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Tryptophan Metabolism and its Relation with CKD Patients

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Abstract

Signs and symptoms of chronic kidney disease (CKD) are usually not present during early stages of disease. If diagnosed early, the progression of CKD could be slowed down. Finding an early diagnostic or predictive marker is of great benefit for both nephrologists as well as patients. Recent development in metabolomics has shown a potential progress in finding a novel biomarker to predict disease progression. In recent years, tryptophan (TRP) metabolites have shown a possible role in CKD pathogenesis and progression of disease. There are accumulations of toxic TRP metabolites in CKD. This review presents possible role of TRP metabolites in CKD. However, for defining their role as a predictive biomarker more and large cohort studies are required.

Keywords: Chronic Kidney Disease; Tryptophan; Indoleamine 2,3-dioxygenase; Kynurenic Acid; Quinolinic Acid; Hemodialysis; Peritoneal Dialysis; Cardiovascular Disease; Chronic Kidney Disease; End Stage Renal Disease

Abbreviations: TRP: Tryptophan; IDO: Indoleamine 2,3-dioxygenase; KYNA: Kynurenic Acid; QA: Quinolinic Acid; HD: Hemodialysis; PD: Peritoneal Dialysis; CVD: Cardiovascular Disease; CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease.

Introduction

Various serious and chronic conditions like, neurological diseases [1-3], psychiatric disorders [1,4-9], the early onset of cardiovascular disease (CVD) [10-14], chronic kidney disease (CKD) and even renal allograft rejections [15] are associated with inflammation, oxidative stress and tryptophan (TRP) metabolism. An increase in symptoms of anxiety, depression and decrease in cognitive functions are often followed by the progression of CKD to end stage renal disease (ESRD) [16-18]. Because there is a flap in between the psychological symptoms and the symptoms of uremia, these are less commonly diagnosed in CKD patients. The frequencies of the hospitalization affected by these symptoms are high and so, they play an important role in the disease progression and mortality rates [19]. Since oxidative stress and inflammation are already noticeable in the moderate stages of CKD, an early intervention is needed [20]. These factors strengthen the TRP metabolism via the kynurenine pathway (KYN).

The synthesis of nictotinamide adenine dinucleotide (NAD) (Figure 1), a coenzyme essential for energy metabolism

is carried out by an essential amino acid L-tryptophan (TRP) [21,22]. Normally, the majority of free TRP (~95%) is metabolized forth the KYN pathway in the liver by the enzyme tryptophan 2,3-dioxygenase (TDO) which is highly expressed in the hepatic cells mostly controlled by TRP levels [23-26]. In the case of inflammation such as chronic low-grade inflammation in old aged people or as in CKD (8) a significant translocation in KYN pathway occurs by an enzyme indoleamine 2,3-dioxygenase 1 (IDO1) mainly expressed extrahepatically induced by pro-inflammatory molecules particularly by the cytokine IFN-Y promoting the production of a sensitive immune response marker neopterin [27]. Quinolinic acid (QA), 3-hydroxykynurenine and kynurenic acid (KYNA) etc. collectively called as kynurenines are eventually produced by KYN pathway and are normally eliminated via urinary excretion. Kynurenines play a vital role in controlling adaptive immunity and are involved in comorbid neuropsychiatric and atherosclerosis symptoms. Patients with CKD (Figure 2) are at high risk of KYN-related pathophysiologies [28]. TRP metabolites may trigger fatigue and promote atherosclerosis in CKD patients by activating oxidative stress and leukocyte activation in endothelial and vascular smooth muscle cells [29]. Hence, in this update article we tried to explain the role of TRP metabolites as predictive markers in patients with CKD.

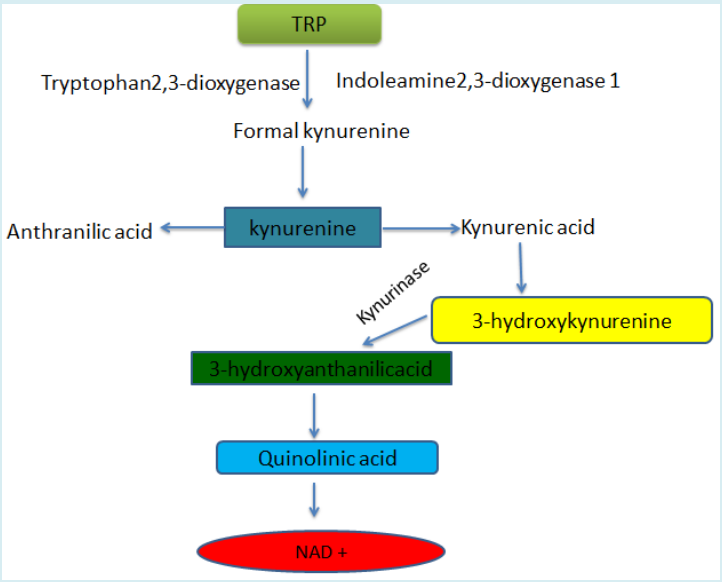

Figure 1: The tryptophan (Trp), metabolism takes place in the liver under the presence of the relevant enzymes and results in the biosynthesis of nictotinamide adenine dinucleotide (NAD+).

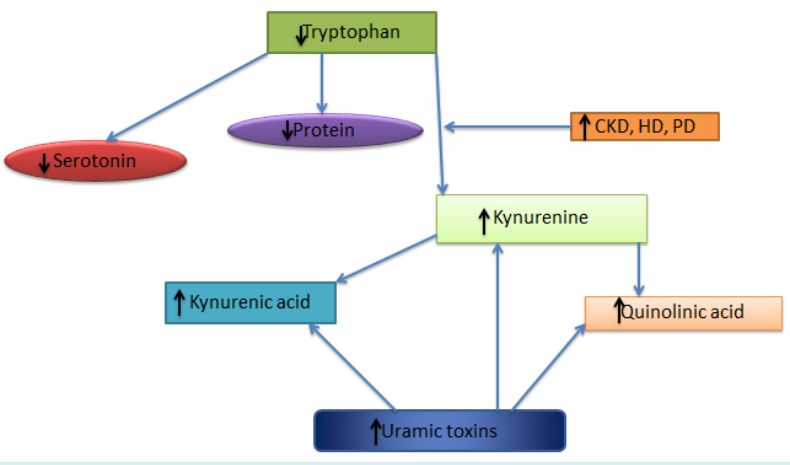

Figure 2: Indications for the accumulation of metabolites of the kynurenine pathway in CKD patients for lower Trp and serotonin levels.

Discussion

Recent studies on TRP and KYN pathway in hemodialysis (HD) and peritoneal dialysis (PD) has shown a promising aspect of using TRP metabolites as inflammatory markers in CKD patients. Study conducted by Bipath Priyesh and Vijoen Margaretha suggested the significant role of TRP in ESRD. They showed the depletion of tryptophan and accumulation of kynurenine and quinolinic acid in the blood of HD patients [30]. Subrata Debnath, et al. concluded that CKD secondary to diabetes mellitus (DM) type 2 may be associated with accumulation of toxic TRP metabolites because of both impaired kidney function and inflammation. They highlighted the need for future studies with large cohort of patients to determine the accumulation of KYN directly contributes to progression of CKD and associated symptoms in DM type 2 patients [31]. Mutsaers, et al. reported that there is a direct connection between TRP metabolism and the circadian rhythm in patients with CKD. They concluded that altered tryptophan metabolism is considered an etiology for CKD-associated fatigue [29]. Studying the tryptophan metabolism and its relation to psychological and cognitive functioning in CKD disease Naam Karu, et al. found the association of indole 3 acetic acid and psychological measures as novel findings [32]. Kato A and his group studied the association of TRP metabolites with atherosclerotic parameters in HD patients. The study included 243 HD patients and it was found that TRP metabolites increases with time on HD, and is associated with advanced atherosclerotic changes in chronic HD patients [33]. In a study conducted on 20 PD, 19 HD and 21 kidney transplant patients by Nigar Yilmaz, et al. showed increased (IDO) levels compared to the control group. The concentration of kynurenine was significantly increased in the PD group compared to the other groups while oxidative stress was found to be related to IDO activity and was most increased in the patients on PD [34].

Symptoms of CKD are normally not visible during early stages. Significant loss of the kidney function is the first obvious sign of the kidney disease. If diagnosed in the very beginning, the progression of CKD can be controlled hence reducing the complications. The systematic review of metabolites like, amino acids, sugars, organic acids, etc. in biologic fluids or samples can be used as predictive biomarkers, generally termed as metabolomics or metabolite profiling [35]. In clinical research the value of metabolite profiling could be achieved when applied to large cohorts. This can be enhanced by assessment of the association of baseline metabolite levels with renal outcomes.

The longitudinal association of baseline levels of 217 metabolites with incident of CKD in eight years and over in 1434 participants were described in the Framingham Heart Study (FHS) [36]. Similarly Goek, et al. investigated longitudinal associations of baseline values of 140 metabolites over seven years in 1017 individuals in the KORA study [37]. Both of the studies identified markers of TRP metabolism are associated with the occurrence of CKD [38-40]. A total of 123 individuals in the FHS study and 106 individuals in the KORA study developed new-onset CKD. In both of the studies, kynurenine/tryptophan ratio was strongly associated with CKD risk, with an odds ratio (OR) of 1.36 per SD (p: 0.003, 95% confidence interval [95%CI], 1.11 to 1.66) after adjusting for eGFR and other CKD risk factors. Whereas in the FSH study, authors highlighted that KYN (OR per + 1 SD, 1.49; p<0.001, 95% CI, 1.25to 1.88) were related to the high risk of future CKD. These findings showed TRP metabolites can serve as predictive marker for incident CKD risk.

Conclusion

Healthy kidneys are important in TRP metabolism and TRP metabolites are eliminated in the urine. In diseased kidneys there are building up of several toxic metabolites including kynurenines collectively called as protein bound uremic toxins. Due to low TRP levels and accumulation of toxic metabolites patients on dialysis experience depression, sleep disturbances, anxiety, impaired cognitive function and other symptoms and complications. A large number of studies have shown the involvement of TRP metabolism in CKD. There is a need of large cohort study to prove its critical role in disease progression and as predictive biomarker.

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