. Inflammatory cachexia, such as in rheumatoid arthritis, shows elevated generation of urea in liver [216]. Severe stress, like pain, upregulates liver function including urea synthesis [61]. The rate of urea synthesis rises during the TNF- α induced acute-phase response [185]. Further study suggested that IL-6 contributes to downregulation of urea cycle genes but displays no effects on the upregulated rate of urea synthesis [184]. What is more, the LPS-induced acute-phase response upregulates urea synthesis in vivo [124].

The urea cycle enzymes are significantly increased in chronic vitamin A deficiency, which causes a much higher rate of urea generation [51]. In acute and chronic uremia, the urea production rate in liver is increased by means of elevated levels of urea cycle enzymes after it went through a temporary early-stage down-regulation [3, 76, 123]. This phenomenon is probably induced by varied glucagon levels in uremia [3]. In rats with obesity, as a result of which the rate of urea biosynthesis is low, all urea enzymes are decreased especially CPS-1 and ASS [16]. The deficit of ureagenesis is also found in fatty liver with low levels of urea cycle enzymes [116, 186]. The generation of urea is increased in patients with active inflammatory bowel disease due to an unknown mechanism [106].

Some compounds have the capacity to influence the generation of urea in liver. Diuretics such as xipamide, mefruside, chlortalidone, and chlorothiazide but not furosemide inhibit urea synthesis from the first step in liver due to an inhibition of mitochondrial carbonic anhydrase that supplies CO₂ to the urea cycle [82]. In contrast, acute moderate dehydration caused by furosemide downregulates urea synthesis; this effect is mediated by reduced glucagon levels [84]. The increased rate of urea synthesis in non-insulin-dependent diabetes mellitus can slow down after prostaglandin E1 infusion [113]. In large-dose caffeine-treated rats, increased urea synthesis has been found as a consequence of upregulated CPS-1 and ASS [89]. Acute exposure to low ethanol concentrations transiently leads to suppression

Table 2.1 Urea concentration in mammalian

	Mice	Rats	Dogs	Humans	Cows
Plasma urea concentration, mmol/l	9	5	4	5	5
Urine urea concentration, mmol/l	1,800	700	620	285	260
U/P urea	200	140	155	60	52
References	Yang and Bankir [215]	Yang and Bankir [215]	Spector et al. [174]	Yang and Bankir [215]	Spek et al. [175]

of the capacity for urea synthesis, presumably due to the decrease in the NAD/NADH ratio during catabolism of ethanol [86]. Protein amounts of CPS-1, ASS, and OTC are all decreased in perfluoroalkyl acids (synthetic toxicant with world-wide environmental distribution)-treated rats [199]. L-carnitine protects mice from an acute ammonia load by means of accelerating the rate of urea generation [42].

Excretion of Urea

Urea, as a terminal product, is subsequently excreted out of the organism after generation. It is well known for centuries that approximately 90 % of urea is eliminated in urine by the kidney, which is the origin of its name [44]. In humans, the daily excretion of urea in urine is around 30 g. Urea is excreted not only by glomerular filtration, but also by tubular secretion [96, 162]. Studies have also found excretion of urea in sweat [164], tears [183], saliva [2, 31], and digestive fluid (feces) [23, 29, 170] in humans.

Table 2.1 illustrates in numbers the special features of urea handling in different mammals. It shows the wide differences among humans, cows, dogs, rats, and mice in urinary urea concentration. The plasma urea level is relatively low (5–10 mmol/l) in these mammals, and the urea concentration in the urine may be 60 times higher than in the plasma in humans and up to 200 times in mice. Thus, a very large fraction of the concentrating effort of the kidney is devoted to the concentration of urea. Though the kidney is the main organ to dispose of urea, the process herein is not just as simple as filtration and concentration. Urea is “sequestered” in the inner medulla [193] via urea transporters that mediate intrarenal urea recycling process [15] (see Chaps. 9 and 13).

Clinical Significance of Urea

Urinary System

Clinicians usually use blood urea nitrogen (BUN) to measure the amount of nitrogen coming from urea in the blood as an index of renal function [187]. An increase in BUN is associated with many factors including the following: (1) Prerenal

causes. The most common manifestation is hypovolemia. Due to a shortage of renal blood supply, the glomerular filtration rate is reduced, causing an increase of BUN. This can occur as a result of massive hemorrhage or diarrhea. (2) Intrarenal causes, such as glomerulonephritis, chronic pyelonephritis, and toxic nephritis. A deficiency of renal function causes reduced excretion and leads to urea accumulation. (3) Postrenal causes. Whatever etiology leads to the blockage of the urinary tract can produce a high BUN level, such as prostatic hypertrophy, urolithiasis, and bladder cancer. These pathological changes press on the urethra and block urine flow, which interferes the major urea excretion pathway.

Above all, urea acts as an indispensable contributor in laboratory diagnosis and has a strong relevance with kidney. Unfortunately, BUN is inferior to other markers to evaluate renal function, even without mentioning that dysfunction of one kidney is often masked by the healthy one. BUN is not a reliable marker because it is easily influenced by causes unconnected to glomerular filtration rate, including tissue breakdown, high protein intake, and major gastrointestinal hemorrhage [187, 197]. It can be elevated in patients suffering from non-alcohol fatty liver disease [104]. Besides, BUN even increases with age while the fractional excretion of urea decreases with age [121]. The importance of evaluating renal function only by urea fades away due to the factors mentioned above.

Nonetheless, recent studies also unveiled clinical significance of urea in other fields. Fractional excretion of urea below 40 % was found to be a sensitive and specific index to differentiate transient from persistent acute kidney injury in patients [47], while another study showed fractional excretion of urea less than 35 % can distinguish acute kidney injury from its two main causes: prerenal state and acute tubular necrosis [33]. But other studies discovered that fractional excretion of urea changes are age related, suggesting that the above statistics may call for a reanalysis [121]. A study even declared that the fractional excretion of urea is a poor predictor of acute kidney injury, especially in distinguishing transient and persistent acute kidney injury [205]. The relationship between fractional excretion of urea and acute kidney injury is still waiting for clarification. Patients with diabetes mellitus and hypertension are predisposed to kidney diseases, and those with significantly low urinary urea concentration as a biomarker have a worse prognosis [20]. For geriatric patients, BUN is an independent predictor of morbidity to get urinary tract infections [60]. BUN is also one of the factors that predict the need for nephrectomy in patients with renal trauma [169].

Acute renal failure is a common complication of rhabdomyolysis [179]. BUN may be one of the important predictive factors to indicate the patients with rhabdomyolysis that may develop acute renal failure [38]. A similar trial in New York suggests that only BUN and blood creatinine can predict which patients with rhabdomyolysis will develop the complications of acute renal failure and require hemodialysis [56]. On the contrary, a case report exhibited the opposite result that BUN is not reliable [198]. The argument whether BUN is an appropriate predictor in this situation may need a further multicenter clinical trial or meta-analysis.

Kidney dialysis adequacy is determined presently through the use of a dimensionless parameter called the urea reduction ratio that compares the predialysis

with the postdialysis levels of BUN as determined through laboratory analyses of blood samples taken at the beginning and at the end of a dialysis treatment [12]. Patients with low or high urea levels exhibited higher mortality than those with medium levels, while both low and high levels of urea are independent predictors of all-cause mortality [177]. Dialysis disequilibrium syndrome is prevented by the use of dialysate-containing urea at a concentration similar to that of the patient's blood [87].

Circulation System

The BUN level has a strong predictive significance for cardiovascular outcomes and all-cause mortality. A number of studies strongly recommend monitoring BUN as a predictor of prognosis in both acute heart failure and chronic heart failure, resulting from the high correlation between increasing BUN and bad outcomes [7, 9, 34, 35, 37, 55, 57, 59, 78, 92, 97, 133, 151, 157, 168, 172, 214]. Quantitatively, a significant cardiovascular risk is associated with the diagnosis of chronic renal failure through the hematocrit, urea in plasma, and gender (HUGE) formula [152]. Moreover, during treatments for heart failure, BUN can identify patients destined-to-experience adverse outcomes associated with the use of high-dose loop diuretics—the patients can get maximum benefit from this double-edged sword by properly monitoring the BUN [128, 182]. A further study also considered BUN as a predictor to reflect the response of diuretics in acute heart failure [192].

The BUN level is a better factor than the creatinine level when it is associated with the hardness of decision to perform a cardiac catheterization on patients who present symptoms of unstable angina without known prior history of coronary artery disease [129, 158]. Still as a predictor, increasing BUN level correlates with a high long-term mortality in patients diagnosed as myocardial infarction [8, 107]. Even after coronary artery bypass grafting, a high BUN is still an independent risk factor for mortality, which strongly suggests cardiologists should monitor a patient's BUN level throughout their hospital course [70].

Respiratory System

Community-acquired pneumonia is common and is associated with a considerable risk of death [6]. After international multicenter derivation/validation studies, CURB-65 score (an abbreviation of confusion, BUN >7 mmol/L, respiratory rate ≥ 30 /min, BP ≤ 60 mmHg, and age ≥ 65 years) gets commonly used and widely practiced as an assessment tool of the severity and short-term mortality of community-acquired pneumonia in daily clinical work. Each element of the CURB-65 score counts 1 point and a bad outcome is revealed when the CURB-65 score is >3 points [99, 120, 213]. Considering its effective prediction of both bacterial

pneumonia [213] and viral pneumonia [120], the CURB-65 score may be an assessment tool regardless of pathogen. The CURSI score, in place of BP and age by shock index (SI), was also established for elderly patients [127]. A recent study of bacteremic pneumococcal pneumonia in elder patients also found a relation between BUN and mortality [155]. Another score called the PORT rule (respiratory rate, temperature, pH, BUN, and sodium concentration) was created to help pulmonologists make decisions about whether to hospitalize patients with mild community-acquired pneumonia [58]. Stevens–Johnson syndrome and toxic epidermal necrolysis are severe life-threatening conditions. Once bronchial epithelial is implicated in these conditions, they can cause acute respiratory failure. Elevated BUN is a variable in a multivariate analysis to predict at-risk patients who need early management of mechanical ventilation [139]. To assist physicians with difficult decisions about hospital admission for patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) presenting in the emergency department, 5 risk factors including prior intubation, initial heart rate $\geq 110/\text{min}$, being too ill to do a walk test, hemoglobin $< 100 \text{ g/L}$, and urea $\geq 12 \text{ mmol/L}$ were set up [176]. Patients who are assessed at score of 2 or higher are strongly recommended for hospitalization.

Digestive System

A large proportion of the digestive tract and glands are associated with urea in clinical practice. *Helicobacter pylori* infection is associated with a wide range of gastrointestinal diseases such as functional dyspepsia, gastroesophageal reflux disease, chronic active gastritis, peptic ulcers, and even gastric malignancies [39, 46, 132]. The marvelous discovery of *Helicobacter pylori* almost kicked peptic ulcer out of the surgical department, except for severe complications such as perforation and massive hemorrhage [201]. Nowadays, diagnosing *H. pylori* infection and then starting an eradication therapy is routine and fundamental knowledge for gastroenterologists in clinical practice around the world [111]. ^{13}C and ^{14}C urea breath tests are broadly used to probe the presence of *H. pylori* in stomach as the best type of noninvasive method in this field [10]. Patients firstly swallow a capsule containing urea labeled with ^{13}C or ^{14}C . If *H. pylori* is present in stomach, the bacterium metabolizes the urea into nitrogen and carbon (as CO_2). The CO_2 would be absorbed across the lining of the stomach into blood. It is eventually excreted through the lungs by breath. The result of a urea breath test is quantitative so as to estimate the integral load of the bacteria and severity of gastritis [134]. Physicians always call for another round of urea breath test to evaluate the eradication treatment, which is helpful for determining the next prescription [171]. As a mature technique and an easily acceptable one, as contrasted with endoscopic biopsy, the efficiency and safety when it is performed on children have been well proved and all-age stages of children have been benefited from this test [32, 194]. However, clinicians and technicians are supposed to realize the influences of baseline caused

by age and gender [115, 219]. Furthermore, in a proof-of-concept study, ^{13}C urea may be a suitable marker to assess the in vivo fate of colon-targeted dosage forms given by mouth (a special type of capsule) [159]. The ^{13}C urea breath test was found as a novel biomarker of diagnosis and treatment for tuberculosis in rabbits, so further research on humans can be valuable [85].

In acute hepatitis A, BUN level >36 mg/L is a predictor of mortality [110]. High BUN level independently contributes to prediction of mortality in pyogenic liver abscess patients [5]. In patients who have a paracetamol overdose, BUN per se can predict hepatotoxicity [200]. A new score consisted of BUN, hemoglobin, systolic blood pressure, and comorbid conditions apply to identify the risk stratification of acute upper-gastrointestinal hemorrhage. It marks the severity of the bleeding and judges whether the patient needs clinic intervention and hospital admission [22].

Acute pancreatitis is a devastating disease with extensive morbidity and mortality so that it is imperative that clinicians recognize patients who may end up in severe outcomes at an early stage. BUN, as a single marker, is a useful, routine, easy-to-perform sensitive index to predict the severity and the mortality of the acute pancreatitis in the early assessment [53, 190, 209, 210]. Pancreaticoduodenectomy, which is performed on patients with pancreatic carcinoma, etc., has a high morbidity rate of complications. A BUN level of 20 mg/dL or greater can help surgeons identify patients who are at increased risk of morbidity and mortality after pancreaticoduodenectomy [204]. Further study exhibited that high BUN on the first postoperative day is associated with an increased occurrence and severity of complications, including the occurrence of pancreatic fistula [150].

A BUN level of more than 40 mg/dL is also an independent preoperative predictor of higher 30-day mortality after esophagectomy [14]. Preoperative BUN/creatinine ratio in primary gastrointestinal cancer patients requiring surgery would be useful to predict the mortality caused by postoperative enteric fistulas [101], and a high BUN level independently predicts worse overall survival in patients with malignant bowel obstruction in the setting of Stage IV non-curative cancer [208]. After colectomy for colon cancer, preoperative BUN is one of the predictive risk factors for 30-day mortality and complications such as pneumonia and systemic sepsis [105].

Nervous System

Urea also plays multiple clinical roles in neuropsychiatry. It has been firmly proved that acute ischemic stroke patients have a bad outcome with renal dysfunction [30, 52, 100, 109, 140, 180, 188, 212]. Just based on the above, studies displayed that the BUN/creatinine ratio may be a novel predictor of early deterioration of stroke [102] and elevated BUN is an independent predictor associated with poor clinical outcome and mortality in acute ischemic stroke patients after

treatment with i.v. tPA [220]. Even though elevated BUN has been precluded as a predictor of pre-eclampsia during pregnancy [112], the decreased fractional excretion of urea ($\leq 35\%$) in pre-eclampsia is relevant. Soon after delivery, the fractional excretion of urea would return toward the normal range (50–65 %) [218]. What is more, BUN is considered as one of the biochemical indicators of delirium happening in the emergency department and intermediate care units [114, 24].

Others

Low BUN in routine pretherapeutic laboratory testing is significantly correlated with a higher T stage in patients with head and neck cancer and also correlates with the appearance of neck metastasis [135]. BUN, one of the elements in day +7 score, identifies risk of transplant-related mortality after hematopoietic stem cell transplantation in the first seven days [13, 173]. By measuring the concentration of urea in diluted lavage synovial fluid, we can estimate intra-articular synovial fluid volume in normal joints and joints with chronic arthritides [94].

In the past, dietary history was depended heavily on an individual's memory and level of motivation, nevertheless based on a randomized double-blind crossover feeding trial, urinary urea holds promise as a quantifiable bioindex of dietary protein intake with a formula: protein intake (g/day) = $63.844 + 1.11 \times (\text{urinary urea, g/creatinine, g})$ [19]. Higher BUN in premature newborns may be associated with the chance of metabolic diseases in later stages of life, such as diabetes, hypertension, and metabolic syndrome [119]. Vaginal fluid urea is a helpful marker in diagnosing premature rupture of membranes because fetal urine is the most important source of amniotic fluid, which helps us avoid unwanted obstetric complications such as chorioamnionitis and preterm birth [90].

Using a logistic model, a retrospective study displayed that the only variable that was independently associated with mortality in *Clostridium difficile* infection was renal failure by observing fourfold higher BUN levels in the non-survivor group [131]. A 13-year-old boy who was eventually diagnosed with blastomycosis after orthopedic surgery had an elevated BUN as his first sign [103]. BUN ≥ 10 mmol/L is a risk factor for bacterial coinfection in dengue patients [165]. BUN is significantly associated with a low concentration of efavirenz, which is widely prescribed for people infected with HIV, in blood [178]. It can hence improve the prediction of efavirenz plasma concentration and optimize its dosing in antiretroviral therapy. In patients with Fournier's gangrene, BUN is significantly different between survivors and non-survivors and it is the only parameter that decreases to normal at the end of the treatment in the survivor group [189].

Urea-containing cream is prescribed for dermatitis, xerosis, ichthyosis, psoriasis, onychomycosis, eczema, tinea pedis, etc., as a topical antifungal emollient and moisturizer [1, 49, 138, 167, 181]. Urea clearance can be used as a relatively simple method to estimate drug-induced blood flow changes in human skin during microdialysis of vasoactive substances [54].

Patients who underwent emergency laparotomy have high 12-month mortality if preoperative BUN >7.5 mmol/L, suggesting that this is an independent predictor [11]. Elevated BUN is a valuable predictor for increased long-term mortality in various critically ill patients regardless of their precise disease [18, 77]. The significance of urea/albumin ratio in predicting the stay and mortality of critical patients was found, based on a retrospective study of patients admitted to ICU with non-chronic kidney disease [65]. These results are accordant with finding that BUN is linked to mortality in a number of diseases. A simple 5-point scoring system, NaURSE (Na⁺, Urea, Respiratory Rate and Shock Index in the Elderly), was created to predict in-hospital mortality in acutely ill older patients. The crude mortality rates were 9.5, 19.9, 34.4, 66.7, and 100 % for scores 0, 1, 2, 3, and 4, respectively [203].

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