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Podocyte involvement in the pathogenesis of preterm-related long-term chronic kidney disease

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Summary. With the continuous advancement of neonatal intensive care technology, the survival rate of preterm infants is gradually increasing. However, this improvement in survival is accompanied by long-term prognostic implications in various systems. In the field of renal diseases, current epidemiological data indicate that preterm birth is a significant risk factor for the development of long-term chronic kidney disease (CKD). This not only imposes an economic burden on patients families but also severely impacts their quality of life. Understanding the underlying mechanisms involved in this process could offer potential strategies for early prevention and management of CKD. Although the nephron number hypothesis is currently widely accepted as a mechanism, there has been limited exploration regarding podocytes - one of the most important structures within nephrons - in relation to long-term CKD associated with preterm birth. Therefore, this review aims to summarize current knowledge on how prematurity influences CKD development overall, while specifically focusing on our current understanding of podocytes in relation to prematurity.

Key words: Podocyte, Chronic kidney disease, Preterm

Introduction

Preterm birth is the leading cause of mortality among children under the age of 5 (Walani, 2020; Guarini et al., 2021; Cao et al., 2022). According to the global preterm birth data released by the WHO in 2018, the worldwide prevalence of preterm births is approximately 10.6%, with China ranking second with an estimated rate of 7.1% (Vogel et al., 2018; Cao et al., 2022; Montemor et al., 2022). While advancements in neonatal treatment technology and care have improved survival rates for preterm infants, particularly those with very low and extremely low birth weights, comprehensive management strategies for these infants are increasingly more crucial (Mercuro et al., 2013; Dutta et al., 2015; Bonadies et al., 2023). In addition to focusing on their immediate survival, attention must also be given to long-term outcomes across various organ systems to ensure individual quality of life (Blencowe et al., 2013; Siffel et al., 2022; Canvasser et al., 2023). Epidemiological studies indicate that preterm birth is a significant risk factor for long-term diseases affecting multiple organ systems (Gubhaju et al., 2011; Jensen and Schmidt, 2014; Ream and Lehwald, 2018; Crump et al., 2021). Currently, chronic kidney disease (CKD) poses a substantial and escalating global burden (Bikbov et al., 2020; Levey et al., 2020), and clinical research has confirmed that preterm birth contributes as a risk factor for CKD development (Eriksson et al., 2018; Crump et al., 2019; Chopra and Saha, 2020; Chainoglou et al., 2022; Grillo et al., 2022). Early kidney development plays a critical role in determining long-term renal outcomes, thus highlighting the increasing importance placed on understanding the mechanism of preterm birth-related long-term CKD. According to current knowledge, the nephron number hypothesis is widely accepted as the primary mechanism involved in long-term CKD related to preterm birth (Thomas and Kaskel, 2009; Nishizaki and Shimizu, 2022; Good et al., 2023). However, there has been limited exploration of the role of podocytes, one of the most crucial structures within the nephron, in this process. Therefore, this review aims to present a comprehensive understanding of the involvement of podocytes in long-term CKD associated with preterm birth.

Preterm birth is an important risk factor for long-term CKD

Effects of preterm birth on kidney development

The development of the human kidney initiates during the first trimester, with glomerular formation

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commencing at 9-10 weeks of gestation. Subsequently, there is an exponential growth of nephrons in the second and third trimesters, culminating in nephron development completion by 36 weeks (Dakovic Bjelakovic et al., 2018; Ryan et al., 2018). There is limited data regarding the impact of preterm birth on kidney development. Autopsy reports indicate that immature glomeruli continue to develop and undergo accelerated maturation after premature infants are born (Rodríguez et al., 2004). Moreover, preterm birth results in a reduction in total glomerular count and an increase in the abnormal glomerular formation proportion, thereby affecting postnatal renal function in preterm infants (Gubhaju et al., 2011; Sutherland et al., 2011; Black et al., 2013). The decrease in glomerular numbers leads to hyperfiltration within the remaining glomeruli, causing glomerular hypertrophy accompanied by secondary damage to both podocytes and the glomerular basement membrane. In addition to its effects on kidney development, adult hypertension is generally associated with kidney and cardiovascular development early in life. Preterm birth results in a reduced glomerular filtration area, which leads to limited sodium excretion and elevated blood pressure. Consequently, this cascade may result in proteinuria, glomerulosclerosis, and ultimately renal failure (Hayashi et al., 2014; Dyson and Kent, 2019; Chainoglou et al., 2022). Furthermore, exposure to various nephrotoxic substances following birth, such as gentamicin, amphotericin B, and indomethacin, can induce acute kidney injury among premature infants (Rodríguez et al., 2004; Fagerudd et al., 2006), potentially leading to the development of CKD.

Correlation between preterm birth and long-term CKD

Epidemiological studies have demonstrated an association between preterm birth/low birth weight and an elevated risk of long-term CKD (Luyckx et al., 2013). Preterm infants exhibit a significantly reduced number of nephrons compared with full-term infants, rendering them more susceptible to CKD development with advancing age (Nada et al., 2017). It is estimated that preterm birth accounts for 80% of low-birth-weight cases, and a meta-analysis conducted by White et al., involving over 2 million individuals from 31 studies revealed that individuals with low birth weight had an approximately 80% higher likelihood of proteinuria and persistently low glomerular filtration rate (GFR) compared with those with normal birth weight. Furthermore, the risk of developing end-stage renal disease (ESRD) in later life was increased by approximately 60% (White et al., 2009). The meta-analysis results also support the aforementioned notion that proteinuria serves as an independent risk factor for both the occurrence and progression of CKD, ultimately leading to ESRD (Tsai et al., 2016; Coresh et al., 2019). In a study conducted by Vikse et al., in 2008, encompassing all registered births in Norway from 1976 to 2004, totaling around 2.18 million people, it was observed that, among the population below the tenth percentile for both birth weight and gestational age, there was a relative risk (RR) increase of ESRD incidence by factors of approximately 1.7 and 1.5, respectively; thus highlighting preterm birth/low birth weight as significant risk factors of long-term ESRD (Vikse et al., 2008). Crump's extensive study published in 2019, which included nearly 4.2 million individuals from a Swedish registration database spanning from 1973 to 2014, provided further evidence of the relationship between gestational age at delivery and long-term CKD occurrence. The incidence of CKD in full-term infants is 4.47 per 100,000, whereas in premature infants, the incidence rises to 9.24 per 100,000, representing a twofold increase compared with full-term infants. In extremely preterm infants with gestational ages of less than 28 weeks, the incidence of CKD reaches as high as 13.3 per 100,000, which is approximately three times higher than that observed in full-term infants. Notably, there is an inverse relationship between gestational age and long-term CKD risk; thus confirming preterm birth as a significant predisposing factor for the future development of CKD based on robust evidence from large-scale studies (Crump et al., 2019).

Mechanism of long-term CKD associated with preterm birth

The general mechanism of long-term CKD associated with preterm birth - nephron number hypothesis

The mechanism underlying the development of long-term CKD associated with preterm birth remains poorly understood. Brenner and Garcia proposed a hypothesis suggesting that individuals born with fewer nephrons in their kidneys are at an increased risk of hypertension and renal disease later in life (Brenner and Garcia, 1988). This theory, known as the "nephron number hypothesis," is currently considered the most plausible mechanism for explaining the link between preterm birth and long-term CKD. From a developmental perspective, human kidney development initiates at 9-10 weeks of gestational age and completes nephrogenesis by 36 weeks (Dakovic Bjelakovic et al., 2018; Ryan et al., 2018). The majority of nephron formation occurs during late pregnancy, which coincides with the gestational age at birth for most preterm infants. Consequently, the kidneys of preterm infants are born before reaching full maturity. Although nephrogenesis can continue up to 40 days after birth, the nephrons formed tend to mature prematurely and exhibit abnormalities (Rodríguez et al., 2004). In this study conducted by Rodriguez et al., they included 56 preterm infants weighing less than 1,000 g and with a gestational age between 24 to 27 weeks. Through pathological analysis of kidney samples from these infants, it was observed that kidney development continues postnatally but does not cease immediately

after birth. Kidney development in preterm infants with a gestational age of 24-27 weeks typically extends until approximately day 40 after birth before stagnating (Sulemanji and Vakili, 2013). Moreover, there was a higher proportion of abnormal nephrons, particularly glomerular structures, in preterm infants compared with term infants. These findings have also been supported by primate studies. Gubhaju et al., established a preterm primate animal model, and their study findings demonstrated that the prevalence of abnormal glomeruli, such as those with dilated Bowman's space and shrunken glomerular tuft, ranged from 0.2% to 18% in preterm animal models (Gubhaju et al., 2009). This suggests a significantly higher proportion of abnormal nephrons in preterm infants compared with full-term infants. Human and primate studies have consistently confirmed an increase in the number of abnormal nephrons due to preterm birth, while the number of normal nephrons is expected to decrease. Additionally, Stelloh et al., using a preterm mouse model, quantified nephrons at 30-35 days post-birth (when mouse kidneys are anticipated to be fully developed) (Stelloh et al., 2012). Their research revealed a significant reduction in the number of nephrons in preterm mice compared with full-term mice. Thus, both human and animal studies support the notion that preterm birth leads to diminished nephron numbers.

In the context of reduced nephron number, renal function may be sustained through hyperfiltration, with proteinuria serving as an early clinical indicator. Several cases have demonstrated the presence of proteinuria in individuals with a history of preterm birth, and Hoy et al., reported that low birth weight contributes to an elevated albuminuria ratio and increased risk of renal disease in a large cohort study (Hoy et al., 1999). Although gestational age information was not available in this study, it is likely that most individuals with low birth weight were born prematurely. During pregnancy, the kidney is in a "stress-free environment" with filtration processes supported by the placenta. Following birth, multiple factors may also affect nephron function, especially in preterm infants. A major shift in hemodynamics occurs at birth, with blood pressure and heart rate rising significantly and renal blood flow increasing. As a result, the developing capillaries of immature glomeruli may not be adequately prepared for hemodynamic transitions at birth, and their formation is adversely affected. These adaptive hemodynamic changes are responsible for glomerular hypertension and glomerular hyperfiltration, which then leads to heightened capillary perfusion pressure, resulting in glomerular injury, hypertrophy, glomerulosclerosis, and CKD. Hodgin et al., in 2009, first identified preterm birth/low birth weight as a significant pathological risk factor of CKD (Hodgin et al., 2009). Their study analyzed six patients aged 32 years with focal segmental glomerulosclerosis (FSGS), whose gestational ages ranged from 22-30 weeks and birth weights ranged from 450-1420 g. Pathological analysis and related factors ultimately determined that the FSGS pathology observed in these six patients represented adaptive changes secondary to decreased nephron count caused by preterm birth. Based on this pathological analysis, the study concluded that preterm birth is a risk factor for long-term pathological changes associated with kidney disease.

Subsequently, Ikezumi et al. conducted a comprehensive study encompassing all patients diagnosed with FSGS at Niigata University Medical and Dental Hospital in Japan between 1995 and 2011. Their findings revealed that a substantial proportion (37.5%) of these patients had low birth weight, which significantly exceeded the local area's overall incidence rate of 9.7%. Renal pathological analysis demonstrated a markedly higher prevalence of glomerular compensatory enlargement and glomerular sclerosis in the low-birth-weight group compared with those with normal birth weight. Notably, the mean gestational age of these cases was determined to be 25.8 weeks, thus confirming preterm birth or low birth weight as significant risk factors contributing to long-term pathological changes associated with kidney disease (Ikezumi et al., 2013). Consequently, it is imperative to consider reduced nephron number resulting from preterm birth as one of the underlying pathogenic mechanisms leading to CKD development.

Cellular mechanism of long-term CKD associated with preterm birth -podocyte depletion hypothesis

While most studies have focused on the general mechanism of preterm birth on nephrons, the underlying cellular mechanisms remain poorly elucidated. In the field of renal diseases, research on the pathogenesis of CKD in both children and adults has indicated that glomerular diseases are primarily responsible for CKD development (Webster et al., 2017). Glomerular disease accounts for approximately 90% of ESRD cases in the United States. The glomerular filtration barrier, composed of podocytes, glomerular basement membrane, and endothelial cells, plays a pivotal role in filtration processes. Podocytes serve as key components within this barrier structure and their quantity and maturation are crucial determinants for proper glomerular filtration function (Griffin 2003; Hishikawa and Fujita 2006). Current evidence confirms that reduced podocyte numbers significantly contribute to the initiation and progression of glomerular diseases while dysfunction or loss of podocytes profoundly impairs overall glomerular function (Wiggins, 2007; Ding et al., 2017). Animal models have demonstrated that a mere 20% loss in podocyte population can lead to mesangial expansion, whereas losses ranging from 20-40% result in denuded areas within the glomerular basement membrane along with segmental sclerosis. As podocyte loss exceeds 40%, progressive glomerulosclerosis occurs until it surpasses a threshold of 60%, leading to a complete loss of filtration function accompanied by varying degrees of proteinuria (Kim et al., 2001;

Wharram et al., 2005). These findings underscore the critical role played by podocytes in kidney diseases. However, limited attention has been given thus far to investigating the involvement of podocytes in long-term CKD associated with preterm birth. In a previous study conducted by Ikezumi et al. kidney podocytes of FSGS patients were stained to estimate their number, revealing a 33% decrease in podocyte count among FSGS patients with low birth weight compared with those with normal birth weight. This finding suggests that the loss of podocytes is more pronounced in children with low birth weight or preterm birth (Ikezumi et al., 2013). Furthermore, another study utilized a unilateral nephrectomy model to simulate nephron loss caused by preterm birth and found that greater nephron depletion led to more severe long-term damage and reduced coverage area of podocytes, indicating an increased risk of long-term podocyte loss (Oliva Trejo et al., 2014; Eladl et al., 2017). Additionally, our research team recently published literature comprehensively confirming the alterations and underlying mechanisms of podocytes in animal models of preterm birth as well as in preterm infants (Ding et al., 2021b; Zhang et al., 2023). In a preterm rat model, we quantified the number of differentiated podocytes after kidney development completion and demonstrated an approximate 18% reduction in total differentiated podocyte count due to preterm birth (Ding et al., 2021a; Zhang et al., 2023). Furthermore, we conducted long-term follow up on these preterm rats and dynamically monitored changes in their podocyte population from birth to 12 months (equivalent to middle age in humans) using two methods: urine-based podometric analysis and kidney sample-based podometric analysis. The mRNA levels of urinary podocytes revealed a gradual increase in podocyte loss among preterm rats, ranging from 1.5-fold at three weeks after birth to 32-fold at twelve months. Additionally, kidney sample evaluation indicated a reduction in podocyte density by approximately 18% to about 32% among preterm rats. This study not only suggests that preterm birth can lead to decreased numbers of podocytes but also drives progressive loss of these cells during growth, ultimately significantly increasing the risk of CKD development. Therefore, for the first time, this study introduces the concept of "podocyte depletion" into the pathogenesis underlying long-term CKD associated with preterm birth. Apart from utilizing animal models for prematurity research, our team also included infants born prematurely at different gestational ages, as well as full-term infants. Urine samples were collected and analyzed for urinary excretion of podocytes once gestational age was corrected. The results revealed a fivefold increase in podocyte loss in preterm infants compared with full-term infants. Additionally, lower gestational age and small for gestational age were identified as high-risk factors associated with podocyte loss. However, this human study lacks follow-up data, and it remains unclear whether the findings from preterm animal models can be extrapolated to preterm infants and whether podocyte loss in preterm infants continues to remain significantly higher during childhood and adulthood compared with full-term infants (Gao et al., 2023). If persistent podocyte loss occurs in preterm infants, according to the podocyte depletion hypothesis, further depletion of podocytes could contribute to the development and progression of CKD, thereby elucidating the specific mechanism underlying the increased long-term CKD risk associated with preterm birth from a perspective centered on podocyte depletion.

Molecular mechanism of long-term CKD associated with preterm birth

Currently, studies have implicated podocytes in the mechanism of long-term CKD associated with preterm birth; however, there is limited research on the molecular mechanisms involved. In a previous study by Magella et al. single-cell sequencing analysis revealed that *GDNF* plays a crucial role in normal branch morphogenesis of ureteral buds during early kidney development. Knocking out this gene resulted in impaired kidney development, providing significant insights into both early kidney development and potential treatment strategies for kidney diseases using progenitor cells and stem cells (Magella et al., 2018). Additionally, Alison et al. reported that TSC1 mediates the Wnt signaling pathway to determine the final number of nephrons (Jarmas et al., 2021). However, these studies primarily focused on the early stages of kidney development, while preterm birth occurs during the middle and late stages. The impact of preterm birth factors on these later stages and their contribution to reduced mature nephron and podocyte numbers remain unclear. Reports on human nephron counts rely heavily on autopsy specimens from kidneys obtained postmortem (Faa et al., 2010). Therefore, it is clinically important to search for alternative markers for evaluating nephron and podocyte numbers. To address this gap, our research team utilized single-cell sequencing to establish a molecular map specifically targeting the middle and late stages of kidney development corresponding to gestational age in preterm rats (Ding et al., 2021b). We observed that the podocytes of full-term rats exhibited a significant enrichment of genes associated with ribosomes, which are essential organelles involved in protein synthesis (Dai and Zhu, 2020). This enrichment suggests a high rate of protein synthesis in podocytes during normal development (Tahmasebi et al., 2019). Conversely, the podocytes of preterm rats displayed an enrichment primarily related to kidney development, including podocyte-specific genes and precursor genes. These findings indicate that preterm delivery may expedite podocyte differentiation (Ding et al., 2021b; Zhang et al., 2023). Our study elucidates the molecular dynamics occurring during the mid-to-late stages of kidney development until maturity and provides valuable insights to further understand the molecular mechanisms

underlying the heightened risk of long-term CKD resulting from preterm birth.

Monitoring and preventive actions of long-term renal disease associated with preterm birth

Though the molecular mechanisms involved in preterm-related long-term CKD are not fully identified, long-term follow-up and early intervention based on the current situation are needed, from preterm infants to adulthood, to protect kidney function. Therefore, it is imperative to implement long-term follow-up and early intervention strategies encompassing the entire lifespan of preterm infants in order to protect kidney function. Follow-up and intervention measures mainly include the following four aspects. The first is to advise preterm individuals to avoid exposure to potentially nephrotoxic drugs and factors that increase the burden on the kidneys. Secondly, regular monitoring of blood pressure levels is essential, with efforts focused on maintaining normalcy and stability within these parameters. Thirdly, reduce currently known risk factors of CKD, such as obesity, anemia, smoking, diabetes, and dyslipidemia. Lastly, routine assessment of kidney function including serum creatinine levels, cystatin C levels, or urine albumin measurements should be carried out (Stritzke et al., 2017; Crump et al., 2019; Grillo et al., 2022).

Conclusions and future perspectives

With the advancement of neonatal intensive care technology, there has been a gradual increase in both birth and survival rates of preterm infants, particularly those born extremely preterm. However, as these preterm infants grow older, the issue of long-term prognosis becomes increasingly prominent. Epidemiological data have confirmed that preterm birth is a significant risk factor for the development of CKD in the long run. The main distinction in kidney development between preterm and full-term infants lies in the postnatal stage experienced by preterm infants outside the womb, which serves as a starting point for long-term CKD development. Therefore, research efforts primarily focus on the early postnatal stage of preterm infants. The pathogenesis related to CKD resulting from preterm birth is relatively complex, with reduced nephron number and structural abnormalities being important factors that may contribute to long-term CKD. Preterm infants typically exhibit an underdeveloped kidney structure and function at birth, resulting in a significantly increased risk of developing CKD from childhood to adulthood. Early identification, diagnosis, monitoring, and timely protection of renal function are crucial for improving the long-term outcomes of preterm infants. Currently, traditional biomarkers such as creatinine can reflect the extent of kidney injury, however, there is a time lag between traditional biomarkers and initial kidney injury; also, the location of kidney injury cannot be distinguished, which has certain limitations in reflecting kidney function, thus limiting their use in early CKD prediction. Thus, there is an urgent need to develop new specific biomarkers that enable real-time identification of changes in renal function for early diagnosis and monitoring of disease progression. Modern omics technology reflects the function and metabolic state of the body, organs, or cells through overall analysis, and is expected to discover new signaling pathways and biomarkers, which will help improve the early monitoring of initial damage and improve the long-term prognosis of the disease. The

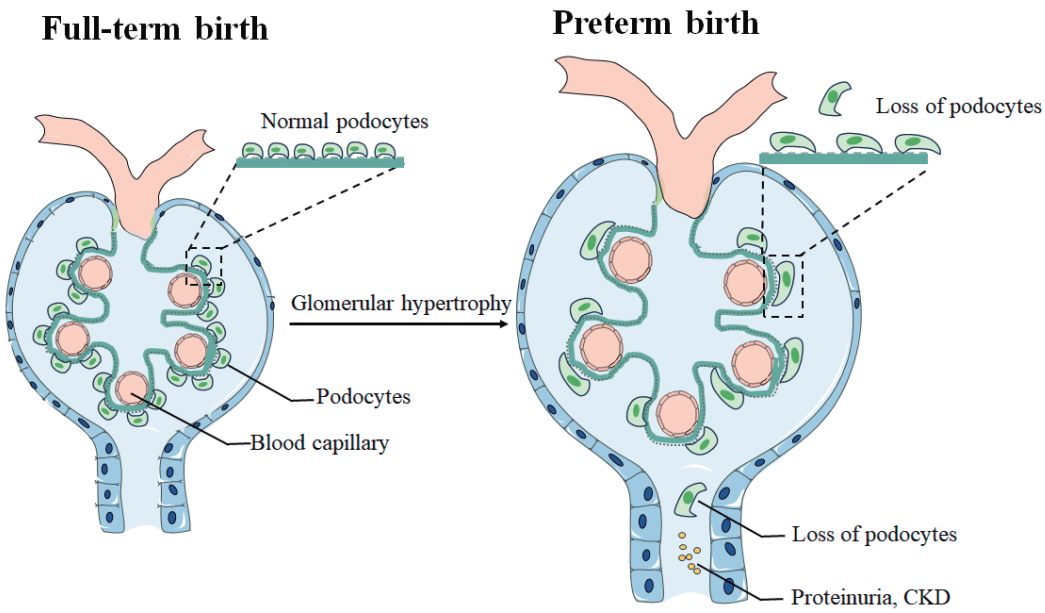

Fig. 1. Cellular mechanism of preterm-related long-term chronic kidney disease. Preterm birth leads to a reduction in podocyte endowment, accelerated podocyte detachment, glomerular hypertrophy, proteinuria, glomerulosclerosis, and then CKD.

field of nephrology omics is still under research but has the potential to accurately predict, treat, and improve clinical outcomes for patients with nephropathy (Joshi et al., 2017; Grobe et al., 2023). In addition, podocytes play a crucial role as key components of the glomerular filtration barrier; thus, their quantity and morphology are core determinants in glomerular disease progression (Fig. 1). Consequently, clinical attention is directed towards preventing and minimizing podocyte injury. Through single-cell sequencing analysis, we have further elucidated the significant involvement of ribosome-related molecules during the middle and late stages of kidney development-enhancing our understanding of how they contribute to long-term CKD associated with preterm birth pathogenesis. Early abnormalities observed in preterm infants lead to a gradual process culminating in long-term CKD-a condition requiring not only attention from obstetrics and neonatology departments but also collaborative efforts from pediatric and adult nephrology departments alike. An in-depth exploration of the stage mechanism is not only beneficial for the prevention and treatment of CKD but also aids in alleviating the financial burden on patients' families. Therefore, it is imperative that relevant studies encompass long-term comprehensive management strategies for premature infants, aiming to identify disease-related risk factors during their growth and effectively intervene in disease occurrence and progression, ultimately enhancing the long-term quality of life of these infants.

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