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Biomarkers identifying deterioration of kidney graft function — usefulness of "liquid biopsy"

Abstract

One of the important challenges of modern transplantology is identifying signs of deterioration in kidney graft function as early as possible and starting effective treatment. While the gold standard in graft monitoring is still the needle biopsy, novel biomarkers with no counterindications and barely any procedure-associated side effects, rise as promising tools. In this review, we summarize up-to-date knowledge about novel biomarkers that can serve as "liquid biopsy" to identify deterioration in graft function in kidney transplant recipients.

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Keywords: graft biopsy; transplantation; acute kidney transplant rejection

INTRODUCTION

Clinical transplant medicine is a dynamic branch of medicine. Improvements in surgical methods and immunosuppressive medication have enabled efficient organ and tissue transplantation [1]. In addition to solid organ transplants, innovative head and face transplantations are now being explored [2, 3].

Kidney transplantation has become standard clinical practice over the past few decades. The number of transplantation procedures performed globally, including kidney transplantation, increases every year. According to the United Network for Organ Sharing (UNOS), there is an average of 19 000 kidney transplants performed each year in the United States [4]. The World Health Organization estimates that around 170 000 kidney transplants are performed around the world each year [5]. By comparison, according to the Polish Transplantation Registry POLTRANSPLANT, in Poland, where we work, the number of kidney transplants in 2022 amounted to 784 from deceased donors and 73 transplantations from living related donors [6].

The main goal of transplant medicine nowadays is lengthening the time of graft survival and securing appropriate graft function while at the same time taking care of the patient's quality of life. To ensure this, early detection of unfavorable changes in the transplanted kidney and, thus, the implementation of appropriate treatment is important. Monitoring of graft function in kidney transplant recipients is based on laboratory blood tests and needle biopsy, which are the gold standard in kidney transplant disorders. However, the usefulness of needle biopsy, due to the invasive character of the procedure, is limited, and the main contraindications include bleeding disorders, uncontrolled hypertension, infection at the biopsy site, or risk of an allergic reaction to local anesthesia. This diagnostic method puts a patient also at risk of complications, starting with as mild as commonly seen post-procedural hematoma or arterio-venous intrarenal fistula, ending up with a very rare occurrence of graft removal or even the patient's death.

Liquid biopsy, in contrast to traditional biomarkers, such as creatinine or glomerular filtration rate (eGFR) commonly used

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to monitor kidney function, enables earlier detection of graft changes, even in cases of subclinical rejection. Traditional biomarkers often have limited sensitivity, which means that they may fail to detect the early stages of graft rejection, with increases occurring only at more advanced stages of kidney damage [7]. This is why the so-called "liquid biopsy" is important. A liquid biopsy, in general, refers to the molecular examination of non-renal tissue samples and searches for special biomarkers serving as a prognostic tool for patients with renal disorders [8]. Although blood and urine are the most commonly used body fluids in these procedures, saliva, feces, and other body fluids can also be employed as sources for liquid biopsies [9].

In this review, we looked at the most promising markers for early diagnosis and predicting the outcome of deterioration in allogenic kidney graft function.

CLUSTERIN (CLU)

Clusterin (CLU), also known as apolipoprotein J, is a glycosylated multifunctional protein involved in both apoptotic and non-apoptotic processes in various organs, including kidneys. It is observed that low base levels of CLU predispose to more serious deterioration in renal function in ischemia, which suggests a link between CLU and ischemic injury [10]. Elevated CLU levels have been found in the blood of patients with delayed graft function, and the level of CLU started to rise within four hours after surgery. That suggests CLU can be used as an early prognostic marker in kidney transplant recipients, and, going further, it may play a role in the development of graft rejection. Some studies have suggested that CLU levels may be used as a marker for the early detection of kidney transplant rejection, although more research is needed to support these observations.

CLU is not a specific marker associated only with kidney damage, but its level may also be increased in other conditions — so it should not be used as a sole indicator for kidney graft injury. However, some studies showed that elevated serum [11, 12], as well as urine [13] CLU levels, were associated with acute rejection episodes in kidney transplant recipients. Detecting transplant rejection by CLU as a marker has been reported with sensitivity of 40% to 80% and specificity around 70–80% [13–15].

CREATININE

Creatinine is a waste product of muscle metabolism that is generally removed from the bloodstream by the kidneys and excreted in the urine. Creatinine is a popular biomarker used to measure kidney function, notably in the context of kidney transplantation [16]. Creatinine levels alone, however, are not a conclusive diagnostic tool for rejection and should be read in combination with other clinical and laboratory data, including needle biopsy results since even a significant increase in the creatinine level alone does not provide adequate evidence of acute kidney transplant rejection. Also, muscle mass and the patient's clinical state influence the creatinine level. It has to be noted that these levels may not change significantly in the early stages of rejection, which makes it a less sensitive test for early detection.

The sensitivity and specificity of creatinine as a marker of acute kidney transplant rejection varied in studies from 72% to 81% and 67% to 83%, respectively [17–19]. Creatinine may be measured in both serum and urine. It has to be underlined that creatinine is one of the cheapest and most easily accessible markers of those mentioned in this review.

CYSTATIN-C

Cystatin-C (Cys-C) is a protein produced by all nucleated cells. It regulates the activity of specific proteases. Cys-C is a marker of kidney function because it primarily reflects the amount of the glomerular filtration rate (GFR) [20, 21]. When eGFR drops, Cys-C level in the blood rises [22]. Cys-C is unaffected by muscle mass or other variables, unlike other kidney function indicators such as creatinine. The role of Cys-C in kidney diseases has been investigated well in the available literature. A study by Liu [23] found that serum Cys-C was a better indicator of changes in renal function than serum creatinine, blood urea nitrogen, 2-microglobulin, or uric acid before surgery and at 1, 3, 5, 7, 14, 30, and 90 days after surgery. Koçak et al. [24] found that while Cys-C exhibited high sensitivity in estimating renal function in the early stages after transplantation, its utility as a GFR marker to indirectly assess kidney function after transplantation declined by the end of the first week. Only several studies have indicated that Cys-C has high sensitivity in diagnosing early acute

rejection, with values ranging from 75–90% and specificity ranging from 80–95% [25–27].

In one study, Liu et al. analyzed 160 kidney transplant patients to establish Cys-C accuracy in diagnosing acute rejection. The findings revealed that Cys-C has 90% sensitivity and 95% specificity in predicting acute rejection. The authors cautioned that sensitivity may diminish in later phases of rejection, especially in patients with severe fibrosis or scarring [27]. Urine and serum Cys-C have both been investigated as indicators of renal rejection. However, most research implies that urine Cys-C is a more sensitive measure of renal rejection than serum Cys-C [28, 29]. The timing of Cys-C rise and its prognostic usefulness may be affected by several circumstances; for example, an increase in Cys-C levels may begin several days to weeks before clinical indications of rejection appear [30], while in other cases, Cys-C levels may not change until after rejection has already occurred. Taking this into account, more research has to be performed, and Cys-C cannot be treated as a single marker of graft rejection. Also, the cost-effectiveness of the method is still doubtful.

C-X-C MOTIF CHEMOKINES

C-X-C motif chemokines, such as CXCL9 or CXCL10, are also examined as potential kidney transplant rejection markers.

CXCL9 is also known as a monokine induced by interferon-gamma (MIG). It is primarily produced by immune cells such as T cells, natural killer cells, and dendritic cells and acts as a chemoattractant for activated T cells and natural killer cells. CXCL9 has been implicated in the development of acute cellular transplant rejection. In this process, the immune system recognizes the transplanted organ as foreign and mounts an immune response against it, leading to inflammation and tissue damage. Elevated levels of CXCL9 have been observed in the serum of patients with kidney transplant rejection, and its presence has been associated with higher risk of rejection. Both Moledina et al. [31] and Tinel et al. [32] showed that patients with acute cellular rejection had significantly higher levels of CXCL9 compared to those without rejection. The aforementioned results are also supported by a meta-analysis by Zhou et al., which comprised five trials with a total of 384 kidney transplant recipients [33]. The authors concluded that CXCL9 may have potential as a biomarker to diagnose acute cellular rejection in kidney transplantation. In general, studies have shown that CXCL9 is a sensitive marker for the diagnosis of acute rejection in kidney transplant recipients, with reported sensitivities ranging from 68% to 94%. The specificity of CXCL9 as a marker of acute rejection is lower, with reported values ranging from 40% to 81% [34, 35].

CXCL10, known as interferon gamma-induced protein 10 (IP-10), is also used as a marker of acute kidney transplant rejection. CXCL10 has been shown to be a more sensitive and specific biomarker for acute cellular rejection compared to other commonly used markers such as serum creatinine and the panel reactive antibody test [35–37]. CXCL10 is a sensitive marker for the diagnosis of acute rejection in kidney transplant recipients, with reported sensitivities ranging from 73% to 91%. The specificity of CXCL10 as a marker of acute rejection is lower, with reported values ranging from 66% to 77% [38]. Additionally, Madhurantakam et al. indicated that CXCL10 levels have been shown to be a predictor of long-term allograft survival in kidney transplant recipients [39]. Notably, CXCL9 and, additionally, CXCL13, due to the mechanism of their production, are also viewed as markers of early infection in patients after transplantation.

DONOR-DELIVERED CELL-FREE DNA

Donor-derived cell-free DNA (cfDNA) is found in a variety of bodily fluids and is mostly derived from blood cells. Circulating cfDNA may be obtained from tumors, donor organs after transplantation, or, in some circumstances, the fetus during pregnancy. Circulating cell-free DNA (cfDNA) is a kind of deoxyribonucleic acid fragment that circulates in the blood and other bodily fluids. Donor-derived cell-free DNA (dd-cfDNA) is cfDNA that comes from a donated organ and is exogenous to the patient. In contrast to an invasive biopsy, dd-cfDNA can be discovered using a non-invasive sample analysis. Studies have found that the level of dd-cfDNA in the blood of kidney transplant recipients is positively correlated with the severity of acute rejection and that measurement of dd-cfDNA levels may be useful in detecting and monitoring acute rejection in those patients. For example, a study by Wijtvliet et al. [40] found that the level of dd-cfDNA in the blood was positively correlated

with the severity of acute rejection in kidney transplant patients. This correlation was also confirmed in studies by Fu et al. [43]. According to Matuszewski et al., the rise in dd-cfDNA concentration occurs before the rise in creatinine, which may allow for early detection of transplant damage and appropriate therapy to minimize premature graft loss [42]. The sensitivity of dd-cfDNA as a marker of acute kidney transplant rejection is relatively high, with values ranging from 60–80%. On the other hand, the specificity of dd-cfDNA as a marker of acute rejection can be lower, with values ranging from 40–60% [43–45]. It should be noted that dd-cfDNA accuracy as a sign of acute rejection can also be affected by the way it is analyzed, type of transplant, and overall health of the patient [46]. That means the method remains experimental.

ENDOCAN

Endocan, formerly known as endothelial cell-specific molecule-1, is a soluble proteoglycan found mostly in vascular endothelial cells of the lungs and kidneys [47]. It is activated by proinflammatory cytokines and is involved in inflammatory, proliferative, and neovascularization processes. Endocan's value as a biomarker in a wide range of disorders is becoming more well-recognized [48–51].

The exact role of endocan in kidney transplant rejection is not fully understood, but the activation of immune cells, including T cells and natural killer cells, is a crucial step in this process, and Endocan has been shown to play a role in this activation. Therefore, many authors think that endocan is a potential target for developing new immunosuppressive drugs [53].

In addition to its role in immune cell activation, Endocan has also been linked to other processes that contribute to transplant rejection, such as oxidative stress and inflammation [50]. The molecule has been shown to increase the production of reactive oxygen species, which can cause oxidative stress, cellular death, and damage to the transplanted kidney. Moreover, Zhao et al. showed that endocan binds to the chemokine receptor CXCR2 on NK T-cells (natural killer T-cells) [53].

Plasma endocan levels appear to give important prognostic information in several kinds of renal failure, including chronic kidney disease, IgA nephropathy, and diabetic nephropathy [54]. Endocan may also aid in early diagnosis of acute kidney illness, chronic renal allograft injury, and acute rejection following kidney transplantation, hence contributing to prompt endothelial cell injury monitoring. Li et al. showed that endocan may reflect the degree of endothelial cell injury in renal allografts and serve as a highly sensitive and specific marker for acute rejection after renal transplantation [55]. Hence, the exact utility of this marker remains unknown, and more research is needed.

INTERCELLULAR ADHESION MOLECULE 1 (ICAM-1)

ICAM-1 is a cell surface protein that is expressed in the kidneys and has been proposed as a marker of acute kidney transplant rejection. Several studies have demonstrated that increased expression of ICAM-1 is associated with acute rejection and suggested that it may play a role in the recruitment of immune cells to the transplanted kidney [56]. This increased expression can be measured in the blood, providing a potential non-invasive marker of acute rejection.

ICAM-1 is a cell adhesion molecule that is involved in the immune response and has been shown to be upregulated in the kidneys during acute transplant rejection. Several studies have demonstrated that increased expression of ICAM-1 is associated with acute rejection, suggesting that it may play a role in the recruitment of immune cells to the transplanted kidney [57]. This increased expression can be measured in the blood, providing a potential non-invasive marker of acute rejection.

However, while ICAM-1 has shown promise as a marker of acute kidney transplant rejection, more research is needed to fully validate its use in clinical practice. Several studies have shown conflicting results, and the exact role of ICAM-1 in the rejection process is not yet fully understood. It is also possible that ICAM-1 expression may be influenced by other factors, such as infection, ischemia, or chronic allograft injury, making it difficult to differentiate between acute rejection and other causes of kidney dysfunction.

Researchers discovered that measuring ICAM-1 expression was a sensitive indicator of acute rejection in kidney transplant patients. This applies to both blood [58, 59] and urine [60] measures. ICAM-1 has been reported to have excellent sensitivity (capacity to detect true positive cases of rejection) but very low specificity in several investigations (i.e., the ability to rule out false positive cases of rejection). Research has shown that ICAM-1 has

moderate sensitivity and specificity as a marker of kidney transplant rejection [60].

In general, the utilization of ICAM-1 as a biomarker of renal transplant rejection is currently being investigated, and additional research is required to completely comprehend its therapeutic relevance. ICAM-1's diagnostic accuracy may also be affected by the rejection stage, graft status, course of the transplantation procedure, and other variables that influence the immune response to the transplanted kidney.

INTERLEUKINS

Another marker that plays a role in immune response following kidney transplantation is interleukin-2 (IL-2). IL-2 is a cytokine that stimulates the growth and activity of T cells, a mechanism that plays a role in the process of acute rejection. IL-2 receptor antagonist medications, such as basiliximab or daclizumab, are used in selected patients at increased risk of rejection, which helps suppress the immune response and lowers the rejection risk. However, it is important to note that IL-2 also has other important functions in the immune system, and the use of IL-2 receptor antagonists can have potential side effects. Furthermore, Witkowska et al. indicated in their study that IL2 serum levels might be used as a late marker of unspecific cancers in individuals after kidney transplantation [61]. Moreover, IL-2 and its receptor are central to lymphocyte activation and are the main targets of calcineurin inhibitors. In addition, the anti-IL-2R antibodies inhibit a key target in immune activation. Since these anti-IL-2R antibodies are well tolerated and since calcineurin inhibitors are intrinsically nephrotoxic, anti-IL-2R antibodies have been used to avoid cyclosporin after transplantation [62].

Interleukin-5 (IL-5) is also a cytokine that promotes the survival, activation, and proliferation of eosinophils, a type of white blood cells. In the context of transplantation, eosinophils can contribute to rejection of the transplanted kidney by promoting inflammation and tissue damage. In patients with graft rejection, IL-5 levels have been observed to be higher than normal. However, it is important to note that elevated IL-5 levels are not always a definitive indicator of rejection, as there may be other factors contributing. Additionally, the exact relationship between IL-5 and kidney transplant rejection is still not fully understood and requires further research. Therefore, IL-5 cannot be treated as an independent marker — but should be used with a combination of clinical and laboratory data to evaluate the possibility of kidney transplant rejection. For example, mitogen-induced peripheral blood lymphocyte IFN-gamma; IL-5 ratios ≥ 15 were highly predictive of allograft failure within 6 months of performing the assay [63].

Interleukin 6 (IL-6) is a multifunctional proinflammatory cytokine that is essential for T cell activation, survival, and differentiation. IL6 increases rejection and abolishes tolerance by acting as a switch that drives the differentiation of naive T cells into Th17 cells while inhibiting their maturation into regulatory T cells. According to a meta-analysis by Omrani et al., a higher serum IL-6 level in renal transplant recipients compared to healthy controls indicated that the serum level of IL-6 might be utilized to evaluate inflammation in ESRD patients undergoing renal transplantation [64]. Urine but not serum IL-6 values are sensitive indicators of rejection [65]. Waiser et al. showed that the sensitivity of urine measurements was much higher (93%) than serum (54%). The specificity in serum (70%) and urine (60%) was reduced by infection, acute tubular necrosis, and antithymocyte globulin treatment. However, the levels of IL-6 soluble receptor (IL-6sR) in the blood and urine did not correspond with rejection.

Another pro-inflammatory cytokine that has been suggested as a marker of acute kidney transplant rejection is interleukin-8 (IL-8). Several studies have linked increased levels of IL-8 to acute kidney transplant rejection. IL-8 is generated by a variety of cell types, including leukocytes, fibroblasts, and renal tubular epithelial cells, and its levels can rise in response to cellular stress, such as immune system activation. High levels of IL-8 were discovered in the blood and urine of patients with acute kidney transplant rejection [66, 67]. However, IL-8 should not be used as a sole diagnostic marker for acute kidney transplant rejection and should be interpreted in the context of other clinical and laboratory findings.

Interleukin-18 (IL-18) is another pro-inflammatory cytokine that is being studied as a possible sign of acute kidney transplant rejection [68]. IL-18 is involved in immune response regulation as well as inflammation mediation. IL-18 is generated by a variety of cell types, including macrophages, dendritic

cells, and renal tubular epithelial cells, and it can be induced by cellular stress, such as infection or tissue damage [69, 70]. Striz et al. [71] showed that upregulation of epithelial IL-18 plays an important role in immune and immunopathological reactions in renal parenchyma and contributes to rejection mechanisms of kidney allograft. Moreover, Kim et al. [72] indicated that the 137GG genotype of the IL-18 gene, encoding higher IL-18 production, seems to be associated with AR (acute rejection) and may be a useful marker of AR risk in renal transplant recipients.

It is important to remember, however, that the interleukins we have discussed so far are just a few examples of this group of mediators that can be used to predict acute kidney transplant rejection.

KIDNEY INJURY MOLECULE-1

Kidney Injury Molecule-1 (KIM-1) is a transmembrane protein that is upregulated in response to kidney injury [73]. It has been shown to play a role in the development of kidney injury [74], including kidney transplant rejection [75].

Studies have found that elevated levels of KIM-1 in the urine or serum of kidney transplant patients are associated with increased risk of acute rejection. KIM-1 has been identified as an independent predictor of graft outcomes and can be used to monitor the progression of kidney transplant rejection. KIM-1 is expressed in differentiated proximal renal tubular epithelial cells in damaged regions. It may participate in the progress of renal injury or repair. Many studies have illustrated different functions of KIM-1 in various renal diseases, including protective functions in acute kidney injury and damaging functions in chronic kidney disease. In injured renal cells, KIM-1 may function as a scavenger, with the phosphatidylserine type-1 receptor overseeing apoptotic cell phagocytosis [76] (Fig. 1). Following a renal injury (either ischemic or toxic), elevated KIM-1 levels may help differentiate acute tubular necrosis from prerenal azotemia and chronic kidney disease (CKD). Different authors proposed that elevated KIM-1 levels may also be used to identify patients at risk of progressing from acute kidney injury (AKI) to CKD, based on the observation that levels are constantly elevated in the latter [77, 80].

In addition to KIM-1's role in the response to kidney injury, KIM-1 has been shown to play a role in the regulation of kidney function by modulating the activities of various signaling pathways (ischemia-reperfusion injury pathway and the antibody-mediated injury pathway) involved in the regulation of renal homeostasis [79, 80].

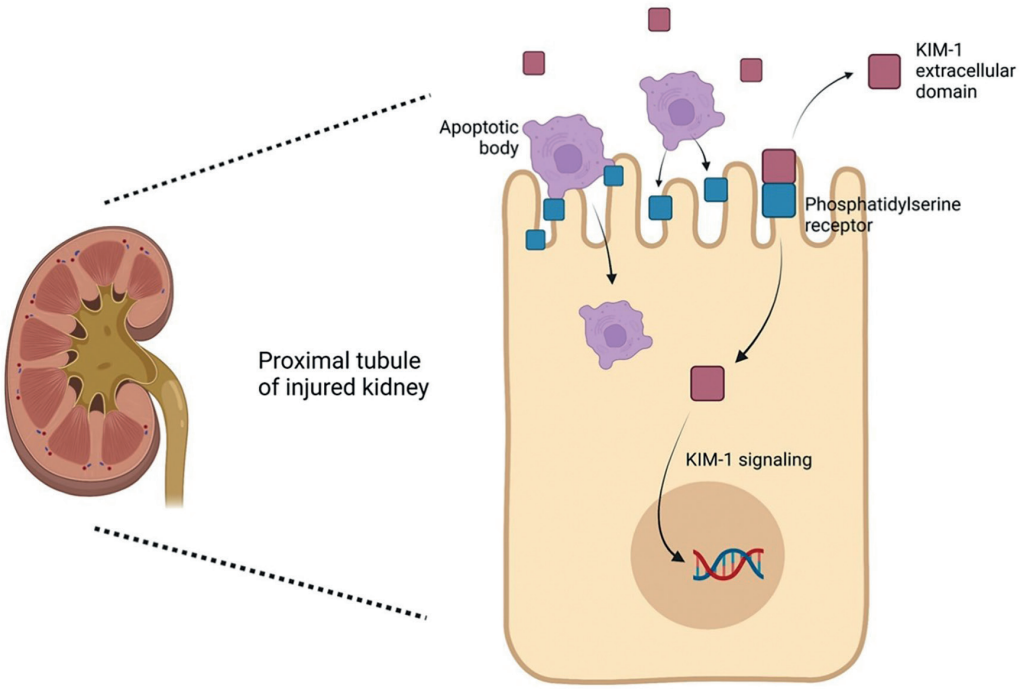

Figure 1. Kidney injury molecule-1 (KIM-1) expression in the proximal convoluted tubule after renal injury with phagocytosis of apoptotic cells

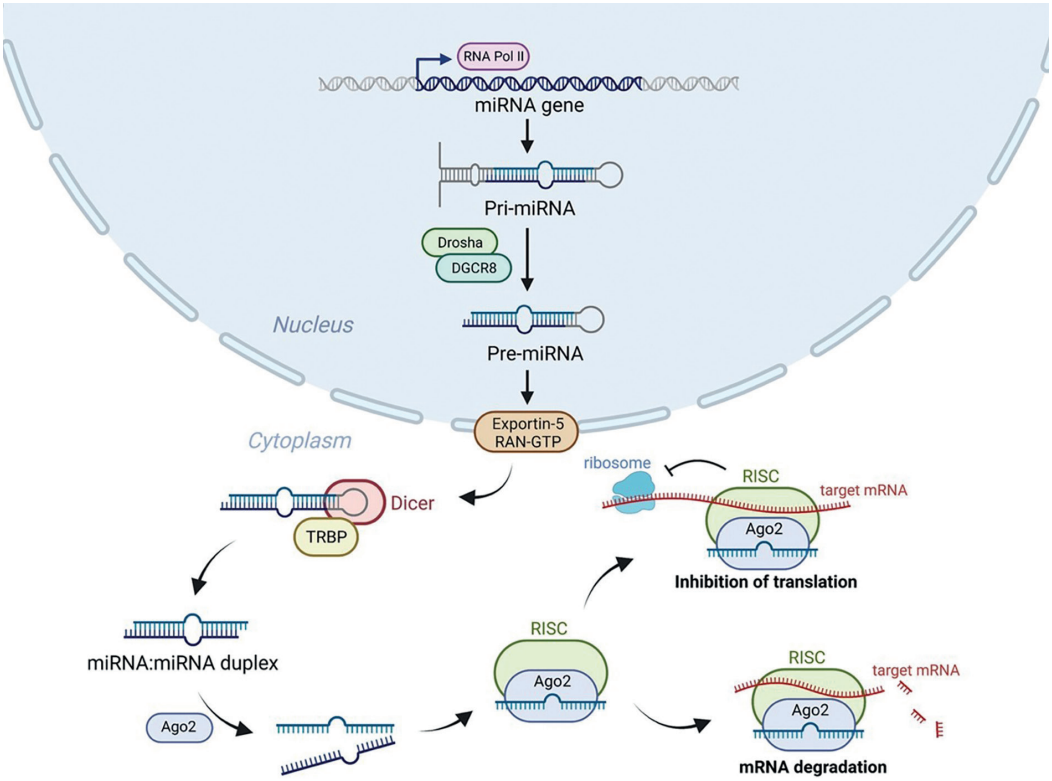

Figure 2. miRNA biogenesis and action mechanisms

Zhang et al. showed that KIM-1 staining sensitively and specifically identified proximal tubular injury and correlated with the degree of renal dysfunction. Moreover, KIM-1 expression is more sensitive than histological assessment treated so far as the gold standard for detecting early tubular injury, and its level of expression in transplant biopsies may indicate the potential for recovery of kidney function [81]. In addition, van Timmeren et al. indicated that urinary excretion of KIM-1 is an independent predictor of long-term graft loss and, therefore, a promising new biomarker in the early prediction of graft loss [82]. The same conclusions were also reached by Szeto et al. [83], which indicates that KIM-1 serum may be the most promising and accurate marker for the prediction of early acute kidney allograft rejection.

miRNA

MicroRNAs (miRNAs) are short, non-coding RNA molecules that play a crucial role in regulating gene expression. At the same time, because they are highly stable in blood, urine, and other body fluids, they are thought to have potential as biomarkers and therapeutic targets for various diseases [84, 85], as well as kidney transplantation [86–88]. However, as Roberts et al. rightly point out, the fact that one miRNA might be implicated in several illnesses remains a concern. Furthermore, standardization of miRNA expression levels throughout analysis remains a challenge [89]. The summary of miRNA biogenesis and mechanism of action is presented in Figure 2. Sui et al. indicated that 20 miRNAs were differentially expressed in three patients with acute kidney allograft rejection [90]. Anglicheau et al. [91] identified several upregulated miRNAs, including miR-142, miR-155, and miR-223, appropriately attributed to graft-invading immune cells and others expressed by resident renal cells that were downregulated (let-7c, miR-10b and miR-30a).

MiR-15a plays a multifaceted role in kidney transplantation, regulating a variety of cellular processes [92]. MiR-15a has been shown to impact the expression of genes implicated in the fibrotic response [93] and to reduce TGF-beta1 production, a key driver of fibrosis [94]. Furthermore, MiR-15a has been shown to affect the expression of other fibrosis-related genes such as type I collagen and alpha-smooth muscle actin. MiR-15a has also been related to immune response regulation, which is critical for the success of kidney

transplants. MiR-15a, for example, has been shown to influence the expression of genes involved in T lymphocyte activation and activity, which play an important role in the immune response. Also, it has been shown that it affects the expression of genes that control the production of cytokines [95].

Also, miR-21 has been identified as a possible biomarker for kidney transplant rejection. There is some evidence that miR-21 is upregulated in response to kidney transplant rejection, and it has been suggested that miR-21 may play a role in the rejection process [96] and that its levels in both blood and urine are linked to rejection [97]. MiR-21 has been shown to control a variety of immune-related cellular processes, including the activation and activity of immune cells such as T cells and macrophages. Furthermore, miR-21 has been discovered to influence the production of cytokines and other signaling molecules involved in the immune response. MiR-21, in particular, has been demonstrated to be a valuable marker for early detection of subclinical rejection, which standard clinical and laboratory approaches might miss. Furthermore, miR-21 levels have been demonstrated to correlate with the degree of rejection, implying that they might be utilized to monitor therapy response. Moreover, Chen et al. found that miR-21-5p, miR-20a-5p, and miR-101-3p all participated in the TGF-beta pathway and can be used as chronic allograft dysfunction-associated miRNAs in the TGF-beta pathway [98].

Elevated miR-125 values also correlate with acute rejection in kidney transplant patients. Sharaby et al. found that increased levels of miR-125 were significantly associated with acute rejection [99]. On the other hand, Zhang et al. found that elevated levels of miR-125 were detectable in urine samples from patients with acute rejection [100].

MicroRNA-142 (miR-142) also plays a role in the development of kidney transplant rejection. According to research, miR-142 levels in the blood of transplant patients experiencing acute rejection are changed. Increased levels of miR-142 have been linked to the activation of immune cells implicated in the rejection process, such as T cells and macrophages [101, 102]. Furthermore, miR-142 has been demonstrated to target genes that govern immune cell activity and contribute to transplant rejection. On the other hand, low levels of miR-142 have been linked to chronic allograft nephropathy, which is common in graft loss.

Another type of miRNA used as a marker in the case of kidney transplant rejection is microRNA-148 (miR-148). According to research, miR-148 expression levels are elevated in the blood and urine of patients who have undergone kidney transplantation and are facing rejection [103, 104]. This shows that miR-148 might be utilized as a non-invasive method for detecting transplant rejection early on.

Studies have shown that elevated levels of miR-155 are associated with kidney transplant rejection as it regulates inflammatory responses by playing a role in activation and differentiation of immune cells, such as T cells and B cells. Boštjančič et al. [105] found that increased levels of miR-155 in peripheral blood mononuclear cells (PBMCs) were associated with acute rejection in kidney transplant patients. Another study found that elevated levels of miR-155 in serum samples were predictive of biopsy-confirmed acute rejection in kidney transplant patients [106].

In turn, Liu et al. [107] indicated that miR-223 might have a significant role in the acute rejection of kidney transplantation. Another study found that mRNA targets of down-regulated miRNAs from serum, such as miR-1224-5p, miR-4508, miR-320, and miR-378a, were universally increased in tissue. When serum miRNA profiles were combined with tissue gene expression, it was discovered that variations in serum miRNAs indicate the function of T-cell mediated pathways in continuous allograft damage [108].

The optimal time for measuring microRNA levels to predict acute rejection in kidney transplantation is currently unknown and subject to ongoing research. Zhang et al. found that elevated levels of miR-125 in urine samples were detectable before the onset of clinical symptoms in patients with acute rejection [109]. This suggests that regular monitoring of miR-125 levels could provide an early warning sign of acute rejection, allowing for prompt intervention and management.

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCAINE

Neutrophil gelatinase-associated lipocalin (NGAL) is an extracellular protein belonging to the lipocalin family. It is also called human neutrophil lipocalin (HNC), lidocaine-2, 24p3, uterocalin, or siderocalin [110]. NGAL has been found to be a reliable

early indicator of acute kidney injury and renal dysfunction, including kidney transplant rejection [10]. NGAL levels are typically measured in the blood or urine of transplant recipients, and a rapid increase in NGAL levels can indicate that the transplant is being rejected and prompt further testing and treatment. Moreover, Li et al. showed that blood NGAL is superior to urine NGAL in the early prediction of delayed graft function (DGF) in kidney transplant recipients [111]. For example, a study by Seeman et al. [112], which involved monitoring the NGAL levels in a cohort of pediatric renal transplant recipients over several months showed that elevated NGAL levels were significantly associated with increased risk of acute allograft rejection. According toa study performed by Lang-Lazdunski et al., NGAL levels were a better predictor of acute rejection than traditional markers such as creatinine levels [113]. However, it is worth noting that NGAL is not a specific marker of transplant rejection, and elevated levels can be seen in other conditions, such as infections, drug toxicity, or kidney injury unrelated to transplantation. This highlights the importance of using NGAL in conjunction with other diagnostic tests to accurately diagnose acute rejection in kidney transplant recipients. This is supported by Cappuccilli et al. [114], who concluded that increased NGAL levels are a strong predictor of acute rejection, especially when combined with other diagnostic assays.

The sensitivity and specificity of NGAL in predicting renal rejection varies according to the research and population under consideration. NGAL has been found in certain studies to have high sensitivity in detecting acute kidney damage and renal transplant rejection. For example, Cho et al. [115] discovered that NGAL has 89.3% sensitivity in detecting acute renal allograft rejection. Bolignano et al. [113] found that the NGAL level was higher in patients with acute renal allograft rejection, but it was also higher in patients with other causes of acute kidney damage. This made it harder to diagnose the exact cause of the increase in the NGAL level. In reaction to severe kidney damage or transplant rejection, NGAL levels might rise within 24–48 hours [113]. NGAL levels greater than 109 mg/mL measured 48 hours after kidney transplantation indicated DGF with 75% sensitivity and 71% specificity [116], which makes it one of the best standardized methods among those discussed in this review.

MONOCLONAL ANTIBODY BINDING PROTEIN (MABP-1)

MABP-1 is a kind of monoclonal antibody that is created in the laboratory using a technique known as hybridoma technology. This method entails combining a specific kind of immune cell (B-cell) with a cancer cell to form a hybrid cell capable of producing an endless amount of a single type of antibody. MABP-1 is made to attach to a specific target on transplanted kidney tissue. This lets it be used as a test to see if a transplant is being rejected quickly.

MABP-1 levels in the patient's blood may be determined using several laboratory techniques, including Western blot analysis or Enzyme-linked Immunosorbent Assay (ELISA) analysis. MABP-1 levels that are elevated may signal that the body is generating an immunological reaction to the transplanted kidney, which is a sign of acute rejection. While MABP-1 can be a valuable marker for acute rejection, increased levels alone may not be sufficient to diagnose rejection. Screening for acute rejection is an important element of post-transplant treatment in kidney transplant patients. MABP-1 levels can be utilized to monitor for acute rejection and to guide treatment decisions, such as immunosuppressive medication adjustments. Regular monitoring of MABP-1 levels can aid in the early detection of rejection and prevent additional damage to the transplanted kidney. Despite that, there is little information on MABP-1's sensitivity and specificity in kidney transplant rejection, MABP-1 may be a sensitive marker for acute rejection, according to some research. MABP-1 exhibited sensitivity of 77% and specificity of 75% in acute rejection [117, 118]. Loga et al. showed in their meta-analysis that MABP-1 had pooled sensitivity of 68.4% and specificity of 84.1% in detecting acute rejection in kidney transplant recipients [119]. It is crucial to note that the sensitivity and specificity of MABP-1 might vary depending on the patient group, test technique, and threshold utilized to identify a positive result [119].

OSTEOPONTIN (OPN)

Osteopontin (OPN) is a glycoprotein that has a role in kidney transplant rejection via a variety of mechanisms. To begin, OPN is a chemoattractant and stimulator of immune cells such as T cells and monocytes, which play a role in transplanted kidney rejection [120]. Furthermore, OPN has been demonstrated

Table 1. Summary of biomarkers used in monitoring transplanted kidney function

Biomarker	Advantages	Disadvantages	Sample type
Clusterin (CLU)	Early detection of delayed graft function; measurable in blood or urine	Not specific to kidney damage, can be elevated in other conditions	Blood; Urine
Creatinine	Widely available, low cost	Low sensitivity in early rejection, influenced by patient's muscle mass	Blood; Urine
Cystatin-C	Not affected by muscle mass, reflects GFR	Sensitivity decreases over time, costly	Blood; Urine
CXCL9/CXCL10	High sensitivity in acute rejection	Low specificity, levels may rise due to infections	Blood; Urine
Donor-Derived Cell-Free DNA	Early detection before rise in creatinine, non-invasive	Low specificity, still experimental	Blood
Endocan	Indicator of endothelial cell injury, involved in immune cell activation	Not fully understood in transplant rejection, more research needed	Blood
ICAM-1	Non-invasive, high sensitivity in rejection	Low specificity, influenced by infection or ischemia	Blood; Urine
Interleukins (IL-2, IL-5, IL-6, IL-8, IL-18)	Sensitive indicators of immune response and inflammation	Non-specific, elevated levels may occur in various conditions	Blood; Urine
KIM-1 (Kidney Injury Molecule-1)	High sensitivity, early detection of tubular injury	May not differentiate between types of injury (acute tubular necrosis *vs.* rejection)	Blood; Urine
MicroRNAs (miR-15a, miR-21, miR-142, miR-155)	Stable in fluids, non-invasive biomarkers, correlate with rejection severity	Interpretation remains complex, many miRNAs are implicated in various diseases	Blood; Urine
NGAL (Neutrophil Gelatinase-Associated Lipocalin)	Early predictor of acute kidney injury and rejection	Non-specific, can rise due to infections or other kidney injuries	Blood; Urine
Osteopontin (OPN)	Sensitive indicator of acute rejection, involvement in immune response	Requires more studies to validate its clinical utility	Blood; Urine
Procalcitonin	Moderate-to-high specificity in acute rejection, widely available	Can be elevated in other conditions such as sepsis	Blood
TNF-Alpha (Tumor Necrosis Factor Alpha)	Indicator of systemic inflammation and rejection	Moderate sensitivity and specificity, can be elevated in other inflammatory conditions	Blood; Urine

to boost the production of pro-inflammatory cytokines, which are inflammation-promoting chemicals. Inflammation is a major component of the immunological response to a kidney transplant, and it can cause tissue damage and rejection. OPN regulates the extracellular matrix, which is a network of proteins and carbohydrates that gives structural support to cells and tissues. OPN has also been shown to interfere the process of getting the immune system to accept a transplanted organ, which is called "inducing transplant tolerance".

Several studies have found that high OPN levels in the blood are linked to increased risk of acute rejection in kidney transplant patients [121, 122]. Ranges of normal values for OPN in blood are typically considered to be below 30 ng/mL and in urine below 20 ng/mL.

Urinary OPN levels were used to diagnose acute rejection in kidney transplant recipients, with sensitivity of 73% to 76% and specificity of 78% to 88% [123]. Yang et al. then assessed blood OPN levels as a biomarker for acute renal allograft rejection [75]. In this study, 82 patients were analyzed, and it was found that serum OPN levels had sensitivity of 60% and specificity of 86% for diagnosing acute rejection.

Some research has also found that blocking or reducing OPN can help minimize the risk of transplant rejection. Researchers have tried a range of ways to suppress OPN in animal trials, including utilizing antibodies that specifically target the protein, decreasing OPN synthesis, and disrupting its interaction with other molecules involved in the immune response.

These studies have shown that inhibiting OPN can minimize the risk of transplant rejection and enhance transplant survival. Wang et al. found in a mouse model of kidney transplantation that suppressing OPN made acute rejection less severe and increased transplant survival [124]. In another study, Wang et al. summarize blocking OPN with an antibody to reduce the incidence of transplant rejection in a mouse model of heart transplantation [121]. Based on these results, it seems likely that targeting OPN could be a way to reduce transplant rejection and improve transplant outcomes.

PROCALCITONIN

Procalcitonin is a biomarker that has been shown to be indicative of acute kidney transplant rejection. Procalcitonin levels in the blood have been linked to the presence of acute rejection in transplant patients. However, procalcitonin is not a particular marker for rejection, and it can be elevated in circumstances other than rejection, such as sepsis and renal damage. Procalcitonin has been reported in certain studies to have moderate sensitivity (60–70%) and moderate to high specificity (80–90%) in identyfying acute rejection in kidney transplant recipients [125, 126]. For example, in a meta-analysis conducted by Zhou et al., the overall sensitivity and specificity of procalcitonin for the diagnosis of acute rejection were 0.68 (95% CI: 0.59–0.76) and 0.83 (95% CI: 0.77–0.88), respectively [127]. However, in other trials, procalcitonin's sensitivity and specificity were lower [128], which makes use of this marker highly questionable in everyday practice.

TUMOR NECROSIS FACTOR ALPHA

Tumor necrosis factor alpha (TNF-alpha) has also been linked to acute kidney transplant rejection [129]. TNF-alpha works by promoting inflammation and activating the immune response [130]. In the case of acute kidney transplant rejection, TNF-alpha can trigger an immune response against the transplanted kidney, leading to inflammation and tissue damage [131]. This immune reaction may inflame and damage the graft tissue, limiting its function and possibly leading to graft failure.

TNF-alpha levels may be tested in serum or urine. Blood TNF-alpha levels are a direct indicator of systemic TNF-alpha levels and may be a useful predictor of systemic immune response and the likelihood of acute kidney transplant rejection. TNF-alpha levels in urine may reflect the local immune response and provide a more accurate evaluation of TNF-alpha in transplanted kidneys [129]. This is especially valuable for tracking acute kidney transplant rejection since it may represent the degree of TNF-alpha-mediated tissue damage in the transplanted kidney.

In clinical studies, TNF-alpha was demonstrated to have moderate to great sensitivity in acute kidney transplant rejection, with sensitivity ranging from 50 to 80%. TNF-specificity alphas, on the other hand, may be moderate as markers for acute kidney transplant rejection, with some studies showing specificity ranging from 30–60% [132, 133].

EXTRACELLULAR VESICLES

Extracellular vesicles (EVs), such as exosomes, are being extensively researched as non-invasive indicators for the detection of kidney transplant rejection. These vesicles transport proteins, lipids, and RNA that indicate the cellular condition of the transplanted organ, providing significant insights into immune activity and tissue injury. We can extract extracellular vesicles from biological fluids such as urine or blood, making them a compelling alternative to conventional biopsy procedures. Their parts, like donor-derived cell-free -DNA, immune-related proteins, and microRNAs, have been linked to acute rejection events. This means that early diagnosis and better monitoring of grafts are possible [134, 135].

GENE EXPRESSION PROFILES IN KIDNEY TRANSPLANT MONITORING

Gene expression profiling (GEP) presents a viable method for assessing kidney transplant outcomes. It enables clinicians to identify immunological activation, inflammation, and tissue damage, before substantial functional deterioration. This strategy emphasizes the identification of alterations in the expression of particular genes associated with rejection, including those that govern T-cell activation and inflammatory responses. Research indicates that GEP testing in peripheral blood can accurately predict transplant rejection. A study showed that gene expression measurement could distinguish between rejection and non-rejection with accuracy of

85% [136]. A study of 155 kidney transplant patients indicated that increased levels of particular gene markers in peripheral blood samples were associated with biopsy-confirmed rejection events. Researchers reported that gene expression patterns can identify mild to severe rejection with sensitivity and specificity scores ranging from 75% to 90% [137]. GEP can evaluate regulatory T-cell activity, which is essential in preventing allograft rejection. A study demonstrated that longitudinal monitoring of T-cell-related gene expression showed a substantial association between lower expression levels and acute rejection, with diagnostic sensitivity of 78% and specificity of 82% [138].

SUMMARY

To conclude, any variations from the commonly used norms of laboratory indicators in patients after transplantation have to be treated with caution as they can suggest graft-threatening circumstances, i.e. the possibility of an adverse immune response, increasing the risk of transplant rejection that is indirectly life-threatening. Moreover, the above-mentioned biomarkers are not always specific for rejection, and their elevated levels might be found in other conditions such as sepsis and renal diseases. So, they should be used along with other clinical and lab results to spot rejection and figure out how to treat it. Moreover, in our opinion, a cross-sectional prospective research study with a large number of kidney transplant patients and multiple biomarkers is required to identify which biomarkers are most useful in predicting acute kidney transplant rejection (AKTR) and how early rejection can be diagnosed. All in all, according to up-to-date knowledge, needle biopsy remains the gold standard for diagnosing AKTR, while the discussed markers can be valuable indicators for histological assessment.

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