

MRI for Evaluating DKD Noninvasively

Subjects: Radiology, Nuclear Medicine & Medical Imaging | Urology & Nephrology | Cardiac & Cardiovascular Systems

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(This entry belongs to Entry Collection "Nuclear Magnetic Resonance")

Definition

Renal magnetic resonance techniques provide noninvasive information on renal volume, function, metabolism, perfusion, oxygenation, and microstructural alterations, without the need for exogenous contrast media.

1. Introduction

Diabetes mellitus (DM) is one of the most prevalent chronic diseases worldwide, and its incidence and prevalence continue to increase [1]. Diabetic kidney disease (DKD) is a major long-term complication of DM and the leading cause of kidney failure [2][3]. Microcirculatory disturbances have been recognized as an early and consistent pathogenic trigger of DKD, although different clinical phenotypes and mechanisms related to the progression of DKD have been identified. The use of renal magnetic resonance imaging (MRI) techniques is breaking new ground in the microstructural evaluation of the kidney [4], providing a better understanding of the pathophysiology at different phases of DKD. These tools are expected to facilitate the early detection of DKD, as well as its progression phenotypes, inform the decision-making/monitoring process for therapies, and pave the way to a more personalized medical care.

2. Pathogenesis and Natural History of DKD

The main clinical manifestation is the presence of albuminuria, which can range from mildly increased albuminuria (albumin-creatinine ratio (ACR) > 30 mg/g) to moderate albuminuria (ACR 30–300 mg/g) or severe albuminuria (ACR > 300 mg/g). In a study of 1 diabetes (T1D) patients over 25 years showed that the development of severe albuminuria was rare before 10 years of diabetes duration and increased steadily thereafter. However, after the diagnosis of severe albuminuria, it was observed a 52% cumulative incidence of regression of albuminuria to less than 300 mg/g at 10 years and a 13% cumulative incidence of regression to less than 30 mg/g. In T1D subjects for an average of 12 years, after the onset of mildly increased albuminuria, and observed that almost one-third of the patients progressed to kidney failure, although nearly half had no significant variations in albuminuria levels.

In DKD, the urinary sediment is usually bland; however, the presence of microscopic hematuria may occur as in any form of glomerular disease [5]. This is important since nondiabetic kidney disease is occasionally seen in diabetic patients, either alone or with superimposed DKD [6]. Depending on the population studied, the most frequent glomerulopathy may be focal segmental glomerulosclerosis (FSGS) [7], hypertensive nephrosclerosis [8], membranous nephropathy, or IgA nephropathy [9].

In contrast to these features, an autopsy study (n = 168) revealed a DKD prevalence of 63% in diabetic subjects with a history of T1D and T2D. Interestingly, 19% of the subjects had never experienced clinical manifestations of DKD during their lifetime. Among these underdiagnosed subjects, a variety of diverse histologic patterns were found. These findings suggest that DKD lesions precede the appearance of clinical manifestations [3].

The classic histological features of DKD include loss of endothelial fenestrations, thickening of capillary, tubular, and glomerular basement membranes, expansion of the mesangial matrix, and loss of podocytes [10]. Subsequently, segmental mesangiolysis, Kimmelstiel-Wilson nodules, and microaneurysms are observed [11].

Subsequently, secondary hyperfiltration by unaffected glomeruli results in increased oxygen consumption and exacerbation of hypoxic renal injury [12]. Furthermore, two of the main risk factors for progression of

DKD (hyperglycemia and hypertension) are implicated in the compromise of renal oxygen supply by promoting ATP production/demand imbalance [13]. The Na⁺/K⁺-ATPase transporter consumes the greatest amount of renal oxygen (ATP consumption) during tubular sodium reabsorption. In addition, Ang II exerts a positive effect on proximal sodium reabsorption, thereby increasing tubular cell oxygen consumption.

As consequence, the state of hypoxia in the kidney of patients with DM leads to glomerular and tubulointerstitial injury, imbalance in the synthesis and degradation of the extracellular matrix, and renal fibrosis [14][15], which in turn may exacerbate hypoxia due to oxygen transport restriction. Despite advances in the pathophysiologic understanding of DKD, clinical translation remains limited, mainly due to the lack of noninvasive methods to assess renal microcirculation, oxygenation, inflammation, and fibrosis. Renal biopsy remains the gold-standard method for analyzing renal microstructure; however, its use in DKD is often reserved for atypical clinical manifestations. Novel renal MRI tools are increasingly available to assess renal perfusion, oxygenation, and fibrosis noninvasively, offering a great potential to shed light onto the pathogenesis of DKD.

Physiologically, renal perfusion provides the pressure necessary for glomerular filtration to occur, as well as supplying nutrients and oxygen to meet the demands of renal metabolism. Hyperfiltration is secondary to decreased afferent arteriolar resistance mediated by vascular factors such as nitric oxide, angiotensin (1-7), and hyperinsulinemia, as well as increased efferent arteriolar resistance due to angiotensin-II, endothelin-1, or reactive oxygen species [16]. All these factors generate a renal microcirculatory disturbance that often goes unnoticed but contributes to structural renal injury [5]. In fact, there may be a significant loss of GFR reserve despite a rate greater than 100 mL/min/1.73 m² and the absence of severe albuminuria (urinary albumin/creatinine ratio above 300 mg/g) [16].

The evaluation of renal microcirculation remains a challenge, due to the difficulty of its direct measurement, the considerable consumption of time and technical personnel, and the risk it may involve for the patient, depending on the technique employed. Traditional methods include dynamic contrast-enhanced MRI, which uses contrast media in combination with MRI to allow the estimation of renal perfusion; however, the use of exogenous contrast media presents the possibility of contrast nephrotoxicity and, specifically in the case of gadolinium-based contrast agents, the risk of developing nephrogenic systemic fibrosis in patients with CKD, which consists of a severe fibrotic skin disorder due to sequestration of its free ionic form (Gd³⁺) in the skin tissue, highly toxic in humans and without a currently effective treatment [17][18]. On the other hand, more precise methods such as endogenous clearance of para-aminohippuric acid (PAH) or radionuclide scintigraphy require invasive techniques, as well as significant human and time resources, without ruling out the possibility of anaphylaxis reactions. Hence, there is great importance of developing a tool that quantifies renal tissue perfusion in a more precise and less invasive manner.

Renal oxygenation is based on a balance between oxygen supply and consumption. At the corticomedullary junction, these arteries become arcuate arteries, which branch into radial cortical arteries, from which afferent arterioles arise supplying blood to the glomeruli. In addition, renal medullary oxygenation is limited by the countercurrent exchange of the descending and ascending vasa recta [19], as well as by a lower medullary hematocrit compared with arterial blood [20]. Under conditions such as diabetes, where there is oxidative stress and impaired nitric oxide function, the efficiency of cellular oxygen utilization is reduced.

As a result, small variations in blood flow and/or local oxygenation can lead to tissue hypoxia, as renal oxygenation depends on several tightly regulated mechanisms. High oxygen demand is due to tubular sodium reabsorption, which consumes more than 80% of the oxygen supplied to the kidney [21]. In addition to renal metabolism, however, oxygen consumption varies according to GFR and RBF. Consequently, the renal balance between oxygen supply (RBF, hemoglobin, blood pH, and oxygen saturation) and oxygen consumption (tissue metabolism, filtration fraction, and active tubular electrolyte transport) [22] is very important for kidney function.

Renal hypoxia is known to play a major role in the progression of DKD [23][24]. Sustained hyperglycemia results in increased kidney oxygen consumption, partly due to mitochondrial dysfunction and reduced electrolyte transport efficiency [22]. In particular, oxidative stress has been identified mainly in the renal medullary zone [25]. Consequently, assessing renal oxygenation is also highly relevant to clinical practice.

Renal biopsy is currently the most valuable tool to assess the renal microstructure. However, it is an invasive procedure which carries the risk of side-effects and sampling bias, as it represents less than 0.002% of the whole kidney. This fact is relevant in DKD because the early injury is patchy and with a wide variety of histological features [11].

Hyperglycemia stimulates type IV collagen synthesis, mediated by transforming growth factor-beta (TGF- β) [26], whose deleterious fibrotic effect is observed in advanced phases of DKD, at both the glomerular and the tubulointerstitial levels. Local inflammation phenomena are involved in this process, with recruitment of inflammatory cells [27], imbalance in the synthesis/degradation of the extracellular matrix [28], and vascular dysfunction [29]. Renal fibrosis is a hallmark feature of progressive DKD, being also related to the decline in kidney function. However, there are currently no validated biomarkers for quantitative and spatial determination of renal fibrosis.

3. Magnetic Resonance Imaging and Clinical Utility

Since the early 1990s, MRI has gradually been applied for a deeper understanding of renal pathogenesis caused by diabetes [30][31]. Subsequently, the progress in these kinds of techniques has been remarkable [32][33]. Renal magnetic resonance techniques are currently in vogue as they provide noninvasive information on renal volume, function, metabolism, perfusion, oxygenation, and microstructural alterations, without the need for exogenous contrast media. In the last 6 years, various international groups have emerged, composed of medical imaging experts, physiologists, physicists, engineers, radiologists, and nephrologists, among other professionals, with the aim of implementing the clinical application of these tools [34][35].

Arterial spin labeling (ASL) MRI applies a radiofrequency pulse to the circulating aortic blood on its course toward the renal arteries, which generates a magnetization inversion effect resulting in magnetically labeled arterial blood water that can be utilized as an endogenous tracer. Its reproducibility and correlation with conventional kidney function measurement techniques have also been established [36][37]. This technique is proving to be one of the most relevant in the study of DKD thanks to its ability to detect small changes in the renal microvasculature, in a pathology in which microvascular involvement plays a crucial role in both the onset and the progression of the disease. As discussed below, this makes it a promising tool for the development of new therapeutic alternatives and the monitoring of therapy already established, as well as the possibility of detecting early alterations and assessing disease progression [38][39].

A previous ASL study in diabetic patients [37] observed a 28% reduction in renal cortical perfusion in comparison with healthy subjects. A smaller but still significant difference in RBF was found between the healthy controls and a subgroup of diabetic patients in spite of not showing differences in kidney function according to the methods traditionally used. In another recent study, diabetic patients with a mean estimated GFR of 51 mL/min/1.73 m² were analyzed for cortical perfusion, diffusion, and oxygenation. Not only observed a significant decrease in renal cortical perfusion in individuals with diabetes and moderately reduced GFR, compared to healthy subjects, but also an association of cortical perfusion and medullary response to furosemide with annual loss of kidney function [40].

Blood oxygen level-dependent (BOLD) contrast is a noninvasive method to evaluate renal tissue oxygenation on the basis of the paramagnetic properties of deoxyhemoglobin. The decay rate increases at higher deoxyhemoglobin concentration, which is inversely proportional to tissue oxygenation. Since the partial pressure of oxygen in blood is considered to be in close equilibrium with the underlying tissue, changes estimated by BOLD can be interpreted as changes in the partial pressure of tissue oxygen. This

technique has been validated in various studies [41][42][43], but these validations have only been performed in animal models, because the gold-standard method for comparison is by direct measurement of tissue pO₂, which requires micro-electrodes located in each kidney.

In regard to clinical application of BOLD-MRI in DKD, a recent and interesting study demonstrated relative renal hypoxia in T1D adolescents, associated with increased albuminuria, renal plasma flow, fat mass, and insulin resistance [44]. Previously, other studies analyzed both renal cortical and medullary oxygenation in diabetic subjects, from early to advanced categories of CKD, observing a positive correlation between medullary oxygenation and GFR and a negative correlation between cortical oxygenation and GFR [45]. The effect on renal tissue hypoxia secondary to nitric oxide inhibition has also been evaluated by BOLD-MRI [46][47]. Renal oxygenation was also investigated by BOLD-MRI in diabetic patients undergoing water overload to determine whether water diuresis would enhance renal tissue oxygenation, with no improvement observed with the intervention [48][49].

Nevertheless, other investigations have presented contradictory results when studying DKD. Wang et al. found lower medullary R2* values suggesting higher oxygenation in DKD patients [50]. The authors ascribed the discrepancies to the fact that their patients had overt DKD, which, in view of the fall in GFR, presupposes a decrease in tubular sodium reabsorption and, therefore, a decrease in oxygen consumption, conversely to what is observed in situations of hyperfiltration in early DKD. However, upon subanalysis in patients with diabetic nephropathy (30% of all CKD patients), no significant correlation was observed. Thus, the R2* increase in humans with diabetes and/or CKD is still unclear with regard to whether it is related to a concomitant decrease in RBF; therefore, future studies should be conducted to clarify the role of BOLD in people with these pathologies.

Thus, external factors such as fibrosis, anemia, or ischemia, which could restrict oxygen exchange between renal microvasculature and interstitium, could have significant effects on the results. These factors are of relevance in diabetic patients due to a higher prevalence of renal interstitial fibrosis, likely related to the described macrophage infiltration [3], anemia, and associated vascular disease in this profile of patients [4]. Additionally, hydration status and salt intake have also been shown to influence renal oxygenation. A significant decrease in medullary R2* was observed after oral water load [51] and high-salt intake [52].

Another reason for these discrepancies is the lack of consensus on how to analyze BOLD-MRI images. For this reason, a number of studies have emerged to improve and homogenize the acquisition and analysis protocols of the technique [43]. In fact, a group of experts created an interesting consensus statement seeking standardization of measurement protocols by giving technical recommendations on imaging parameters according to some patients' situations, as well as patient preparation prior to the examination [53].

Diffusion-weighted imaging MRI (DWI-MRI) is a technique which has emerged as a promising method for assessing renal microstructure. By applying diffusion gradients, it generates image contrast that is sensitive to water motion in the kidney tissue. Accordingly, it is a tool to probe the renal microstructure, able to estimate the presence of renal fibrosis and/or cellular infiltration. Thus, a lower diffusion capacity may indicate greater fibrosis, as a fibrotic renal interstitium decreases the Brownian motion of the water molecules by collision. The apparent diffusion coefficient (ADC) consists of the overall measure of water diffusion and microcirculation in the tissue. For this reason, although ADC measures global diffusion, it is not able to describe the directionality of the movement. imaging MRI (DTI-MRI) measures the diffusion signal in a greater number of directions, allowing an analysis of the spatial dependence of diffusion and, thus, the tissue microarchitecture, through the quantification of tissue anisotropy (fractional anisotropy) (0% = complete isotropy, 100% = complete anisotropy) [54]. A recent study by IVIM-DWI identified restricted water diffusion in the renal tissue of T2D patients with a relatively intact kidney function [55].

Decreased ADC has been observed in renal parenchyma of T2D subjects in comparison with healthy

volunteers. These findings were recently confirmed in patients with mild DKD, including the ability to detect renal lipid deposition [56], and in diabetic murine models, finding association with histopathological changes of interstitial fibrosis and glomerulosclerosis [57][58][59]. However, a recent study performed in CKD patients who underwent renal biopsy of either native kidney (22% of whom had DKD confirmed by renal biopsy) or allograft kidney (none with DKD in the graft) showed an interesting result, suggesting that the corticomedullary ADC difference correlates better with interstitial fibrosis than absolute cortical or medullary ADC values [60]. However, Prasad did not observe significant differences between diabetic subjects with moderately reduced GFR and healthy volunteers or an association with eGFR, but ADC was indeed associated with renal perfusion [40].

A third available tool is diffusion kurtosis imaging (DKI). It evaluates the non-Gaussian motion of water. This method avoids the artefact caused by structural barriers at the level of the renal medulla which affect the diffusion of water molecules that do not follow a Gaussian distribution. In the presence of early structural alterations in DKD, this tool shows promise for assessing pathological changes in the diabetic kidney (thickening of the glomerular basement membrane, glomerulosclerosis, and tubulointerstitial alteration) from early categories of disease [61].

A potential area of application of MRI biomarkers is the selection of personalized treatments in patients with diabetes both with and without established DKD on the basis of a more specific knowledge of the mechanisms affecting each individual. It would also be very useful in the monitoring of possible nephrotoxic effects of new drugs under development.

In the last years, SGLT2 inhibitors have shown an important efficacy in the prevention of progressive DKD [62]. During hyperglycemia, there is an increase in glucose delivery to the proximal convoluted tubule (PCT), which results in increased tubular glucose uptake and increased sodium reabsorption, through the sodium-glucose cotransporter-2 (SGLT2). This generates a diminution in sodium delivery to the distal tubule, sensed by the macula densa as a reduction in effective circulating volume. Through tubuloglomerular feedback, this situation generates vasodilatation of the afferent arteriole and vasoconstriction of the efferent arteriole. These hemodynamic changes lead to intraglomerular hypertension and hyperfiltration, causing podocyte stress [10]. In the last few decades, the only treatment considered the cornerstone in the prevention and management of DKD has consisted of RAS inhibitors. RAS inhibition reverses vasoconstriction of the efferent arteriole, reducing glomerular afterload. Recently, SGLT2 cotransporter inhibitors (SGLT2i) have emerged as an attractive option due to their effect on the restoration of tubuloglomerular feedback and the reversal of hemodynamic changes [13], as well as for improving the metabolic profile of patients by increasing renal excretion of glucose [63]. Despite this, few tools exist for noninvasive, real-time assessment of renal pharmacokinetics and pharmacodynamics of new therapies, such as SGLT2i or glucagon-like peptide 1 receptor (GLP-1) agonists.

In this line, novel MRI techniques are of particular interest because of their noninvasive design and proven clinical feasibility. Preliminary results have shown that they allow the assessment of renal microperfusion, as well as edema, tissue oxygenation, and renal fibrosis. Several studies have demonstrated the validity of these tools in pharmacological analysis and compartmental individualization of the kidney, providing information on the function of each kidney separately and its compartments (cortex and medulla) [64][43][65][66][67]. For instance, a possible clinical application in pharmacology would be the validation of the Gomez equations for estimating the renal hemodynamic profile [68], replacing the need to use PAH clearance by quantification of RBF by ASL-MRI.

Previous reports showed in patients using RAS blockers an increase in RBF detected by ASL-MRI [64][66]. Ritt et al. demonstrated a significant positive correlation between the change in renal perfusion after the use of RAS blockers (telmisartan), quantified by ASL-MRI, and the change exerted with the same drug after estimation by PAH clearance [64]. ASL-MRI revealed that RAS inhibition with losartan was able to reverse the detrimental cortical perfusion present in some kidney allograft recipients [66].

In several studies, BOLD-MRI showed the response in renal medullary and cortical oxygenation to certain selective diuretics [45][69][70]. As it is known, furosemide causes an inhibition of active transport in the ascending limb of the loop of Henle, which leads to a lower oxygen consumption and, therefore, medullary oxygenation improvement [41]. This effect was quantified by BOLD-MRI in murine models [69][71] and in combination with acetazolamide [43][70]. Analyzing CKD subjects (33% with diabetes), the oxygenation response to furosemide was blunted in the medulla, as denoted by a flatter R2* slope [43]. BOLD-MRI has also been useful to evaluate the nephrotoxic effect of iodinated contrast agents in experimental DKD models [72].

DWI-MRI, as a potential biomarker of fibrosis, demonstrated the renoprotective effect of miR-29a in DKD [67].

4. Conclusions

Several MRI techniques are currently being developed that would be of interest in the assessment of diabetes; nevertheless, technical validation is still required. Among them, quantitative magnetization transfer analyzes the spin exchange between proton clusters in different environments to assess the macromolecular content of the tissue. Quantitative magnetization transfer has been used to explore and quantify renal fibrosis in DKD [73]. Furthermore, dynamic nuclear polarization MRI technique was recently used to study the pathophysiological role of renal hypoxia in diabetes [74].

The MRI tools described here have shown an important development in the last 10 years; however, work is yet to be done in the standardization of protocols to reduce the outcome differences across working groups and facilitate clinical translation, in addition to continuing stimulating research to improve the predictive power of these tools [75]. Looking ahead, an important concept to promote is the possibility of combining different bioimaging methods in order to acquire a more comprehensive view of renal pathophysiology, in highly prevalent diseases such as DKD, with the aim of improving predictions of CKD progression and gaining a better understanding of therapeutic tools. In addition, it is important to emphasize that MRI imaging techniques enable estimation of processes that are common to various diseases; therefore, their role is not intended to distinguish between diverse entities when the differential diagnosis is based on molecular or ultrastructural aspects, such as the presence of IgA or subepithelial deposits and/or podocyte foot process effacement. Improvements in pharmacological knowledge may orient toward a more personalized DKD patient management, as well as find indicators that allow us to prevent the onset or progression of DKD.

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Keywords

diabetic kidney disease;magnetic resonance imaging;arterial spin labeling;blood oxygen-dependent level;diffusion

weighted imaging;oxygenation;perfusion;fibrosis;chronic kidney disease;kidney function

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