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Review

Assessment of Cardiovascular Disease in Autosomal Dominant Polycystic Kidney Disease

Antonietta Gigante *, Adolfo Marco Perrotta, Francesca Tinti, Eleonora Assanto, Maurizio Muscaritoli, Silvia Lai † and Rosario Cianci †

Department of Translational and Precision Medicine, Sapienza University of Rome, 00185 Rome, Italy; silvia.lai@uniroma1.it (S.L.)

* Correspondence: antonietta.gigante@uniroma1.it

† These authors contributed equally to this work.

Abstract: Autosomal dominant polycystic kidney disease (ADPKD) is an inherited kidney disease which leads to progressive kidney failure. About 5–10% of patients requiring renal replacement therapy are affected by ADPKD. Cardiovascular diseases are the main causes of morbidity and mortality in these patients with ADPKD; arterial hypertension (AH) is the first symptom with a very early onset. Anyway, some other cardiovascular abnormalities have been reported in ADPKD regardless of the presence of AH. With this background, we conducted a systematic review, collecting all randomized controlled trials (RCTs) and quasi-RCTs found on the main databases; we evaluated the evidence about different imaging techniques to grade the cardiovascular risk in a very early stage of disease. This review aims to describe all cardiovascular assessments in ADPKD patients to improve clinicians' ability to discover cardiovascular involvement early, allowing appropriate therapies promptly.

Keywords: autosomal dominant polycystic kidney disease; left ventricular hypertrophy; heart rate variability; cardiovascular risk; flow-mediated dilation; carotid intima–media thickness; pulse wave velocity

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1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a heterogeneous genetic disorder included in ciliopathies. The cystic dilatation of renal tubules and the progressive destruction of renal parenchyma leads to end-stage renal disease (ESRD) in half of affected patients aged 50 to 60 years. Thus, ADPKD is the fourth most common cause of renal replacement therapy worldwide, with an estimated prevalence between 1:1000 and 1:2500. ADPKD is characterized by the age-dependent growth of kidney cysts, and it is mainly caused by mutations in the PKD1 and PKD2 genes encoding for polycystin 1 (PC1) and polycystin 2 (PC2), which regulate differentiation, proliferation, survival, apoptosis, and autophagy [1]. More recently identified genes such as GANAB (encoding glucosidase II subunit α (GIIα)), PMM2, DNAJB11, ALG9, and IFT140 are also responsible for the development of cysts.

Mutations in PC1 and PC2, transmembranes glicoproteins that are colocalized to the primary cilium of the kidney tubular epithelial cells, cause lower intracellular levels of calcium and increased intracellular cyclic adenosine monophosphate, with aberrant cell proliferation and fluid secretion into cysts. ADPKD is a systemic disease that may involve different organs, showing high phenotypic variability [2].

The advances in knowledge of multiple molecular pathways underlying the pathophysiology of ADPKD involve the understanding of multiple mechanisms associated with extrarenal manifestations, including cardiac manifestations.

Cardiovascular disease is a major cause of morbidity and mortality in patients with ADPKD, and cardiac-related death in these patients is estimated to be 1.6- to 3.2-fold higher

compared to the general population, with 33% of deaths mainly due to ischemic heart disease and congestive heart failure [2].

Beyond the classic cardiovascular complications characterized by heart failure and coronary artery disease, well known in chronic kidney disease (CKD), ADPKD itself results in a genetically defined increased risk of cardiovascular complications.

Arterial hypertension (AH), a common finding in these patients, often occurs before the onset of renal failure and is associated with the most rapid progression to ESRD, with an increased cardiovascular risk.

The frequency of AH is increased at young age and is more frequent in patients with mutations in *PKD1* than in *PKD2* and in polycystic patients with hypertensive parents.

Early diagnosis is facilitated by the self-measurement of blood pressure or ambulatory BP monitoring (ABPM), particularly in those patients with masked hypertension who do not show a normal BP decrease at night-time (non-dippers) [3].

The pathogenesis of AH in ADPKD is not fully elucidated, but specific mechanisms such as the activation of the renin–angiotensin–aldosterone system (RAAS), impaired nitric oxide (NO)-related vasorelaxation, increased sympathetic nerve activity, increased plasma endothelin-1 concentrations, and insulin resistance have been revealed.

Sodium overload is also characteristic of ADPKD patients, and sodium-sensitive hypertension is described, associated with increased total kidney volume [3].

Left ventricular hypertrophy, a powerful, independent risk factor for cardiovascular morbidity and mortality, frequently occurs in patients with ADPKD. Both AH and left ventricular hypertrophy have important roles in cardiovascular complications in these individuals. The effect of cyst enlargement on renal vessels with parenchyma ischemia explains the activation of RAAS, which plays an important role in the development of hypertension in ADPKD [3]. Altered intrarenal hemodynamics cause endothelial dysfunction, NO production, and the hyperactivation of the sympathetic nervous system (SNS). The RAAS is stimulated at an early stage of the disease, even before the appearance of hypertension and other clinical findings. Similarly, increased left ventricular mass indices and diastolic dysfunction are reported in ADPKD patients with well-preserved renal function before the development of AH. Endothelial dysfunction, inflammation, and accelerated atherosclerosis are early-stage changes in ADPKD patients [4]. Biventricular diastolic dysfunction, endothelial dysfunction, increased carotid intima–media thickness (IMT), and increased arterial stiffness are present even in young ADPKD patients with normal blood pressure and well-preserved renal function [5]. Over the years, many innovations have been reported in renal imaging with computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate, in addition, to renal volume, intermediate volume or renal fibrotic and perfusion volume [6,7] with important prognostic implications for ADPKD patients.

Intracranial aneurysm (ICA) is one of the cardiovascular manifestations of ADPKD, but information about the natural history of ICA in ADPKD patients comes from small, single-center observational studies. These mainly describe an increased prevalence of asymptomatic ICA detected via magnetic resonance angiography (MRA), with 9–12% of patients demonstrating ICA, compared with ~2–3% of the general population. The prevalence is higher in ADPKD patients with a positive family history compared to ADPKD patients with a negative family history. Family history is recognized as the main risk factor for ICA rupture as well, which occurs at the average age of 40, almost 10 years earlier than in the general population [8].

Data from pre-symptomatic screening demonstrated that the majority of ICA localize in the anterior circulation of the circle of Willis, with nearly all being of a small size <7 mm, falling in the low-risk category for rupture.

Therefore, guidelines suggest to only perform screening for ICA in ADKPK patients with family or personal history of ICA rupture. All patients with ADPKD should receive counseling about the risk of ICA, considering the pros and cons of pre-symptomatic

screening and reserving diagnostic imaging for those individuals who remain anxious about their risk and individuals with high-risk professions [8,9].

Vascular disorders such as aneurysms and arterial dissections of large arteries, including aorta, coronary, and splenic arteries, are reported in ADPKD patients, representing an important cause of death. However, the prevalence of abdominal aortic aneurysms does not seem to be increased in patients with ADPKD.

Polycystin proteins have a role in epithelial cell/matrix interactions, and polycystin mutations are associated with collagen and extracellular matrix abnormalities. The high expression of PKD1 and 2 in the human adult vascular wall, particularly in the dense plaques of the smooth muscle cell, accounts for the risk of vascular wall modification. Characteristic phenotypes of some ADPKD patients showing arachnodactyly, high-arched palates, pectus deformities, joint laxity, flat feet, and positive thumb signs should alert clinicians toward an increased predisposition to vascular involvement [10].

There is no standard assessment suggested in these patients, and the clinical presentation of vascular disorders may be highly variable and mimic many common conditions. Given the high risk of complications in these patients, contrast-enhanced computed tomography should be considered when suggestive symptoms develop for differential diagnosis.

The other major extrarenal complications of ADPKD include hepatic and pancreatic cysts, colonic diverticula, dolichoectasias, abdominal wall hernias, cerebral and ascending thoracic aorta aneurysms, seminal vesicle cysts, and male infertility [2].

ADPKD is also associated with significant pain and discomfort, which may affect the quality of life of these patients. The quality of life (QOL) of patients with ADPKD could be associated with abdominal distention, pain, and anorexia caused by liver and kidney enlargement, even if other associated symptoms could also affect QOL such as sleep disturbance, heartburn, urinary tracts, fever, and hematuria [11].

Current treatment strategies include conservative therapy and reducing cyclic adenosine monophosphate levels, cell proliferation, and fluid secretion with somatostatin analogs and vasopressin V2 receptor antagonists that have been shown to slow the deterioration of renal function and the growth of renal and hepatic cysts [1].

A thorough clinical evaluation is essential to characterize the high cardiovascular risk in these patients through cardiovascular imaging to report important prognostic evaluations. Therefore, we conducted a systematic review of the current knowledge on cardiovascular assessment via imaging in ADPKD patients.

2. Methods

All randomized controlled trials (RCTs) and quasi-RCTs evaluating the current knowledge about imaging cardiovascular assessment in ADPKD patients were included.

1. Cochrane Renal Group's specialised register;
2. ClinicalTrial.gov (http://www.clinicaltrials.gov, accessed on 1 April 2023);
3. WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/, accessed on 1 April 2023);
4. MEDLINE.

We checked the reference lists of nephrology or cardiology textbooks, review articles, and relevant studies.

3. Results

The results of the research are summarized in Figure 1.

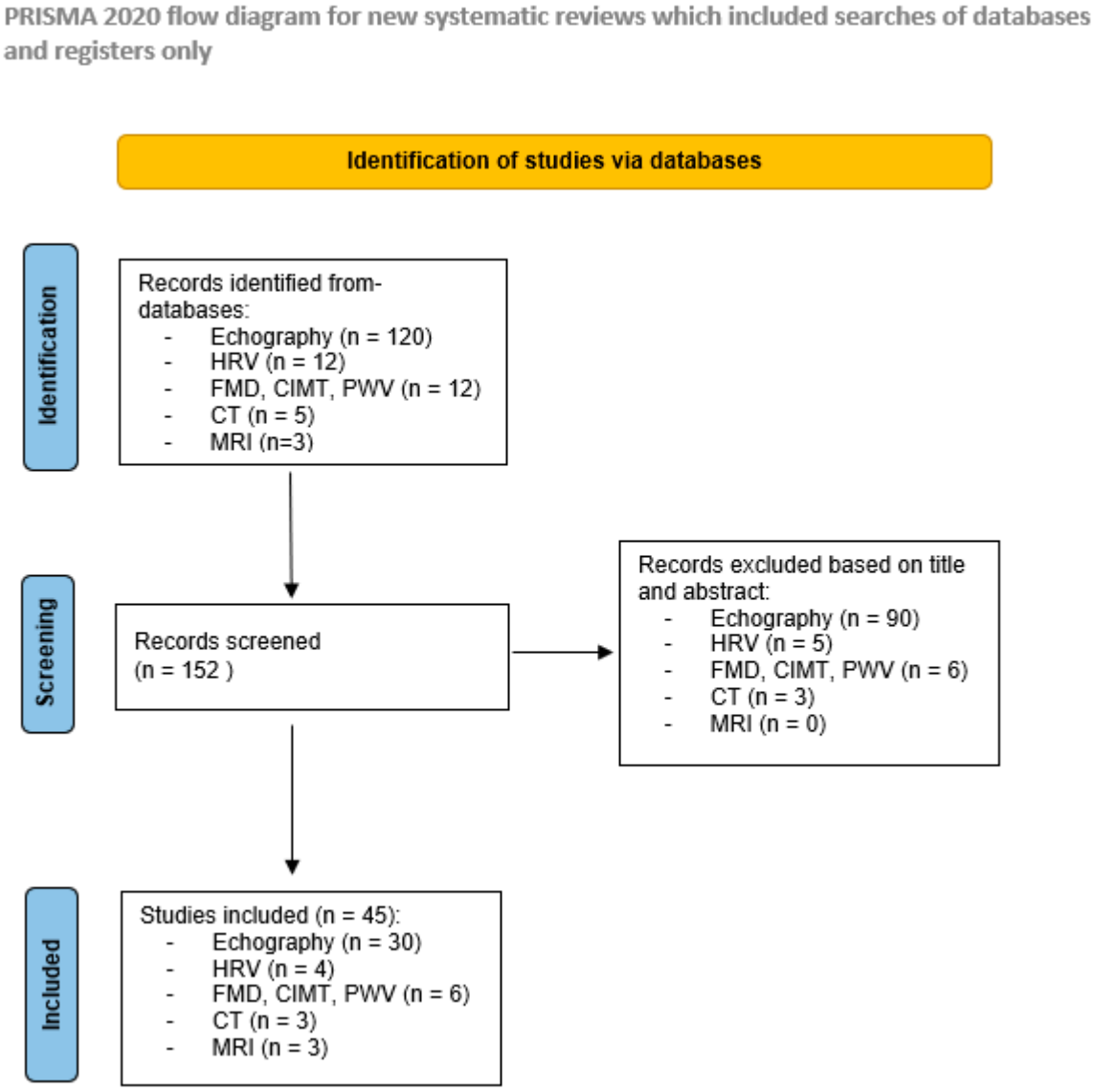

Figure 1. Abbrev.: HRV, heart rate variability; FMD, flow-mediated dilation; CIMT, carotid intima–media thickness; PWV, pulse wave velocity; CT, computed tomography; MRI, magnetic resonance imaging.

4. Echocardiography

Echocardiography findings in ADPKD patients have been well known for a long time [12–15]. Specific cardiac abnormalities related to mutations of PC1 and PC2 have not been reported, but all valvular apparatuses are involved in this condition; the most reported valvular defects are mitral valve prolapse, mitral incompetence, and tricuspid valve prolapse. Regardless of other possible causes, these abnormalities are more frequent in affected patients than in the general population [16–20]. According to the study by Lumiaho A. et al., mitral valve prolapse occurs in 26% of patients with PKD1, 14% of unaffected relatives, and 10% of control subjects [16].

Some observations report an increased incidence of large- and small-vessel aneurisms localized on ascendent aorta and coronary arteries [21,22]. These are specific experiences, not based on large studies; thus, is not possible to correlate ADPKD with a higher rate of aneurisms on these sites.

A matter to explore is the mechanism which leads to these abnormalities. It seems that cardiovascular disease is not totally related to kidney disease. An interesting study

conducted by Timio et al. on three cohorts of patients (affected individuals, non-affected familiars, and the general population) showed a higher prevalence of valvular abnormalities not only in affected people (3-fold higher than in healthy controls) but also in non-affected familiars (1.5-fold higher than in healthy controls) [23]. The mechanisms which underline these abnormalities are still unclear and probably need to be better understood to set up a specific prevention. We could suppose other pathogenetic pathway, different from the ones that cause kidney disease and cystic formation, involved in the changes in cardiac architecture.

4.1. Left Ventricular Hypertrophy and Molecular Mechanisms

Another debated issue is the prevalence of left ventricular hypertrophy (LVH) in ADPKD patients. Some authors consider LVH a consequence of early arterial hypertension onset. In any case, PC1 and PC2 are involved in several intracellular signaling pathways, which can influence cardiac function. PC-1 regulates mammalian target of rapamycin (mTOR) and PC-2 can influence B-cell lymphoma-2 (Bcl-2), leading to a down-regulation of mitophagy and apoptosis; both include pathways which can trigger hypertrophy in cardiac muscle [24–30]. Based on this hypothesis, PC-1 or PC-2 abnormalities in the heart could lead to an impairment in cardiac structure and function independently of kidney function or blood pressure. Different studies which investigate the prevalence of LVH among ADPKD patients underline that hypertrophy is more prevalent in young, affected patients than in the general population, regardless of the presence of AH [31–33]. Moreover, Pietrzak-Nowacka et al. [34] found higher left ventricular mass indexes (LVMIs) in male ADPKD patients (13%) than in the healthy group (2%) when comparing ADPKD patients and age- and sex-matched patients with essential hypertension [35]. Otherwise, not all the authors agree with this hypothesis, and this correlation is still uncertain; in fact, some studies do not show a higher incidence of LVH in ADPKD patients when compared with hypertensive patients [35]. A possible source of uncertainty was explained in the review conducted by Alam et al. [36]. In this study, the prevalence of LVH in ADPKD patients was 20–40% when assessed via echocardiography; when they took studies which assess LVH using MRI into consideration, the prevalence fell to 4%. These differences could be related to the imaging modality, variations in the parameters used to define LVH, or demographic differences in the study populations.

4.2. Novel Echographic Parameters for Cardiovascular Risk

Beyond the classical echocardiographic parameters, some studies show that PC1 and PC2 mutations are also related with novel risk factors and novel radiological markers [7]. In recent years, several studies have been focused on the correlation between epicardial adipose tissue and other possible cardiovascular risk factors. In three studies, ADPKD patients had more epicardial adipose tissue (EAT), associated with a higher risk of cardiovascular events [37,38]. EAT is considered a proper tissue with neuroendocrine functions, and its thickness is related with all the classical cardiovascular risk factors such as IMT and LVH.

In conclusion, the prevalence of cardiac abnormalities seems to be particularly high in ADPKD patients compared with the healthy population and hypertensive population.

An early assessment of these abnormalities is clinically relevant, considering the high rate of cardiovascular events in the ADPKD population. An adequate diagnostic pathway could improve therapeutic choices. Thus, we can suggest performing echocardiography in the affected patients, despite the presence of hypertension, to more accurately stratify the cardiovascular risk.

5. Heart Rate Variability (HRV)

In ADPKD patients, there is a dysregulation of the autonomic nervous system (ANS) [39]. The ANS is related to the cardiovascular system through heart rate control by the sympathetic and parasympathetic branches; catecholamines, released from the sympathetic nervous system, accelerate the heart rate. Additionally, contraction force and conduc-

tion are linked to sympathovagal balance, and changes in this equilibrium result in autonomic dysfunction.

The assessment of heart rate variability (HRV) reflects the influence of ANS (sympathetic and parasympathetic) on the cardiovascular system. Since cardiovascular complications are the main causes of death in patients at different stage of CKD, it is important to assess HRV as sign of cardiovascular impairment. HRV is defined as the variation in time intervals between consecutive heart beats over a period of observation (time of recording). Commonly using an Electrocardiographic Holter-Recording, this period can last 24 h or 5–10 min (a long or short time of recording, respectively), representing both the time domain and frequency domain able to evaluate global autonomic activity with the standard deviation of all normal-to-normal intervals (SDNN), sympathetic activity with low frequency (LF), parasympathetic activity with high frequency (HF), and sympathovagal balance with a sympathetic/parasympathetic ratio (LF/HF ratio) (Figure 2). Sympathovagal influence on the sinoatrial node (SA node) is indicated by HRV, an indirect index of cardiac neural control. The increased activation of the sympathetic system, mainly expressed by LF, causes a variation in heart rate and can promote hypertension, myocardial hypertrophy, and fibrosis, conditions associated with the risk of sudden cardiac death [40]. HRV and QT corrected for heart rate (QTc) interval evaluation can help in evaluating the arrhythmic risk and the autonomic dysfunction of patients [41]. In advanced CKD, regardless of the cause, the alteration of the autonomic system expressed by changes in HRV parameters represents a predictive factor for the rapid progression of CKD. In an observational study by the National Taiwan University Hospital conducted in 326 non-dialysis patients (median follow up period 2.02 years), a correlation between the late stage of CKD and low HRV was reported [42]. Among HRV parameters, SDNN, expressed as global autonomic function, LF (sympathetic system), HF (parasympathetic), and the LF/HF (sympathetic/parasympathetic) ratio were higher in early stages of CKD, while lower LF, HF, and LF/HF were correlated to late stages of CKD, which means a stronger compromission of ANS. Extremely lower LF and LF/HF were found in the rapid CKD progression group (diabetic and non-diabetic patients with worse values of serum creatinine, eGFR, proteinuria, albumin, hemoglobin, and HBA1c). Kidneys are directly innervated by the sympathetic nerve, which is one of the factors regulating the tubular and vascular function of glomeruli [42–44]. The pathogenetic mechanism of autonomic disfunction in ADPKD is not clear. Some hypotheses, such as uremic toxins, irregular erythropoietin secretion, and the overproduction of inflammatory mediators, are mentioned as causes of damage to autonomic kidney innervation. An imbalance between the sympathetic and parasympathetic system is also responsible for essential hypertension, which is the main feature of most ADPKD patients in the early stage of the disease. This is likely due to the presence and the enlargement of cysts in ADPKD, which cause an activation of the RAAS through renal arterial ischemia. A similar activation of RAAS is observed in bilateral atherosclerotic renal artery stenosis. RAAS activation causes autonomic disfunction with sympathetic prevalence [41]. Increased sympathetic tone is also caused by the reduction in baroreflex sensitivity due to high arterial stiffness related to elevated blood pressure. This process can be found in hypertensive and ADPKD patients with hypertension, because it is related to both these diseases. One study conducted on 65 patients evaluated the HRV in mild hypertensive patients with ADPKD (21 patients) versus patients with hypertension and organ damage (20 patients) and versus healthy controls (24 patients). HRV was more significantly reduced in ADPKD patients than in healthy controls, and the LF and LF/HF ratio were higher than in healthy controls. In hypertensive patients with organ damage, the same level of HRV abnormality was observed as in the ADPKD patients [41]. Since HRV variation is also detectable in young ADPKD patients without hypertension and/or CKD, it plays an important role as a predictive risk factor and therefore can be detected early in the disease course.

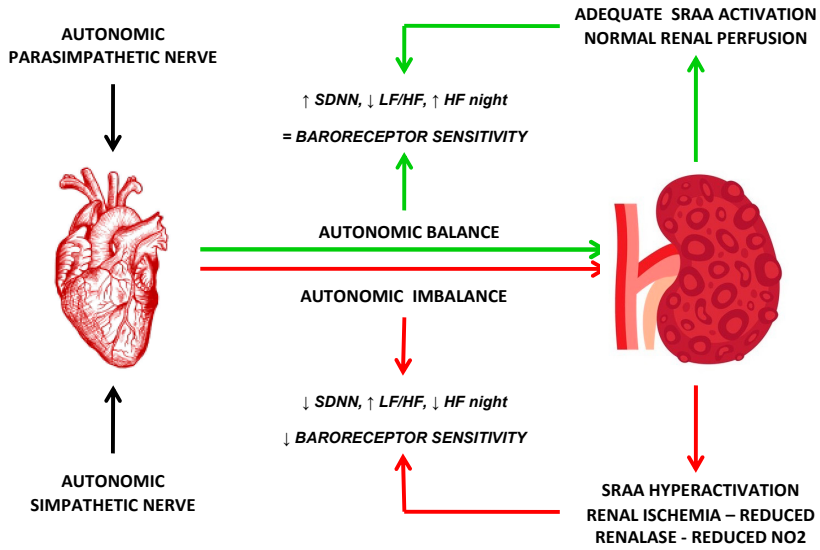

Figure 2. Autonomic dysfunction in autosomal dominant polycystic kidney disease. Abbreviations: SDNN: standard deviation of all sinus rhythm RR intervals; LF: low frequency, HF: high frequency, LF/HF: low frequency/high frequency, SRAA: systemic renin angiotensin aldosterone; NO: nitric oxide.

The evaluation of HRV can contribute to risk stratification by evaluating the imbalance of the sympathetic/parasympathetic system linked to cardiac complications such as coronary artery disease, arrhythmia events, and sudden cardiac death.

In conclusion, although no specific guidelines or standardized protocols for HRV measurement are available in ADPKD patients, it is an important, easy, and economic tool which contributes to the better assessment of cardiovascular risk in this cohort of patients.

6. Flow-Mediated Dilation (FMD), Carotid Intima–Media Thickness (IMT), and Pulse Wave Velocity (PWV)

Changes in endothelial function and increased carotid IMT and arterial stiffness are present in the early stages of the disease in young ADPKD patients and are associated with increased cardiovascular risk [5]. Endothelial cells produce more collagen and dysregulate matrix metalloproteinases as a consequence of the inflammatory status and stress factors present in ADPKD, which increase arterial stiffness. This is associated with uncontrolled arterial blood pressure and increases peripherical resistance, worsening hypertension and exposing patients to an increased rate of cardiovascular events and mortality [44].

A damaged endothelium loses its atheroprotective effect, as impaired vasomotion is responsible for the abnormal regulation of blood vessel tone [44,45]. When endothelial dysfunction occurs, the composition of the endothelial bilayer changes: the intima–media thickness is augmented and the amount of collagen is increased, worsening arterial stiffness. The pathogenetic process underlying endothelial dysfunction in ADPKD is still an object of debate, suggesting a role of the inflammatory status and vascular oxidative stress, as demonstrated by high levels of circulating NF-κB. Endothelial dysfunction is characterized by changes in the barrier permeability, which expose the vessels to aging and atherosclerosis, and by an altered vasodilatation/vasoconstriction ratio, mediated by the reduction in NO [5,45]. Endothelium dysfunction leads to the stiffness of the vessels increasing the peripherical arterial resistances, worsening arterial hypertension. Thus, endothelial dysfunction is a risk factor for cardiovascular events, such as stroke and coronary artery disease, with an increased mortality rate.

Some studies suggest that the activation of RAAS, mediated by the extension of cysts, can contribute to vascular dysfunction in addition to autonomic dysfunction [43].

In fact, the activation of RAAS, impaired NO-related vasorelaxation, increased sympathetic nerve activity, increased plasma endothelin-1 concentrations, and insulin resistance have also been observed [1,2].

Hyperaldosteronism contributes to the further growth of cysts, renal fibrosis, and the progression of cardiorenal disease. This effect is attributed to the aldosterone-induced target organ inflammation and fibrosis and the development of metabolic syndrome. The mechanisms by which aldosterone exerts its negative effect include oxidative stress and endothelial dysfunction through the decreased synthesis and release of NO, the production of reactive oxygen species mediated by nicotinamide-adenine-dinucleotide-phosphate-oxidase-dependent mechanisms, inflammation, and fluid retention, determining vascular remodeling, hypertrophy, and fibrosis. Furthermore, aldosterone also seems to be involved in the development of metabolic syndrome, dyslipidemia, endothelial dysfunction, and insulin resistance. The majority of these effects are mediated by the activation of the mineralocorticoid receptors that are expressed in cardiomyocytes, cardiac fibroblasts, and vascular smooth muscle cells, and they are mediated by the genomic and non-genomic effects of the hormone. The mechanisms by which aldosterone may contribute to insulin resistance include the increased degradation of insulin receptor substrates, the reduced transcription of the insulin receptor gene, interference with insulin signaling mechanisms, inflammation, reduced adiponectin production, and increased oxidative stress [4,43].

Moreover, experimental evidence suggests that PC1 and PC2 serve as mechanoreceptors in endothelial cells and smooth muscle cells, which sense the shear stress of the blood flow. The reduction in these glycoproteins may implicate an alteration in intracellular signaling, leading to reduced NO production. The reduction in NO may promote oxidative stress, vasoconstriction, hypoxia, and vascular remodeling, contributing to renal function decline and cardiovascular morbidity [44]. Increased oxidative stress and inflammation are other factors that contribute to the reduction in NO availability [44]. The evaluation of a possible therapy to improve endothelial-dependent vasodilatation is in progress, through the brachial infusion of dopamine in normotensive APDKD patients in order to restore NO bioavailability [44].

In fact, some authors showed that the stimulation of dopamine type 5 receptor on polycystin-deficient endothelial cells restores cilia length and shear-stress-induced calcium-dependent NO release, which suggests that stimulating dopamine receptors may have beneficial effects in ADPKD patients [44]. Studies over the past 2 decades have indicated the presence of an inflammatory component in ADPKD human and murine models [45].

NOXs are enzymes present in the vascular wall, and their primary task is to produce reactive oxygen species (ROS) superoxide, at physiologically low levels, in vascular cells. Some evidence showed overactive NOX systems in the initiation and progression of vascular disease via excessive ROS production by cells of the artery wall at levels that are cytotoxic. These ROS may lead to the activation of proinflammatory pathways; the depletion of antioxidants; and oxidative damage to proteins, lipids, and DNA. Among the NOX isoforms, NOX2 is believed to have the greatest implication in vascular disease. The overexpression of NOX2 in mice results in significantly increased superoxide production, and NOX2 knockout mice show significantly reduced ROS levels. Therefore, the increased activation of NOX2 could contribute to the diminished bioavailability of NO, and thus endothelial dysfunction and vascular cell hypertrophy. NOX2 upregulation could also explain the oxidative stress observed in patients with ADPKD, including endothelial dysfunction [4,45].

Due to the important role of the endothelium in the homeostasis of vessels, for example, in mediating vasodilatation related to shear stress (increasing or decreasing the speed of blood flow), in the regulation of inflammation, it is important to detect endothelial dysfunction.

Some non-invasive methods are used to detect endothelial disfunction. One of these methods is flow-mediated dilation (FMD) characterized by the evaluation of the diameter of the brachial artery before and after reactive hyperemia through the ultrasound technique.

FMD is realized through the measurement of the diameter of a peripheric artery, a usual brachial artery, with a linear ultrasound transducer. The diameter of the artery is valued on a specific position at rest (baseline), then after inflation, lasting 15 s, and consequently upon the deflation of a sphygmomanometer cuff, which simulates shear stress. FMD is generally calculated as FMD (%) = (Peak diameter − baseline diameter)/(baseline diameter) [43]. After this shear stress factor, endothelia should produce NO to stimulate vasodilatation and then reactive hyperemia. In ADPKD patients, there is endothelium dysfunction in the inflammatory state, with low NO available and increased arterial stiffness worsening flow-mediated vasodilatation [44–49].

A meta-analysis of 27 studies, including a total of 1967 ADPKD patients with preserved renal function (eGFR > 60/mL/min/1.73 m^2) compared to healthy controls, showed increased vascular stiffness and endothelial disfunction in patients with ADPKD. These damages were already present at the early stage of renal disease [46]. In particular, FMD was estimated to be significantly lower in ADPKD patients compared to healthy controls. ADPKD was also linked to significantly higher pulse wave velocity (PWV) and carotid IMT with the stiffening of large elastic arteries, contributing to cardiovascular dysfunction [46]. Carotid IMT is evaluated via the ultrasonographic technique as the distance between the lumen–intima and media–adventitia is 1–2 cm proximal to the carotid bulb.

The link between high IMT (intima–media thickness) and cardiovascular risk is well known. IMT represents the medial hypertrophy and thickening of smooth muscles and increases when the endothelium is damaged. An increased IMT contributes to the creation of a turbulent blood flow, which is a risk factor for atherosclerosis [3,5,36]. For these reasons, periodically valuating IMT, as a measure of endothelial dysfunction, is important to assess CV risk in ADPKD hypertensive and non-hypertensive patients.

Carotid IMT and FMD have also been used to assess endothelial dysfunction in a study conducted on 54 ADPKD patients, 20 of them being smokers, and 45 healthy controls, 19 of them being non-smokers. Healthy smokers and ADPKD non-smoker patients had similar values of FMD and CIMT. Smoker ADPKD patients had a higher IMT and lower FMD compared to ADPKD non-smoker patients [46]. The increased stiffening of large elastic arteries in ADPKD patients can be detected through a higher Carotid–Femoral PWV and Carotid–Radial PWV. Pulse Wave Velocity is non-invasively measured through a transcutaneous tonometer positioned at the carotid, brachial, radial, and femoral arteries [49]. At each site, two distinct waves are recorded: the first one reflects the left ventricular ejection and the second one is the reflected wave from peripheral segments. Pulse wave velocity is calculated as distance divided by time between the lowest part of the obtained waveforms. From these values, the Stiffness Index can be calculated [49]. One study on 55 ADPKD patients has shown that increased arterial stiffness is related to the occurrence of ESKD and cardiovascular complications (myocardial infarction, stroke, and cardiovascular interventions) in ADPKD, particularly in patients with multiple cardiovascular risk factors (obesity, hypertension, diabetes mellitus, smoking, and lipid abnormalities) [49]. The evaluation of arterial stiffness and endothelial disfunction is one of the main predictive factors of cardiovascular complications and renal disease progression in ADPKD patients. It can already be identified in the early stage of renal disease and even in not-yet hypertensive patients [44]. Increased arterial stiffness is found in people with CKD, and its etiology has an influence on the degree of arterial stiffness: in ADPKD patients, arterial stiffness develops earlier and the progression is more rapid than in patients at comparable stages of kidney disease [49]. Further studies and trials are necessary to evaluate the therapeutic implications of these parameters.

7. Computed Tomography

The study of the heart in ADPKD patients with CT is rarely performed because of the risk of contrast-induced nephropathy linked to the administration of contrast media in patients often affected by CKD. No randomized control trials or quasi-RCTs are available on heart CT scans in ADPKD patients.

Rare cardiac manifestations of ADPKD have been described beyond valvular abnormalities, in particular aortic aneurysm, coronary arterial aneurisms (CAAs) and dissections of coronary arteries (CADs). Different prevalence rates were reported by gender, patients' characteristics, and AH. The male gender is prevalent in CAAs, while patients diagnosed with CADs are mainly female. Presentation before 50 years of age is also a characteristic of these patients. The frequent concomitant presence of atherosclerosis and AH was described in CAA patients. The left anterior descending artery was most affected in CADs, while right coronary artery predominance was described in CAAs [50].

Coronary dissection showed female and left descending anterior artery predominance, with features similar to non-ADPKD patients, but the median diagnostic age was below the expected value (41 vs. 50 years old). Coronary aneurysms had male and right coronary artery predominance but a lower median diagnostic age (44 years old) and a higher rate of multiple vessel affection than that reported for non-ADPKD patients [50].

Diagnoses of coronary artery disease are primary made using coronary angiography, which allows contemporary diagnosis and treatment via coronary angioplasty.

Only one case of spontaneous coronary artery dissection (SCAD) underwent diagnosis via a coronary CT scan performed during a health check in a 59-year-old man. In this case, renal function was within the normal limits, and the CT scan helped in the diagnosis of SCAD [51]. Coronary artery dissection is a rare complication described in ADPKD patients, characterized by unstable angina, acute myocardial infarction, or even sudden cardiac death [50,52].

Only one more paper reported a CT angiogram of the chest revealing a Stanford type A and DeBakey type I aortic dissection involving the aortic valve and extending to the abdominal aorta with the coeliac, superior and inferior mesenteric, and left renal arteries arising from the false lumen [52]. The authors suggest that patients with ADPKD should be investigated for intracranial, coronary, and aortic vascular anomalies to prevent such devastating outcomes. A CT scan should only be used for the diagnosis of acute dissection.

8. Magnetic Resonance Imaging

Several studies reported the presence of LVH in patients affected by ADPKD. The prevalence ranges widely depending on age, gender, and hypertension, varying between 19 and 48% [16,53].

In the general population, the gold standard for the assessment of LV mass (LVM) is cardiac magnetic resonance imaging (MRI), but the evaluation of LVH and LVM is mainly performed via echocardiography. Cardiac MR more accurately determines left ventricular dimensions and the LV mass, enhancing information about the pattern of hypertrophy and myocardial fibrosis. In ADPKD patients, MRI is not usually performed for the evaluation of LVM.

One single study performed cardiac MRI for the assessment of LV mass and LVH, reporting significantly a lower prevalence value compared to echocardiographic studies [54]. Five hundred and forty-three hypertensive patients with GFR > 60 mL/min per 1.73 m^2 underwent the MR assessment of LVM before starting an intensive angiotensin blockade. The enrolled patients were younger than 50 years, with the satisfactory control of blood pressure and a high incidence of angiotensin-converting enzyme inhibitor (ACEi) administration. The prevalence of LVH was 0.93% using LVMI and 3.9% using non-indexed LV mass. The normal range of LVM via MR was lower than that reported via echocardiography, as described in previous studies comparing LVM indexes determined via cardiac MRI and echocardiography [54]. The indices of LVM were accounted for body size, reporting that LVMI demonstrated the strongest correlation in patients with ADPKD. Systolic blood pressure measured at office, serum creatinine, and urine albumin were directly associated with LVMI. Female gender was inversely associated, as expected, because of the relation between gender and body size. The authors suggest that aggressive blood pressure control and use of ACEi in patients with ADPKD was associated with decreased LVH. Left ventricular mass determined from cardiac MR appeared to be lower than that

determined via M-mode echocardiography; the greater accuracy of MRI should account for this discrepancy and may lead to different management options for patients [54–56].

Some authors also used MRI in ADPKD to evaluate pericardial effusion and found larger pericardial effusion thickness in ADPKD subjects compared to a population control matched for age, gender, and GFR. Liu et al. [55] used MRI, including ECG-gated cine MR of the aorta and heart, to evaluate pericardial effusion independently with three observers, measuring the maximum pericardial effusion thickness in diastole using electronic calipers. All MRI exams were obtained on a 1.5 T using a body array coil (Signa HDXT, GEHealthcare, Waukesha, WI, USA, or Magnetom Aera, Siemens Healthineers, Erlangen, Germany). Patients with ADPKD and a mean eGFR of 67 mL/min/1.73 m^2 demonstrated a significantly higher prevalence of pericardial effusion > 5 mm compared to matched controlled patients (21% in ADPKD patients, vs. 3% in control population). The occurrence of pericardial effusion was independent of heart failure, rheumatologic disease, increased fluid intake, or thyroid dysfunction. Pericardial effusion thickness significantly correlated with gender and right and left pleural effusion and negatively correlated with age. The retrospective measurement of pericardial effusion thickness was similar in MRI and echocardiography when echocardiographic images were retrospectively analyzed, but only two out of eight effusions seen on MRI were reported on the initial echocardiography reading performed when blinded to MRI results. The evidence of pleural and pericardial effusion on MRI highlights the need for further investigations in these patients to explain the pathophysiology.

Moreover, considering that intracranial aneurisms have a higher prevalence in ADPKD than in the general population [55], the current guidelines only suggest performing brain MRI in the subjects with a positive familiar history of subarachnoid hemorrhage (SAH) or kidney transplantation candidates [57].

9. Cardiopulmonary Exercise Testing (CPET)

Cardiopulmonary exercise testing (CPET), also referred to as a VO_2 (oxygen consumption) test, is a specialized type of stress test or exercise test that measures exercise ability. This test provides information about the heart and lung function to understand if patients' response to exercise is normal. CPET defines the maximum exercise capacity through the measurement of peak oxygen uptake (VO_2). Oxygen uptake ($V'O_2$), carbon dioxide production ($V'CO_2$), and minute ventilation (V'E) are determined. CPET consists of a steady-state resting period, then one minute of warm-up without a load, followed by a stepwise protocol in which the work rate is increased in 1 min intervals by increments of 10 Watt. The exercise test is considered maximal for a value of respiratory exchange ratio (RER) > 1.05. The Lactic Threshold (LT) is detected individually using the V-slope method [58]. Workload (W), LT, maximal oxygen consumption ($V'O_2max$), HR peak values, and BP are evaluated and compared with those obtained in a group of healthy subjects matched for age, height, weight, and gender. Oxygen uptake and ventilatory patterns obtained during the submaximal portion of CPET also give valuable information because of the possibility to evaluate the ability to perform activities of daily living during low-level exercise. CPET has become an important clinical tool to evaluate exercise capacity and to predict outcome in patients with heart failure and other cardiac conditions. It provides the assessment of the integrative exercise responses involving pulmonary, cardiovascular, and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function. CPET is being used increasingly in a wide spectrum of clinical applications for the evaluation of undiagnosed exercise intolerance and for the objective determination of functional capacity and impairment [58].

Few studies assessed the role of CPET in ADPKD, showing reduced tolerance to stress and decreased anaerobic thresholds in patients with preserved kidney function [59,60]. VO_2 peak and anaerobic threshold are the major predictors of all-cause and cardiovascular disease, and in ADPKD patients, they are often out of the normal range. It is impor-

tant to confirm that exercise capacity is impaired in ADPKD with preserved kidney and cardiac function.

Therefore, early and non-invasive markers of cardiovascular risk and CPET should be performed in ADPKD patients, in the early stages of disease, despite the cost implication. Note that Parmar et al. [61] reported a case of subarachnoid hemorrhage from a ruptured berry aneurysm after stress testing in a patient with ADPKD.

10. Myocardial Scintigraphy

(99m) Tc-sestamibi myocardial perfusion imaging is frequently performed in conjunction with exercise or pharmacologic stress testing for the evaluation of coronary heart disease, but this method has never been used to evaluate the cardiovascular performance of ADPKD patients. Occasionally, incidental non-cardiac findings are detected upon review of the projectional images. In particular, a case of a patient with a history of ADPKD who was found to have a large abdominal photopenic area on the projectional images consistent with hepatic cysts was described [62].

Clinical Implications

Cardiovascular problems are a major cause of morbidity and mortality in ADPKD patients. Hypertension occurs in 50–70% of patients before the reduction in glomerular filtration at an earlier age than the general population, and it is associated with an increased rate of progression to ESRD [1,2]. Additionally, LVH occurs frequently and has important roles in cardiovascular complications in patients with ADPKD. Moreover, endothelial dysfunction, biventricular diastolic dysfunction, increased carotid intima–media thickness, and impaired coronary flow velocity reserve are present even in young ADPKD patients with normal blood pressure and well-preserved renal function [3,5,43]. Coronary and cerebral aneurysms and dissections represent a source of coronary syndromes and death in ADPKD. Clinical disparities may suggest a different mechanism of aneurysm formation compared to the population without ADPKD; in fact, the genetic mutations of ADPKD may predispose individuals to coronary abnormalities, especially aneurysms.

These findings suggest that cardiovascular involvement starts very early during ADPKD. Intracranial and extracranial aneurysms and cardiac valvular defects are other potential cardiovascular problems in patients with ADPKD. The early diagnosis and treatment of hypertension with drugs that block the renin–angiotensin–aldosterone system have the potential to decrease the cardiovascular complications and slow the progression of renal disease in ADPKD.

11. Conclusions

Cardiovascular involvement is prevalent in patients with ADPKD and represents the main cause of mortality. The main pathological findings are characterized by hypertension, LVH, aneurysms, cardiac valvular defects, aortic root dilation, and other cardiovascular manifestations. These abnormalities in clinical practice correlate with disease progression in ADPKD.

The main instrumental examination used for the assessment of cardiovascular disease in ADPKD is echocardiography, which is now performed early in all patients.

In addition, non-invasive, easy, economic diagnostic tests to assess cardiovascular risk, such as HRV, CPET, FMD, and PWD, are also performed to better assess high and early cardiovascular risk in ADPKD patients.

Most of the abnormalities are potentially subclinical. In fact, the early signs of the atherosclerosis process are characterized by endothelial dysfunction and high IMT, even in ADPKD with normal renal function and blood pressure. Understanding the association between ADPKD and increased cardiovascular risk leads to the establishment of an early and effective diagnostic assessment of cardiovascular changes to improve the time management of medications, to evaluate cardiovascular and kidney outcomes, and to improve the cardiovascular prognosis of ADPKD patients.

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