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Chapter 4

Non-Invasive Diagnosis of Acute Renal Allograft Rejection – Special Focus on Gamma Scintigraphy and Positron Emission Tomography

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Additional information is available at the end of the chapter

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1. Introduction

The number of patients treated for end-stage renal failure continuously increases. Because treatment alternatives are limited and transplants are often the first therapeutic choice, the numbers of patients joining the waiting lists in countries world-wide rises. At present transplantation medicine is one of the most progressive fields of medicine. Gradually the "half-life" of renal transplants improved and the five years survival rate ranges now above 80% [1;2]. Despite of the advances made within the last decades, acute rejection (AR) is still a risk for graft survival. The incidence of rejection episodes depends on several factors, e.g., the organ (status), co-morbidities, medication and compliance. Thus, in different situations the incidence of AR varies between 13-53% in the first year after transplantation [3], and, in most cases, cellular and humoral immunity mediated rejections can be distinguished. Usually, AR proceeds substantially as an acute cellular rejection whereas humoral rejection comprises only a smaller proportion of AR [4]. Every single episode of an AR is a negative prognostic factor, increasing the risk for development of chronic allograft deterioration and worsening long-term graft survival [5;6]. Interestingly, the impact of AR on chronic renal allograft failure as the main cause for death-censored graft-loss after kidney transplantation increases, whereas the severity of the episode itself is an independent risk factor [7-9]. Therefore, early detection and rapid and effective treatment of AR are essential to preserve graft`s function. Clinically established screening methods such as elevated serum creatinine, occurrence or aggravation of proteinuria, oliguria, hypertension, graft tenderness, or peripheral edema, often lack the desired sensitivity and specificity for early diagnoses of AR. Hence,a compelling need for high sensitive

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and specific detection of early AR exists, with core needle biopsy still being the "gold-standard" in rejection diagnostics. However, biopsy as an invasive procedure is cumbersome to the patient, carries the risk of graft injury, and cannot be applied in patients taking anticoagulant drugs. Additionally, the sampling site is small and one might miss AR, i.e., when rejection is focal or patchy. Thus, in diagnostics, non-invasive image-based methods visualizing the whole graft would be superior.

Allograft rejection is the result of interactions between the recipient`s innate and adaptive immune system and the graft antigens serving as a target. Cytotoxic T lymphocytes (CTLs) are central effectors within AR whereas B cells and parts of the congenital immunosystem such as the complement system, monocytes/macrophages, neutrophilic granulocytes, and dendritic cells, have their share, too [4;10]. By recognition of their donor antigen CTLs are activated, undergo clonal expansion and differentiation into effector cells. Subsequently, they migrate into the transplant initiating its destruction [4;10;11]. Before CTLs reach the graft parenchyma, they have to pass the vascular endothelium. This extravasation is mediated by chemoattractant cytokines/chemokines. Chemokines induce the expression of vascular adhesion molecules allowing leukocytes to roll, adhere, and transmigrate into the parenchyma [12]. CTLs destroy their targets through the release of perforin and granzyme or by initiation of the Fas/FasL pathway inducing cell death by triggering the inherent caspase-mediated apoptotic response or caspase-independent cell death [13]. These two cell death-inducing strategies account for almost all contact-dependent target kills. However, activated CTLs can release additional cytokines, such as tumor-necrosis factor and interferon causing apoptosis or necrosis upon secretion [11,13]. Moreover, inflammatory edema and micro thrombi / hemorrhage caused by damaged endothelium add ischemia-dependent hypoxic damage to the graft [11]. All of these single, simplified processes sum up and promote allograft dysfunction. However, if they are characterized at least in part, they can be addressed by different imaging technologies discussed in the following.

2. Ultrasound

Standard care in detection of AR includes (Doppler-) ultrasound examination. Typical ultrasound findings in cases of AR are rejection-related graft enlargement (swelling, more globular shape), reduction of corticomedullary differentiation, increased echogenicity, prominent medullary pyramids, or irregularities in the graft perfusion (reversed plateau of diastolic flow), but its specificity and sensitivity for AR is limited, even when echo enhancers are applied [14;15]. Elevated resistance indices can occur in the presence of acute as well as chronic rejection. However, values lower than 0.8 are expected and usually values above 0.8 indicate increased intrarenal pressure as it occurs for example in acute tubular necrosis (ATN) or AR and is linked to a poor longterm renal allograft function [16-18]. Notably, sensitivity and reliability of this method mainly depend on the investigators experience. A comprehensive overview of "What ultrasound can do and cannot do" in diagnostics of renal transplant pathologies was published by Cosgrove and Chan [16]. Using contrast agent or targeted ultrasound in the

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future, this method might offer significant potential, whereas at present studies are at best at experimental stage and are completely lacking in patients with renal AR.

3. Computed tomography

Computed tomography (CT) is commonly available, technology and techniques as well as the applied contrast media constantly improve. CT contrast agents allow accurate evaluation of parenchymal, perirenal, renal sinus, pyeloureteral and vascular diseases in renal transplantation in great detail and at lower costs than by magnetic resonance (MR) imaging. Information gathered by CT indicating AR are loss of corticomedullary differentiation, decreased graft enhancement, and delayed or absent contrast excretion [19]. However, this information is rather unspecific and the contrast media used still are nephrotoxic. Thus, at present CT has no role in diagnostics of renal AR.

4. Magnetic resonance imaging

Kalb *et al*. provide a recent overview about MR-based approaches for functional and structural evaluations of renal grafts including a section on diagnostics of AR [20]. Beside exact anatomical information, MR can assess different aspects of renal function. Typical MR findings occurring in AR are enlargement of the graft (due to edema) with loss of corticomedullary differentiation and elevated cortical relative signal. There might be edema of and surrounding the kidney and the ureter. The high spatial and temporal resolution of MR allows perfusion imaging which might be useful to distinguish AR from ATN. 3D gradient echo perfusion imaging might show enhancement of the cortex and markedly delayed excretion of contrast [20]. Recent research with blood-oxygen level-dependent (BOLD) MR was promising for differentiating AR from ATN and a normal functioning kidney [21,22]. Furthermore, MR renography has been applied for diagnosis of the cause of acute dysfunction after kidney transplantation [23,24]. These two studies rely on quantitative evaluation of the shape of the renal enhancement curve to diagnose acute dysfunction. One can observe delayed and lower medullary enhancement in ATN whereas cortical and medullary enhancement curves decrease in AR. However, further studies verifying the results are needed and still some issues about gadolinium-containing contrast agents and nephrogenic systemic fibrosis and gadolinium nephrotoxicity need to be resolved. More recently, Yamamoto *et al*. proposed a new quantitative analysis method of MR renography, including a multicompartmental tracer kinetic renal model for diagnosis of AR and ATN, but state in their paper that findings in patients with normal graft function, AR, and ATN showed a substantial overlap with those of the normal population [25]. Another strategy followed was imaging of macrophage infiltration with ultrasmall superparamagnetic iron oxide particles [26]. Grafts with AR showed significant accumulation of iron particles but only within a time frame of 72 h which is much too late for potential clinical application.

5. Single photon (gamma) imaging and positron emission tomography

Because gamma camera/ single photon emission computer tomography (SPECT) and positron emission tomography (PET) offer high intrinsic activity, excellent tissue penetration (depending on the tracer), cover the whole organ/ body, are relatively independent of the experience of the investigator and provide a huge variety of clinically tested molecular imaging agents/ tracer, SPECT and PET-based approaches for the detection of renal AR are discussed in the following [27;28]. Steps of AR addressed by SPECT or PET-based approaches include recruitment of activated leukocytes into the transplant with consecutive cytokine release, cell death, edema, hypoxia and loss of function.

A comprehensive overview of the studies performed is provided in Table 1.

SPECT				
Target	**Molecular Marker**	**Graft/Organ**	**Species**	**References**
Fibrin thrombi	^{99m}Tc-Sulfur Colloid	Kidney	Human, dog	[64;65]
Proximal tubule uptake	^{99m}Tc-DMSA	Kidney	Human	[66;67]
Renal uptake and excretion	^{99m}Tc-MAG3	Kidney	Human	[68]
Renal perfusion and filtration	^{99m}Tc-pentetate (DTPA)	Kidney	Human	[69;70]
Leukocytes	^{99m}Tc-OKT3	Kidney	Human	[40]
Inflammation	^{99m}Tc- Leukocytes	Kidney	Human	[39]
	^{67}Ga citrate	Kidney	Human	[64;65]
Renal function	^{131}I-OIH	Kidney	Human	[71]
PET				
Metabolism/Inflammation	^{18}F-FDG	Kidney	Rat	[43;44]
Leukocytes	^{18}F-FDG-Leukocytes	Kidney	Rat	*In press*

A Medline literature search by PubMed was performed to select papers in which AR and SPECT/PET play any role. The search period was set from 1970 to July 2012. We used ("Acute renal or kidney rejection" and "positron emission tomography (PET)" or "single photon gamma imaging (SPECT)" or "molecular imaging") as search query. Only papers with an English abstract have been included.

Table 1. Results of literature analysis: SPECT/PET-based diagnosis of renal AR.

5.1. Inflammation

Sterile inflammation is central to the rejection process. Hence, it seems logically to assess inflammatory targets for the diagnosis of AR. In inflammation imaging, one can focus on target mechanisms such as measurement of the metabolic activity (i.e. with the "classical" tracer ^{18}F-fluordesoxyglucose (FDG)), binding to cytokines/chemokines (receptors), assessment of physically trapped tracers in the inflammatory edema, or using leukocytes. Recently, Signore *et*

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al. published an excellent review on imaging of inflammation discussing different techniques, targets, and approaches [27].

5.2. Vascular adhesion molecules

AR is associated with the expression of cell adhesion molecules like vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), LFA-1 (lymphocyte function-associated antigen-1, and endothelial leukocyte adhesion molecule (E-selectin) on the endothelium of organs undergoing rejection. They are "essentially needed" for the adherence and transmigration of leukocytes into the parenchyma. Because radiolabeled antibodies exist for some of these easily accessible vascular targets, they can be addressed by noninvasive imaging. However, data regarding adhesion markers in SPECT/PET-based imaging are rare and have not been transferred to renal AR imaging yet.

5.3. Imaging using *ex vivo* radiolabeled leukocytes

Because recruitment and activation of inflammatory cells, i.e. lymphocytes, is crucial to AR, efforts have been made to image infiltration by means of labeled leukocytes. Application of *ex vivo* radiolabeled leukocytes is clinically well established particularly in the diagnostic workup of infectious disorders without a focus. Hitherto, white blood cells (WBC) are labeled using for instance ^{99m}Tc-HMPAO or ^{111}In-oxine for SPECT and ^{18}F-FDG or ^{64}Cu for PET analysis, respectively [29]. These cells are considered to accumulate highly specific in inflamed tissues [30-33].

After injection of labeled leukocytes a typical distribution pattern can be observed. First, cells shortly accumulate in the lungs and then continuously migrate from the blood pool into spleen, liver, and bonemarrow, the so called reticulo-endothelial system, and certainly in inflamed sites [34-36]. After endothelial adhesion, labeled leukocytes migrate through the vessel`s wall to the focus of inflammation providing a typical radioactivity pattern indicating infiltration. For instance, Forstrom *et al.* have shown that ^{18}F-FDG labeled leukocytes exhibit comparable distribution patterns in normal human subjects compared with ^{111}In or ^{99m}Tc-labeled WBC [37]. Although ^{18}F-FDG seems to exhibit the lowest labeling stability when compared to ^{111}In and ^{64}Cu only neglectible free ^{18}F-FDG uptake can be observed [37]. However, labeling stability is relevant in order to assure that assessed activity refers to accumulation of labeled leukocytes and not to the unlabeled tracer only. Since half-life time of ^{18}F-FDG is 109 min, longtime stability of ^{18}F-FDG labeled leukocytes for clinical analysis is not of interest. However, if longtime stability is of interest this could be addressed using other tracers like ^{99m}Tc with a half life of approximately 66h.

Successful imaging using labeled leukocytes depends on viability of labeled cells. Several studies assessed cell viability after labeling concluding satisfactory and comparable viability rates for ^{111}In, ^{99m}Tc, ^{18}F-FDG and ^{64}Cu in the first 4h after labeling [38]. However, cell viability significantly decreases within one day limiting long term monitoring of AR using a single shot approach.

At present only a few preclinical and clinical studies are published dealing with labeled leukocytes and detection of AR in intestine, hearts, pancreas islets and skin. Only one study performed in a small cohort of kidney transplant recipients evaluated ^{99m}Tc-mononuclear cell scintigraphy for diagnosis of AR. In this study, the authors were able to show that AR was diagnosed correctly and successfully discriminated from ATN [39]. In a further development of their approach, we established leukocyte PET imaging using very low amounts of ^{18}F-FDG for the diagnosis of AR in a rat kidney transplant model. *Ex vivo* ^{18}F-FDG labeled human CTLs were able to diagnose renal AR within a time frame of 1 h after application and discriminate AR from important differential diagnoses such as acute cyclosporine toxicity or ATN (*Grabner et al. in press*) (Fig. 1).

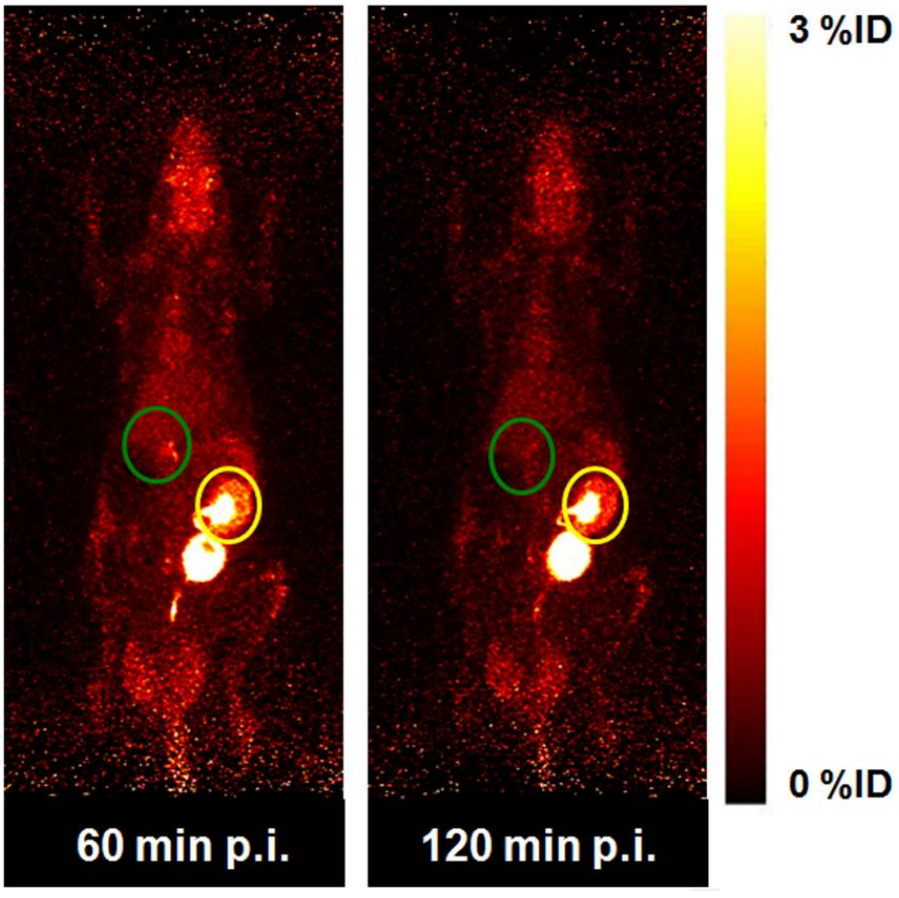

Figure 1. Representative PET-images of dynamic whole body acquisitions of a series of an allogeneically kidney transplanted rat on postoperative day 4 60 min and 120 min after tail vein injection of 30 x 10^{6}^{18}F-FDG labeled CTL. While the parenchyma (yellow circle) of renal allograft developing AR accumulates ^{18}F-FDG-CTLs, the native kidney (green circle) does not show any accumulation at any time. Please note that the renal pelvis can contain eliminated ^{18}F-FDG/^{18}F-fluoride. Therefore, it has to be excluded from the measurements. ID: injected dose

Since infiltration of leukocytes, especially CTLs, in allografts appears before physiologic or mechanical manifestations of organ dysfunction is apparent, nuclear imaging employing leukocytes might be a promising tool for specific, sensitive and early detection of AR.

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5.4. Imaging using *in vivo* radiolabeled leukocytes

Instead of employing *ex vivo* labeled leukocytes, radiolabeled monoclonal antibodies (fragments) (mAbs) have been established for detection of leukocyte (related) antigens. Their advantages include standardized production, easier storage and handling, while they are highly specific for their target leading to a good background/target ration. However, limitations might be the targeting of extravascular antigens and potential but rare allergic complications, when using the antibodies in a patient.

As discussed, CTLs are the major cell type involved in AR. Martins *et al.* used ^{99m}Tc-OKT3 targeting CTLs in recipients of renal transplants [40]. In their preliminary results they state that out of 22 patients they successfully identified 3 patients with AR using ^{99m}Tc-OKT3 scans. Apparently, their results published in 2004 have to be confirmed in further studies. A recently published attractive, being somehow better biocompatible, alternative might be CD3 targeting ^{99m}Tc-SHNH-visilizumab which needs to be evaluated in the future [41].

5.5. Metabolic activity (^{18}F-FDG)

^{18}F-FDG is a daily routine tracer to assess regional glucose metabolism as a surrogate for metabolic activity widely used for the PET-based routine detection of tumors, infection and inflammation. The major energy source in leukocytes during the metabolic burst is glucose. Analogously, activated leukocytes highly accumulate ^{18}F-FDG (in the same way they take up glucose but without further processing) which can be quantified by PET [42]. A clear limitation when using free ^{18}F-FDG is that an increased uptake can be observed in any kind of cellular activation (high glycolytic activity). Hence, ^{18}F-FDG is not a disease or target specific tracer.

Nevertheless, ^{18}F-FDG is one of the few tracers successfully applied for the non-invasive detection of AR. Others have applied ^{18}F-FDG in settings of lung, heart and liver transplantations. We have demonstrated very promising results for ^{18}F-FDG-PET in diagnostics of renal AR [43;44]. Using a rat model of renal AR, ^{18}F-FDG-PET performed well in terms of early, accurate detection and follow-up of AR [43] (Fig. 2). Using ^{18}F-FDG, we discriminated AR non-invasively from important differential diagnoses like ATN or acute cyclosporine toxicity. Moreover, therapy response monitoring by ^{18}F-FDG might be useful to identify treatment unresponsive AR for earlier escalation of immunosuppressive regimen [44]. This might reduce graft damage by shortening AR episodes because at present (steroid) resistant rejection is diagnosed lately [45].

One important issue of imaging of kidney AR with ^{18}F-FDG is that it is eliminated with the urine in contrast to normal glucose. Thus, drainage of ^{18}F-FDG into the renal pelvis must be taken care of when assessing ^{18}F-FDG-uptake in the renal parenchyma. We avoided this problem by using late acquisitions after ^{18}F-FDG injection to reduce the instantaneous amount of tracer in the urine during the PET scan. Moreover, an impact of renal function on ^{18}F-FDG-uptake has to be excluded e.g. by renal fluoride clearance (a non-invasive measure of renal function) [46].

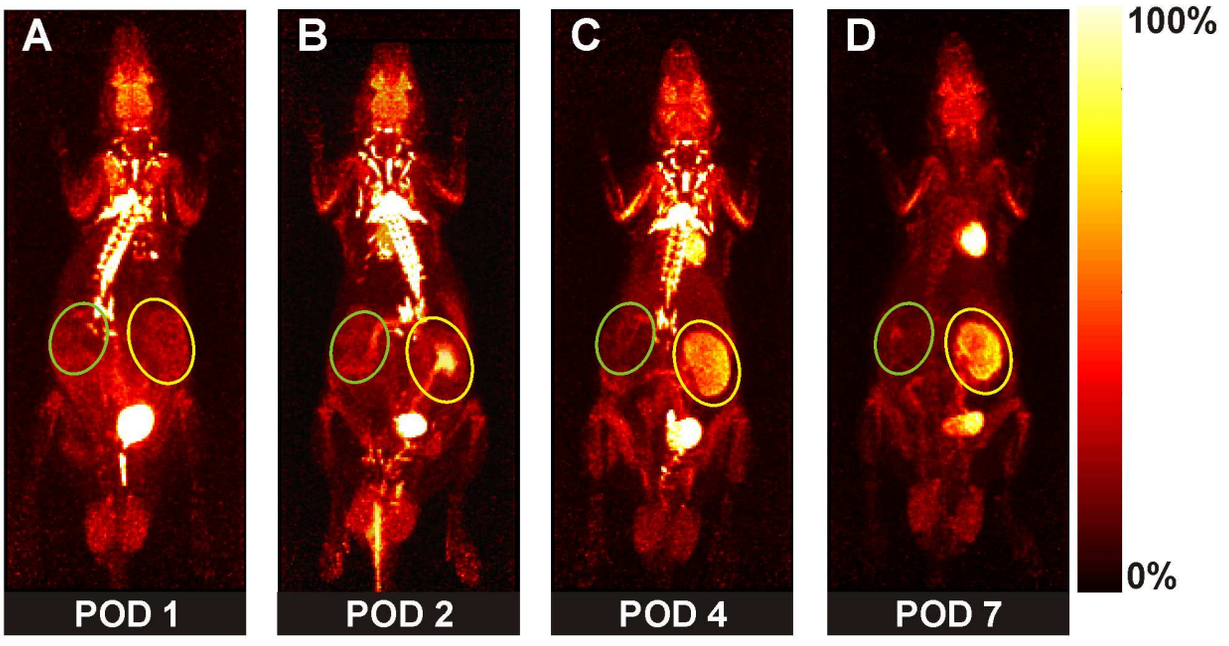

Figure 2. Representative PET-images of dynamic whole body acquisitions of a series of an allogeneically kidney transplanted rat (POD 1 (A), 2 (B), 4 (C), and 7 (D), after tail vein injection of ^{18}F-FDG. While the parenchyma (yellow circle) of renal allograft developing AR accumulates ^{18}F-FDG with a maximum on post operative day (POD) 4, the native kidney (green circle) does not show any accumulation at any time. Please note that the renal pelvis can contain eliminated ^{18}F-FDG/^{18}F-fluoride. Therefore, it has to be excluded from the measurements. Figure taken from [43]. Scale bar: percent injected dose

5.6. Matrix metalloproteinases

One step further, one cannot assess infiltrating leukocytes only but rather their tissue damaging activity by detection of activated matrix metalloproteinases (MMPs). Leukocyte-derived MMPs, like MMP-2 or MMP-9, were found to be active in AR [47;48]. Since MMP activity can be assessed using radiolabeled MMP-inhibitors in SPECT or PET this approach for detection of AR might be evaluated in future studies [49-52]. Maybe one can gather additional information regarding graft`s prognosis because MMPs are involved in tissue remodelling, too.

5.7. Hypoxia

Acute tissue inflammations regardless of their origin present with a unique and challenging microenvironment including hypoxia (low oxygen), anoxia (complete lack of oxygen), hypoglycemia (low blood glucose), acidosis (high H^+ concentration) and abundant free oxygen radicals. These conditions are characteristic features of inflamed tissues, along with the influx of leukocytes. In renal allografts, hypoxia and hypoxic adaptation are common within 2 weeks

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after surgery whereas graft hypoxia assessed in the long run is associated with clinical/subclinical rejection [53]. Therefore, assessment of hypoxia by targeting hypoxia (related gene products), i.e. hypoxia inducible factors (HIF), might offer additional diagnostic information in subclinical or ambiguous cases of AR.

Two major classes of hypoxia tracer, nitroimidazoles and *bis*(thiosemicarbazonato)copper(II) complexes, have been extensively investigated for measuring hypoxia. The applications of both tracer as well as several alternative reagents tested e.g., ^{18}F-fluoroerythronitroimidazole (^{18}F-FETNIM) and ^{18}F-fluoroazomycin-arabinofuranoside (^{18}F-FAZA), are summarized in a review recently published by Krohn *et al.* [54]. Until present and to the best of our knowledge, no study has been performed assessing hypoxia in renal AR by SPECT or PET so far. At least one has to evaluate if the SPECT and PET-based approaches are advantageous when compared to BOLD MR.

5.8. Apoptosis

Apoptosis in AR is probably the result of different events occurring in AR. It may be a direct consequence of different cytokines discharged by leukocytes or directly provoked e.g. by CTLs. Within the inflammatory milieu of AR apoptosis might, among other factors, also be related to hypoxia, acidosis, or reactive oxygen species. Non-invasive detection of apoptosis in AR might be attractive because it may not serve for early detection of AR only, but also for monitoring of rejection kinetics and therapy response. Especially, early assessment of therapeutic success or failure is interesting to promptly adjust the therapeutic regimen. Likewise, quantification of apoptosis might provide information regarding the extent of graft damage and therefore for its prognosis. However, small studies with different tracers targeting different steps in apoptosis have been performed in both, animal and man. A comprehensive review on detecting cell death *in vivo* has been recently published by us [55]. Two main operational strategies are followed. While imaging of caspases` activity using substrate-derived agents offers high selectivity, the detection of membrane phospholipid redistribution using extracellular agents has the advantage of high target density and accessibility [56]. We and others recently proposed different isatin analogues for ^{18}F-labeling and detection of apoptosis [55]. However, studies detecting apoptosis in renal grafts using radiotracers for evaluation of their potential clinical value in AR have not been performed yet.

5.9. Imaging allograft function

A rather unspecific but reasonable approach is to simply determine graft function as a surrogate for stable function or (acute) graft affection.

Especially scintigraphic methods have been established for the assessment of renal function. Primarily, two types of imaging are common: static and dynamic. ^{99m}Tc-dimercaptosuccinic acid (DMSA) is the tracer used in static imaging allowing on the one hand identification of pathological conditions such as anatomical abnormalities or scarring, on the other hand accurate assessment of the differential function of the kidneys [57]. DMSA uptake correlates with the effective renal plasma flow, glomerular filtration rate, and creatinine clearance. Therefore,

DMSA has been successfully applied in the evaluation of renal function in living donors (before and after transplantation) and in kidney recipients [58]. For dynamic imaging ^{99m}Tc-mercaptoacetyltriglycine (MAG-3) and diethylenetriaminepentaacetic acid (DTPA) are the most commonly used tracers, whereas MAG-3 is going to replace DTPA because of superior extraction efficiency. It was proposed that MAG-3 scintigraphy can be useful for discrimination of AR from ATN [59]. Despite a reasonable perfusion and tracer extraction in ATN as assessed in these studies, tracer excretion rate is low, whereas one of the typical findings in AR is impaired perfusion. This fact was already taken into account by Hilson *et al.* in the seventies who developed a DTPA-based perfusion index which allows separation of rejection from ATN and, particularly, rejection from healthy kidneys [60]. These findings are somehow discrepant to typical findings in ultrasound when assessing RI which reflects renal perfusion as well. High RIs can be observed in ATN as well as in AR denying a differentiation of these entities by ultrasound-based measure of renal perfusion. Potentially, the modified renal perfusion index using ^{18}F-fluoride developed by us can be used for further clarification [61]. Aside from this recent studies using PET for the evaluation of renal function other approaches have been emerged. Renal blood flow for instance was successfully measured with $H_2{}^{15}O$ in rats and man [62,63]. Furthermore, we established ^{18}F-fluoride clearance for assessment of renal function in different renal failure models including AR [43,46]. As said before, decreased renal function is not disease specific but can assist in the differential diagnoses of AR.

6. Conclusion

The diagnosis and therapy follow-up of AR in transplant recipients demands for non-invasive and serial imaging approaches *in vivo*. Molecular and cellular imaging has significant potential for transplantation medicine as it may serve for monitoring the graft. With more optimal tracers as they are numerously being developed, PET (and other devices) may serve as valuable tools for the diagnosis and management of renal AR. In this term, these techniques will find their share to impact on detection of AR, graft function, assessment of therapy response as well as of the progression of lesions and therefore on graft´s prognosis.

Taken the new developments in molecular imaging into account, non-invasive methods including ultrasound, magnetic resonance, as well as SPECT and PET get increasingly helpful for research. Currently, nearly all of these promising new approaches are still at an experimental stage and have to evidence their potential in humans in daily routine in the future.

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