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EDUCATIONAL REVIEW

Oxidative stress in autosomal dominant polycystic kidney disease: player and/or early predictor for disease progression?

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD), caused by mutations in *PKD1* or *PKD2* genes, is the most common hereditary renal disease. Renal manifestations of ADPKD are gradual cyst development and kidney enlargement ultimately leading to end-stage renal disease. ADPKD also causes extrarenal manifestations, including endothelial dysfunction and hypertension. Both of these complications are linked with reduced nitric oxide levels related to excessive oxidative stress (OS). OS, defined as disturbances in the prooxidant/antioxidant balance, is harmful to cells due to the excessive generation of highly reactive oxygen and nitrogen free radicals. Next to endothelial dysfunction and hypertension, there is cumulative evidence that OS occurs in the early stages of ADPKD. In the current review, we aim to summarize the cardiovascular complications and the relevance of OS in ADPKD and, more specifically, in the early stages of the disease. First, we will briefly introduce the link between ADPKD and the early cardiovascular complications including hypertension. Secondly, we will describe the potential role of OS in the early stages of ADPKD and its possible importance beyond the chronic kidney disease (CKD) effect. Finally, we will discuss some pharmacological agents capable of reducing reactive oxygen species and OS, which might represent potential treatment targets for ADPKD.

Keywords ADPKD · Oxidative stress · Early stages · Endothelial dysfunction · Cardiovascular complications · Young adults · Children

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Abbreviations

ACEi	Angiotensin-converting enzyme inhibition
ADMA	Asymmetric dimethylarginine
ADPKD	Autosomal dominant polycystic kidney disease
AMPK pathway	AMP-activated protein kinase pathway
CKD	Chronic kidney disease
eNOS	Endothelium nitric oxide synthase
HtTKV	Height-adjusted total kidney volume
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
MDA	Malondialdehyde
mTOR pathway	Mammalian target of rapamycin pathway
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NO	Nitric oxide
OS	Oxidative stress
Oxidized-LDL	Oxidized-low density lipoproteins
PWV	Pulse wave velocity
RAAS	Renin-angiotensin-aldosterone system

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ROS	Reactive oxygen species
SOD	Superoxide dismutase

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease with a prevalence between 1:400 and 1:1000 live births [1]. This disease is caused by mutations in either the polycystic kidney disease 1 gene (*PKD1*) (located at 16p13.3; in approximately 78% of the families) or the *PKD2* gene (located at 4p21; in approximately 15% of the families) [2], which encode for polycystin-1 (PC1) and polycystin-2 (PC2), respectively [3, 4]. Recently, a third gene has been identified to cause ADPKD, namely *GANAB*, encoding glucosidase II subunit α (located at 11q12.3; in approximately 0.3% of the families) [2, 5]. ADPKD is characterized by the continuous formation and growth of innumerable cysts in both kidneys leading to their enlargement and to a loss of their normal architecture, which ultimately results in chronic kidney disease (CKD) [6, 7]. Although cyst development appears in childhood, the decline in the glomerular filtration rate (GFR) starts in most patients between the third and sixth decade of life [8, 9], leading to end-stage renal disease (ESRD) in approximately half of the ADPKD patients by the age of 60–70 years [9–11]. Besides the deterioration of the renal function, several cardiovascular complications including hypertension, left ventricular hypertrophy (LVH), atherosclerosis, and arterial stiffness have been reported in ADPKD [6, 12].

Hypertension occurs even before the first observed reduction in the GFR [13] and is related to impaired endothelial-dependent relaxation, LVH, and nitric oxide (NO) deficiency [7, 14]. Impaired endothelial-dependent relaxation, also known as endothelial dysfunction, is an early predictor of vascular injury and atherosclerosis. NO, on the other hand, plays a key role in the maintenance of the cardiovascular homeostasis and has both vasodilatory and beneficial hemodynamic effects in the human body. Endothelial dysfunction and decreased endothelial NO synthase activity are observed in patients with ADPKD [15]. Moreover, it has been reported that there is a link between endothelial dysfunction, NO deficiency, and oxidative stress (OS) [12, 16].

Oxidative stress is a state of imbalance between excessive oxidant formation (such as free radical production) and the degradation of those radicals by antioxidants as an in-house defense mechanism. Oxidant compounds such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) are formed under physiological conditions in the human body. These compounds are called reactive because they are unstable by nature and because of their interactions with surrounding molecules [17, 18]. However, reactive species are not necessarily harmful to the cells. At moderate concentrations, ROS/RNS function as second messengers and regulate the intracellular signal transduction pathways. In case of a lack of antioxidative defense, there is a local accumulation of ROS/RNS in the cell, which creates an imbalance in the prooxidant/antioxidant equilibrium. This imbalance results in oxidation products of lipids, DNA, and proteins [18]. Especially, the oxidation end-products of lipids are used to assess the redox state in human samples: oxidized-low density lipoproteins (oxidized-LDL), malondialdehyde (MDA), and F2-isoprostanes like 8-epi-prostaglandin $F_{2\alpha}$ [19, 20].

In the current review, we aim to summarize the cardiovascular manifestations as well as the relevance of OS in ADPKD and more specifically in the early stages of the disease. First, we will briefly introduce the link between ADPKD and the early cardiovascular complications including hypertension. Next, we will describe the potential role of OS in the early stages of ADPKD and its possible importance beyond the CKD effect. Finally, some pharmacological agents that are capable of reducing reactive oxygen species and OS, which might represent potential treatment targets for ADPKD, will be highlighted.

Link between autosomal dominant polycystic kidney disease and endothelial dysfunction

The underlying proteins in ADPKD, PC1 and PC2, are both membrane-bound glycoproteins and a subfamily of transient receptor potential (TRP) channels. Both proteins are present in the plasma membranes of the primary cilia of endothelial cells of all major vessels, where they form a heterodimeric molecular complex via their C-terminal chains [21, 22]. PC1 can also be found in the plasma membranes at focal adhesion, desmosomes, and adherens junction sites, whereas PC2 is also located in the endoplasmic reticulum [23]. The interaction between both proteins is important for both the translocation to the plasma membrane of the primary cilia and for the maturation of PC1 [24]. The PC1/PC2 complex is necessary for normal vascular development, since it is required for endothelial cilia to sense fluid shear stress through complex biochemical cascades involving many factors, including NO [25].

Deficiency of either PC1 or PC2 causes reduced NO levels [16]. Impaired endothelial response to shear stress with attenuation in vascular relaxation, also called impaired endothelial-dependent relaxation or endothelial

dysfunction, is caused by the defect in NO release correlating with a reduction in Ca^{2+}-dependent endothelial NO synthesis activity [21]. Interaction between PC1 and PC2 has a central role in regulating the intracellular Ca^{2+} homeostasis. Mutations of *PKD1* or *PKD2* can lead to lower cytoplasmic Ca^{2+} concentrations, which in turn causes an increase in adenylyl cyclase-6 activity and a decreased phosphodiesterase activity, leading to an increased cAMP abundance [21]. Alterations in the Ca^{2+} homeostasis seem to have a role in the cardiovascular pathogenesis of ADPKD, since these alterations display changes in Ca^{2+} signaling with reduced total intracellular and sarcoplasmic reticulum Ca^{2+} levels [22].

Endothelial dysfunction is present in many cardiovascular and metabolic disorders such as hypertension, dyslipidemia, and type 1 and 2 diabetes. It also appears to precede the clinical manifestations of many of these disorders. Therefore, endothelial dysfunction is one of the earliest hallmarks of vascular abnormality [26]. In ADPKD, endothelial dysfunction has been shown in hypertensive, borderline hypertensive, and normotensive patients with well-preserved renal function [7, 12, 14, 15, 27–32].

About 20 years ago, Wang et al. demonstrated that impaired endothelium-dependent relaxation was present in the resistance vessels from heterozygous PKD rats and even to a lesser extent in the healthy Han:SPRD rats. Back then, they concluded that these abnormalities may lead to the development of hypertension and vascular disease later in life, perhaps when the renal disease develops [27]. Only a few years later, the same researchers found that acetylcholine-induced endothelium-dependent relaxation was indeed harmed in the resistance vessels from ADPKD patients. Additionally, this impairment was also present in ADPKD patients in the early normotensive phase with a good renal function [15]. Furthermore, this impairment seemed exaggerated in hypertensive ADPKD patients [14]. Therefore, endothelial dysfunction in ADPKD seems to appear as a primary defect in ADPKD patients, while hypertension leads to a further defect in endothelial function [14, 28]. This was associated with a defective NO release from the endothelium [15].

Considering these findings, endothelial dysfunction has an important role in the pathogenesis of vascular disease. Kocaman et al. showed that hypertensive ADPKD patients with preserved renal function had a significantly greater left ventricular mass index (LVMI) compared with normotensive ADPKD patients in the early stages of the disease [28]. Moreover, the LVMI was, although not significant, also greater in normotensive ADPKD patients compared to healthy controls. Additionally, it was reported that the carotid intima-media thickness was significantly increased in the same group of hypertensive ADPKD patients compared with the same normotensive patients [28]. On the other hand, both hypertensive and normotensive ADPKD patients showed a significant biventricular diastolic dysfunction, which suggests that cardiac involvement starts early in ADPKD [29]. It was also found that hypertensive ADPKD patients have significantly less decline in nocturnal blood pressure compared to patients with essential hypertension [30]. This decline is even attenuated in normotensive ADPKD patients compared to healthy controls. Moreover, it has also been found that the endothelial-dependent dilatation was significantly less in nondipper ADPKD patients compared to dipper ADPKD patients. In addition, a lack of nocturnal blood pressure fall (nondipping) is a good predictor of cardiovascular prognosis [30]. All the findings above about an early-onset endothelial dysfunction were proved by a study that reported a decrease in coronary flow velocity reserve in both hypertensive and normotensive patients [31]. Along with this study, Borresen et al. found that the pulse-wave reflection was amplified in ADPKD patients, even in young patients who have normal blood pressure and renal function [32]. Recently, Nowak et al. demonstrated that even children and young adults with ADPKD had impaired endothelial-dependent dilatation and increased arterial stiffness [12]. All of this together shows that the pathological changes in the arterial system of ADPDK occur in the early stages of the disease [13].

Most of the cardiovascular disorders are associated with overproduction of ROS or increased OS. Both an overproduction of ROS and increased OS reduce vascular NO bioavailability and promote cellular damage. Hence, increased OS is considered to be a major mechanism involved in the pathogenesis of endothelial dysfunction [26, 33]. Since endothelial dysfunction is important for the development of several cardiovascular disorders, like hypertension, and since it is associated with OS, endothelial dysfunction will be mentioned a number of times throughout this review.

Link between autosomal dominant polycystic kidney disease, endothelial dysfunction, and hypertension

Hypertension is associated with progression of renal disease and with an increased risk for development of cardiovascular disease and mortality [13, 34, 35]. Moreover, cardiovascular abnormalities are described from a young age onwards, and hypertension is the most frequent complication among ADPKD patients. With an average age at diagnosis of 30 years, hypertension affects 60–75% of young adults and 5–44% of children diagnosed with ADPKD [36–38] before any substantial reduction of GFR is detected [13, 39].

Both endothelial dysfunction and the activation of the renin-angiotensin-aldosterone system (RAAS) play a major role in the pathogenesis of hypertension in ADPKD patients [13, 39, 40]. The decrease of NO bioavailability in ADPKD patients will cause the activation of the RAAS [13, 35, 41]. On the other hand, the enlargement of renal cysts will cause

compression of the renal vasculature, which, in turn, favors local renal ischemia, renal structural changes, and again the stimulation of the RAAS [13, 42]. Furthermore, there is a relationship between a significantly greater renal volume and hypertension, both in adults [43] and in children [44]. Also, hypertension is related to vascular remodeling and NO deficiency and is preceded by endothelial dysfunction [14]. The balance between vasoconstrictor and vasodilatation factors is disrupted since there are elevated levels of vasoconstrictor factors, like endothelin-1, in ADPKD patients [42]. In addition, the renal tissue NO synthase activity is also reduced, which may activate local OS pathways contributing to renal damage [14]. Besides the many processes involved in the pathophysiology of hypertension, OS strengthens the development of hypertension due to the excess production of vascular ROS, as discussed in the accompanying review by Daenen et al. in this issue [45]. In particular, the activation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is strongly associated with hypertension. The excess of vascular ROS causes a decreased NO bioavailability and a decreased antioxidant capacity [46, 47].

Besides the logical fact that the systolic as well as the diastolic blood pressure is elevated in early hypertensive and borderline hypertensive ADPKD patients compared to early normotensive ADPKD patients [48, 49], it is shown that the blood pressure is also elevated between early normotensive ADPKD patients and healthy controls (Tables 1 and 2) [28, 32, 35, 54–56]. Interestingly, between the ages of 20 and 40 years, there is a clear difference in the occurrence of hypertension between male and female patients. The number of male ADPKD patients suffering from hypertension is significantly greater between those age classes than the number of female ADPKD patients suffering from hypertension [57]. Furthermore, the likelihood of hypertension in both male and female ADPKD offspring is significantly higher with hypertensive ADPKD parents compared to ADPKD offspring of normotensive ADPKD parents [58]. To support a relationship between OS and hypertension, a recent study showed that myeloperoxidase (an oxidative stress biomarker) is positively and independently associated with blood pressure [59]. Additionally, it is known that a decrease in blood pressure due to antihypertensive drugs also has a beneficial effect on the endothelial function and is associated with a reduction in OS [60]. Based on these findings, a decreased blood pressure may also have beneficial effects, since hypertension is associated with the increased cardiovascular morbidity and mortality in ADPKD patients [61].

Additionally, both in young adults and children, the extent of hypertension is correlated with the increase in volume and growth rate of renal cysts, the increase in total kidney volume, the development of LVH, and a more rapid progression to ESRD. Therefore, both hypertension and LVH are important risk factors for premature cardiovascular disease, which is the most common cause of death in patients with ADPKD [13, 36, 43, 48, 49]. Moreover in childhood, not only a significant difference between the day- and nighttime systolic and diastolic blood pressure is seen but also a significant correlation between these blood pressure values and renal structural abnormalities is found [62, 63].

It has been suggested that blood pressure target values with drug treatment should aim at values of < 130/80 mmHg in adults [64]. The HALT-PKD study confirms this and suggests that aggressive blood pressure control (< 120/80 mmHg) is better to delay progression of the disease in patients with preserved GFR compared to standard blood pressure control (< 135/80 mmHg) [61]. The HALT-PKD study examined this effect with the administration of lisinopril alone or in combination with telmisartan. Patients with lower blood pressure had a significant reduction in kidney volume growth and a significant reduction of the left ventricular mass index (LVMI). However, there was no significant difference in GFR loss [61]. Interestingly, the improvement of blood pressure control by using angiotensin-converting enzyme inhibitors (ACEi) results in a later onset of ESRD both in males and females with ADPKD [57]. Although the cohort in the HALT-PKD study represented early stages of ADPKD, this is not applicable to children with ADPKD. A 5-year randomized clinical study to assess the effect of blood pressure control on the disease progression of 85 children and young adults with ADPKD using ACEi failed to demonstrate a significant effect on renal growth [65]. In the total cohort, the hypertensive children were at risk for increases in renal volume and LVMI and for a decreased renal function. In this particular group, ACEi treatment was associated with stable renal function and LVMI. In the same study, an intervention with ACEi would benefit the ADPKD children with borderline hypertension (75th–95th percentile) to ameliorate cardiovascular disease progression and loss of renal function over time. An ACEi treatment with the aim to achieve a blood pressure of ≤ 50th percentile has been shown to prevent the increase in LVMI and decline in renal function [65]. KDIGO, on the other hand, states that treatment of hypertension in pediatric ADPKD patients should follow prevailing pediatric guidelines. This means that the goal is blood pressure below the 90th percentile for age, sex, and height, with the only exception that RAAS blockade is preferred as first-line treatment [66]. Given these findings, it was suggested recently to use ACEi in adolescents and children with borderline hypertension or hypertension, to achieve a goal blood pressure below the 50th percentile. When ACEi is not tolerated well by the patients, angiotensin receptor blockers can be used instead [37].

Although the data supporting disease-specific blood pressure targets are limited in ADPKD, the recommendations of the KDIGO Clinical Practice Guideline as well as the HALT-PKD study suggested a blood pressure target ≤ 140/90 mmHg in adults [61, 66]. It is also very important to highlight that in

Table 1 Summary of the studies on cardiovascular complications related to oxidative stress in early stage ADPKD in children

Reference	No. of patients			Complication	Controls	ADPKD	
	Control	ADPKD					
Zeier et al., 1993 [50]	Mean age 9.6 years ($n = 12$)	Mean age 9.8 years ($n = 12$)		Daytime mean arterial blood pressure	No value given	No value given but not significantly different from the blood pressure of the control	
				Nighttime mean arterial blood pressure	No value given	No value given but not significantly different from the blood pressure of the control	
				LVMI	61.3 g/m^2	66.6 g/m^2	
Cadnapaphornchai et al., 2008 [49]	Not included	12.0 ± 0.8 years Normotensive ($n = 30$)	13.6 ± 0.8 years Hypertensive ($n = 28$)	Systolic blood pressure	Not included	109 ± 2 mmHg	130 ± 3 mmHg
				Diastolic blood pressure	Not included	64 ± 1 mmHg	72 ± 2 mmHg
				LVMI	Not included	No value given	No value given but significantly higher compared to normotensive children
				Renal volume	Not included	No value given	No value given but significantly larger compared to normotensive children
Seeman et al., 2003 [36]	Not included	12.3 ± 4.3 years Normotensive ($n = 40$)	12.3 ± 4.3 years Hypertensive ($n = 22$)	Renal volume	Not included	1.2 ± 2.5 SDS	2.7 ± 2.3 SDS
				Daytime systolic blood pressure	Not included	118 ± 7 mmHg	130 ± 8 mmHg
				Daytime diastolic blood pressure	Not included	71 ± 5 mmHg	80 ± 7 mmHg
				Nighttime systolic blood pressure	Not included	103 ± 6 mmHg	114 ± 6 mmHg
				Nighttime diastolic blood pressure	Not included	56 ± 5 mmHg	65 ± 7 mmHg
Cadnapaphornchai et al., 2011 [48]	Not included	12 ± 4 years Normotensive ($n = 49$)	14 ± 4 years Hypertensive ($n = 28$)	Systolic blood pressure	Not included	112 ± 10 mmHg	130 ± 16 mmHg
				Diastolic blood pressure	Not included	64 ± 6 mmHg	73 ± 11 mmHg
Nowak et al., 2017 [12]	Age- and sex-matched (± 2 years) ($n = 15$)	6–22 years Normotensive ($n = 15$)		Systolic blood pressure	108 ± 3 mmHg	114 ± 5 mmHg	
				Diastolic blood pressure	59 ± 2 mmHg	63.3 ± 3 mmHg	
				PWV	478 ± 17 cm/s	544 ± 23 cm/s	

ADPKD autosomal dominant polycystic kidney disease, *LVMI* left ventricular mass index, *PWV* pulse wave velocity, *SDS* standard deviation score

Table 2 Summary of the studies on cardiovascular complications related to oxidative stress in early stage ADPKD in young adults

Reference	No. of patients			Complication	Controls	ADPKD	
	Control	ADPKD					
Gabow et al., 1990 [43]	Not included	29.6 ± 1.7 years (male) (n = 22) 31.1 ± 0.9 years (female) (n = 49) Normotensive	32.7 ± 1.1 years (male) (n = 42) 32.3 ± 0.9 years (female) (n = 34) Hypertensive	Mean arterial blood pressure (male) Mean arterial blood pressure (female) Mean renal volume (male) Mean renal volume (female)	Not included Not included Not included Not included	99 ± 2 mmHg 94 ± 1 mmHg 390 ± 43 cm^3 339 ± 24 cm^3	112 ± 2 mmHg 105 ± 2 mmHg 624 ± 47 cm^3 466 ± 32 cm^3
Borresen et al., 2007 [32]	34 ± 5 years (n = 18)	34 ± 5 years Normotensive (n = 18)		Systolic blood pressure Diastolic blood pressure PWV	101 ± 11 mmHg 74 ± 10 mmHg 5.7 m/s	111 ± 12 mmHg 81 ± 9 mmHg 6.1 m/s	
Kocyigit et al., 2012 [51]	35.4 ± 6.4 years (n = 50)	36.6 ± 9.9 years Normotensive (n = 50)		Systolic blood pressure Diastolic blood pressure PWV LVMI	113.8 ± 8.0 mmHg 75.3 ± 4.6 mmHg 5.8 ± 1.1 m/s 149.4 ± 37.3 g/m^2	116.7 ± 9.1 mmHg 76.8 ± 6.0 mmHg 9.6 ± 1.3 m/s 153.3 ± 46.5 g/m^2	
Kocaman et al., 2004 [28]	38.1 ± 8.8 years (n = 24)	35.8 ± 8.8 years Normotensive (n = 16)	39.6 ± 7.2 years Hypertensive (n = 15)	Systolic blood pressure Diastolic blood pressure LVMI	119 ± 14 mmHg 75 ± 9 mmHg 95 ± 17 g/m^2	120 ± 18 mmHg 74 ± 8 mmHg 108 ± 24 g/m^2	138 ± 18 mmHg 85 ± 11 mmHg 132 ± 23 g/m^2
Chapman et al., 1997 [52]	33.2 ± 1.0 years (n = 77)	40.7 ± 1.1 years Normotensive (n = 116)		Systolic blood pressure Diastolic blood pressure LVMI	116 ± 1 mmHg 74 ± 1 mmHg 96 ± 3 g/m^2	135 ± 2 mmHg 90 ± 1 mmHg 115 ± 3 g/m^2	
Pietrzak-Nowacka et al., 2012 [53]	34.6 ± 7.9 years (male) (n = 21) 38.5 ± 9.9 years (female) (n = 28)	34.4 ± 10.0 years (male) (n = 18) 37.5 ± 11.7 years (female) (n = 29) Normotensive		Systolic blood pressure (male) Systolic blood pressure (female) Diastolic blood pressure (male) Diastolic blood pressure (female) LVMI (male) LVMI (female)	125.3 ± 13.6 mmHg 119.9 ± 15.9 mmHg 86.6 ± 8.9 mmHg 80.2 ± 9.0 mmHg 91.4 ± 20.2 g/m^2 68.8 ± 15.5 g/m^2	134.2 ± 17.6 mmHg 133.6 ± 21.9 mmHg 94.4 ± 14.1 mmHg 91.5 ± 11.7 mmHg 102.2 ± 21.7 g/m^2 87.9 ± 68.8 g/m^2	
Orscelik et al., 2013 [54]	35 ± 10 years (n = 30)	35 ± 7 years Normotensive (n = 30)		Systolic blood pressure Diastolic blood pressure PWV LVMI	112.1 ± 6.8 mmHg 73.0 ± 5.1 mmHg 5.5 ± 1.1 m/s 146.6 ± 45.5 g/m^2	115.2 ± 7.9 mmHg 73.5 ± 5.8 mmHg 8.8 ± 1.6 m/s 152.9 ± 47.4 g/m^2	
Martinez-Vea et al., 2000 [55]	46.1 ± 11.9 years Essential hypertensive (n = 20)	46.7 ± 13.3 years Hypertensive (n = 20)		Systolic blood pressure Diastolic blood pressure LVMI (male) LVMI (female)	148.9 ± 16.8 mmHg 99.5 ± 9.5 mmHg 109 ± 19.6 g/m^2 104.3 ± 28.3 g/m^2	146.8 ± 12.6 mmHg 97.9 ± 8.9 mmHg 130.2 ± 18 g/m^2 96.4 ± 27.5 g/m^2	
Martinez-Vea et al., 2004 [56]	24.5 ± 6 years (n = 18)	24.1 ± 6 years Normotensive (n = 18)		Systolic blood pressure Diastolic blood pressure LVMI	118.9 ± 13.9 mmHg 65.2 ± 9.3 mmHg 77.5 ± 18.6 g/m^2	123.3 ± 7.6 mmHg 69.4 ± 8 mmHg 93.3 ± 21.4 g/m^2	

ADPKD autosomal dominant polycystic kidney disease, *PWV* pulse wave velocity, *LVMI* left ventricular mass index

the KDIGO consensus it recommends having children with a family history of ADPKD tested and treated for hypertension [66]. Additionally, early treatment of hypertension contributes to improve the morbidity and mortality [13, 39]. The recently revised American College of Cardiology/American Heart Association (ACC/AHA) high blood pressure guidelines are also worth mentioning [67]. With these guidelines, lower thresholds (≥ 130/80 mmHg) will be specified to define hypertension.

Cardiovascular complications in adults and children with ADPKD and preserved kidney function

In the later stages of ADPKD, cardiovascular disease consists of (i) arterial stiffness and atherosclerosis, ultimately resulting in LVH, and (ii) endothelial dysfunction (which further predisposes to atherosclerosis). Generally, the accelerated atherosclerosis process as seen in patients with CKD is not so frequently observed in ADPKD, especially not in early ADPKD. The only evidence of subclinical atherosclerosis in young adult ADPKD patients is the significantly greater carotid intima-media thickness in hypertensive ADPKD patients compared to normotensive ADPKD patients and in normotensive ADPKD patients in comparison with healthy controls [28, 31, 68]. Therefore, in this review, in addition to hypertension and endothelial dysfunction, we focus on the remaining important cardiovascular complications in ADPKD, in particular arterial stiffness and LVH.

Arterial stiffness

Because of the decreased NO availability, adult patients with ADPKD not only suffer from endothelial dysfunction but also from increased arterial stiffness, both of which are important predictors for cardiovascular events and mortality [12]. The gold standard to measure arterial stiffness is the determination of the carotid-femoral pulse wave velocity (PWV) [69]. In young adults, despite a normal blood pressure, the PWV is increased when ADPKD patients are compared with healthy controls (Table 2) [32, 54,]. In addition, the same trend is seen in children with ADPKD, where the PWV was 14% higher compared with healthy controls (Table 1) [12].

Left ventricular hypertrophy

It has been reported that there is a greater prevalence of LVH in hypertensive ADPKD patients than in the general population [56]. The HALT-PKD study was set up to look at the effect of angiotensin blockade on the progression of total kidney volume and LVH. A recent study investigated this effect on LVH and found, with prior use of ACEi, a low prevalence of LVH in hypertensive ADPKD patients (< 50 years) [70]. An aggressive blood pressure control approach, as suggested by the HALT study, seems beneficial for the young adult patients, since it more effectively reverses LVH in comparison with standard blood pressure control [57, 61]. The HALT study thus suggested a reduced prevalence of LVH in ADPKD, possibly as a result of earlier blood pressure control. Recently, a greater prevalence of LVH in ADPKD patients with preserved kidney function has been reported in comparison with healthy controls (13 vs 2%) []. When hypertensive ADPKD patients are compared with patients with essential hypertension, male ADPKD patients showed a high LVMI but, in contrast, female patients with essential hypertension showed a higher LVMI in comparison with female ADPKD patients []. Moreover, hypertensive young adult ADPKD patients have a significantly greater LVMI compared to normotensive young adult ADPKD patients, patients with essential hypertension, and healthy controls (Table 2) [28]. In addition, both hypertensive ADPKD and borderline hypertensive ADPKD children had a significantly higher LVMI than normotensive ADPKD children, with no significant difference between the hypertensive and borderline hypertensive groups (Table 1) [49].

Link between endothelial dysfunction, hypertension, cardiovascular disease, and oxidative stress

The endothelium, an active metabolic organ, plays a crucial role in the maintenance of vascular homeostasis. This maintenance is done by the release of vasoactive factors which regulate and balance the vasoconstriction and vasodilatation to provide adequate perfusion to target organs. One of these vasoactive factors is NO, which is synthesized from the amino acid L-arginine by one of the NO synthases (neuronal, inducible, or endothelial NOS) with NADPH and oxygen serving as co-substrates. Not only NO but also ROS species play an important role in the vascular system by controlling the endothelial function and vascular tone under normal physiological conditions. Endothelial NOS (eNOS) is responsible for the NO production in the cardiovascular system and in endothelial cells [71]. Under pathological conditions, eNOS can produce ROS by itself, which is called ‘eNOS uncoupling’ [45]. In addition, excessive generation of ROS can also cause eNOS uncoupling, mainly due to NADPH oxidase-mediated superoxide generation.

Both the decline in NO bioavailability and OS itself represent major risk factors for the development of endothelial dysfunction [72, 73]. Moreover, OS and endothelial dysfunction were proposed to have a pivotal role in the pathogenesis of cardiovascular disease, like atherosclerosis, hypertension,

and heart failure [33, 71, 74, 75]. Furthermore, it has become evident that changes in the bioavailability of NO are crucial in determining whether atherosclerosis will develop or not [71]. Eventually, a dysfunctional endothelium leads to cardiovascular disease due to the fact that an imbalance in NO production and consumption creates ideal conditions for the activation of platelets, leukocytes, and cytokines, leading to reduced antioxidant, anti-inflammatory, and antithrombotic properties. This results in structural damage of the arterial wall with smooth muscle cell proliferation and atherosclerotic plaque formation [33, 71, 76].

Relevance of oxidative stress in early autosomal dominant polycystic kidney disease

Since cardiovascular disease is the major cause of death in patients with ADPKD and since OS is a key player in the progression and development of cardiovascular events, one may speculate that OS may play a role in ADPKD pathophysiology. As also discussed in the accompanying review by Daenen et al. in this issue, there are many regulators of OS involved in the early stages of CKD [45]. When those are compared to the key regulators of OS in the early stages of ADPKD, there are a number of similarities, as well as particular pathways highlighted in CKD but not yet explored in the context of ADPKD.

Established biomarkers of OS in ADPKD

Similar to CKD, patients with ADPKD, also in the early stages with preserved GFR, present significantly increased asymmetric dimethylarginine (ADMA) concentrations, 8-epi-prostaglandin $F_{2\alpha}$ and MDA levels as well as oxidized-LDL levels in their plasma, in comparison to controls [7, 16, 77, 78]. The plasma superoxide dismutase (SOD) concentrations seem to also be decreased in ADPKD patients [77]. Table 3 summarizes the different OS end-products used in the evaluation of OS in early ADPKD, as well as the evidence for a decrease in antioxidant defense mechanisms. Additional disturbances have been described in the CKD population, like decreased glutathione levels, or increased NADPH oxidase activity [45]. Whether this also accounts for ADPKD is not elucidated.

Theoretical mechanisms of OS in ADPDK

eNOS uncoupling and endothelial dysfunction

As mentioned supra, a possible deficiency in NO synthesis and onset of endothelial dysfunction can be identified by a change in plasma and urinary ADMA concentrations. Indeed, several studies on early ADPKD patients showed increased plasma and urinary ADMA concentrations, together with a reduction in plasma NO levels (Table 3) [7, 16, 78]. The elevated plasma and urinary ADMA levels in early ADPKD may contribute to defective vascular relaxation by inhibiting eNOS [6]. Raptis et al. suggested that the elevation of ADMA is positively associated with both 15-F_{2t}-isoprostane and oxidized-LDL levels [78]. Altogether, it can be suggested that both endothelial dysfunction and OS may be involved in the development and progression of kidney injury in patients with ADPKD [78]. Several studies, conducted on ADPKD rat models (Han:SRPD:PKD strain), support this hypothesis. Particularly, a defect in eNOS function and impaired endothelium-dependent relaxation were observed in the mesenteric resistance arteries of rats [27] and later in patients [14, 15] with ADPKD. Later, the same group reported on a reduced expression of NO synthase in macula densa cells of Han:SRPD:PKD rats, as well as in cystic epithelium [79]. Interestingly, the 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors (statins) are known to restore the endothelial function by increasing the NO bioavailability [80]. In cultured human endothelial cells, it has been demonstrated that statins increase eNOS activity via post-translational activation of the PI3K/Akt pathway [81, 82].

eNOS uncoupling and hyperuricemia

Not only is the elevation of ADMA levels associated with endothelial dysfunction, but also hyperuricemia. The latter is common in ADPKD, even in patients with preserved kidney function, and represents a risk factor for cardiovascular events (Table 3). It has been shown that endothelial dysfunction in early ADPKD is related to an increase in both serum uric acid levels and plasma ADMA levels [84]. In addition, elevated serum uric acid levels are associated with early onset of hypertension in ADPKD and with an increased risk of early development of ESRD. Also, uric acid may be a novel marker for reduced renal blood flow, since higher serum uric acid is correlated with a larger total kidney volume and renal uric acid excretion is dependent on the GFR, tubular reabsorption, and secretion. Renal blood flow appears to rapidly fall in early ADPKD, even prior to a decline in the GFR, which can affect the excretion of uric acid [84].

Mitochondrial dysfunction in ADPKD

In addition to the eNOS mechanism, mitochondrial dysfunction has been recently investigated in ADPKD rodent models and human cyst-derived cells as a source of OS [85]. Kidney cyst-lining cells from a mouse model of rapidly progressing ADPKD and from a rat model of slowly progressing ADPKD showed tubular cell morphological abnormalities such as swollen mitochondria with indistinct and damaged cristae.

Table 3 Summary of the studies on the role of oxidative stress in early stage ADPKD in humans

Reference	No. of patients			Biomarker	Controls	ADPKD	
	Controls	ADPKD					
Wang et al., 2008 [7]	Age-matched ($n = 30$)	($n = 27$)		Plasma ADMA	391.0 ± 67.0 nmol/L	604.0 ± 131.0 nmol/L	
				Urinary ADMA excretion	15.2 ± 3.0 nmol/μmol creatinine	22.0 ± 4.0 nmol/μmol creatinine	
				Urinary ADMA clearance	36.0 ± 4.0 mL/min	27.0 ± 3.0 mL/min	
				Plasma HODE	230.0 ± 38.0 nmol/L	316.0 ± 64.0 nmol/L	
				Urinary HODE excretion	316.0 ± 40.0 nmol/μmol creatinine	467.0 ± 67.0 nmol/μmol creatinine	
				Plasma NO	32.0 ± 6.0 μmol/L	21.0 ± 5.0 μmol/L	
				Urinary NO excretion	138.0 ± 27.0 μmol/μmol creatinine	59.0 ± 7.0 μmol/μmol creatinine	
Menon et al., 2011 [77]	Age-matched ($n = 51$)	No hypertension ($n = 42$)	With hypertension ($n = 50$)	Plasma 8-epi-$PGF_{2\alpha}$	No given value	No given value but significantly higher compared to the controls	
				Plasma SOD	No given value	No given value but significantly lower compared to the controls	
Helal et al., 2013 [83]	Not included	Early onset of hypertension (≤ 30 years) ($n = 206$)	No or late onset hypertension (> 30 years) ($n = 451$)	Serum uric acid	6.72 ± 0.13 mg/dL	5.77 ± 0.09 mg/dL	
Kocyigit et al., 2013 [84]	Not included	Normal serum uric acid ($n = 22$)	Elevated serum uric acid ($n = 69$)	Plasma ADMA	Not included	1.19 ± 0.2 μmol/L	1.47 ± 0.3 μmol/L
Klawitter et al., 2014 [16]	Age-matched ($n = 18$)	($n = 61$)		Plasma ADMA	0.52 ± 0.19 μmol/L	0.89 ± 0.19 μmol/L	
				Plasma 8-epi-$PGF_{2\alpha}$	No given value but significantly lower	90.8 ± 55.6 pg/mL	
Raptis et al., 2013 [78]	Age- and sex-matched ($n = 26$)	($n = 26$)		Plasma ADMA	0.51 ± 0.2 μmol/L	1.26 ± 0.7 μmol/L	
				Plasma 15-F_{2t}-IsoP	383.1 ± 86.0 pg/mL	788.8 ± 185.0 pg/mL	
				Plasma oxidized-LDL	6.4 ± 2.6 EU/mL	11.4 ± 6.6 EU/mL	

ADPKD autosomal dominant polycystic kidney disease, *NO* nitric oxide, *ADMA* asymmetric dimethylarginine, *13-HODE* 13-hydroxyoctadecadienoic acid, *8-epi-$PGF_{2\alpha}$* 8-epi-prostaglandin $F_{2\alpha}$, *15-F_{2t}-IsoP* 15-F_{2t}-isoprostane, *oxidized-LDL* oxidized-low density lipoproteins

Moreover, expression of peroxisome proliferator-activated receptor-ɣ coactivator-1α (PGC-1α), a regulator of mitochondrial biogenesis, was decreased. Reduced levels of this regulator correlate with the onset of OS [86]. The OS biomarker, 8-hydroxy-2′-deoxyguanosine, indeed showed a significant increase in the disease models [85]. Furthermore, human ADPKD immortalized cyst-derived cells established from a single cyst obtained from distal cortical tubules of an ADPKD patient with a homozygous *PKD1* mutation and immortalized cyst-derived cells established from a single cyst obtained from proximal cortical tubules collected from an ADPKD patient with a heterozygous *PKD1* mutation were examined. Consistent with the findings in rodents, these cells showed morphological and functional abnormalities, including increased mitochondrial superoxide and a reduction in PGC-1α levels [85]. Interestingly, resveratrol, a natural polyphenolic compound mainly found in the skin of grapes and well known for its antioxidant properties, seems to activate those PGC-1α levels. By doing this, it prevents diseases commonly associated with mitochondrial dysfunction [87]. Additionally, resveratrol activates the AMP-activated protein kinase (AMPK) signaling pathway, which again is related to the activation of PGC-1α levels and the beneficial effects of resveratrol on mitochondrial function [88, 89]. Furthermore, in a recent study, treatment with resveratrol showed promising results for the delay in PKD progression in Han:SRPD:PKD rats by inhibiting inflammation [90]. These preliminary observations will prompt further research in ADPKD patients [85].

Completed and ongoing clinical trials in ADPKD, with a focus on oxidative stress pathways

Thanks to the current knowledge on cellular mechanisms and different dysregulated signaling pathways in ADPKD, several potential targets and candidate drugs have been proposed for the management of the disease [91].

Completed clinical trials with effect on OS

Pravastatin in young ADPKD patients—NCT00456365

A 3-year randomized double-blind placebo-controlled phase III clinical trial of pravastatin treatment in 110 children and young adults (age 8–22 years, GFR > 80 mL/min/1.73 m^2) was conducted. The participants were randomly divided in two groups: one group received a placebo and the other group received 20 mg daily (8–12 years) or 40 mg daily (13–22 years). All patients were also treated with the ACEi lisinopril, with an initial dose of 2.5 mg/day in normotensive patients (blood pressure < 95th percentile for height, age, and sex). The primary outcome variable was if a participant had a ≥ 20% increase in total kidney volume corrected for height (HtTKV), LVMI, or urinary albumin excretion over the 3-year interval [92]. A significant difference was noted for the primary endpoint; 69% of the statin group demonstrated a ≥ 20% increase in HtTKV, LVMI, or urinary albumin excretion compared to 88% in the placebo group. This finding was primarily related to the increase in HtTKV (46% of the statin group vs 68% of the placebo group). There were no significant differences in the percentage of participants demonstrating ≥ 20% increase in the LVMI (25 vs 38%) or urinary albumin excretion (47 vs 39%). Furthermore, a significant decrease in the pravastatin group was found in the percentage change of HtTKV adjusted for age, sex, and hypertension status (23 ± 3 vs 31 ± 3%) [93].

Additionally, mass spectrometry-based analysis of biomarkers of endothelial dysfunction, inflammation, and OS was performed. Significant changes in the plasma concentrations of proinflammatory and OS markers were shown between the two groups. The pravastatin group exhibited a significantly lower biomarker increase compared to the placebo group. The inflammatory and OS biomarkers used were 9-hydroxyoctadecadienoic acid (9-HODE), 13-HODE, and 15-hydroxyeicosatetraenoic acid (15-HETE). Furthermore, the urinary 8-HETE, 9-HETE, and 11-HETE were positively associated with the change in HtTKV in the pravastatin group [94].

Recently, because no large trials were available to test the effect of statins in adults, a post hoc analysis on the adults in the HALT-PKD trials, with 438 participants in group A (age 15–49 years, GFR > 60 mL/min/1.73 m^2) and 352 participants in group B (age 18–64 years, GFR 25–60 mL/min/1.73 m^2), was performed. Interestingly, no differences were found in any outcome between the two groups, which implies no potential benefit for the statin therapy in those populations [95].

Ongoing clinical trials on ADPKD patients with a possible effect on OS

Pravastatin in adults—NCT03273413 (phase 4)

As mentioned supra, no large trials were available to test the effect of statins in adults with ADPKD. In the meantime, beginning on August 31, 2017, there is an ongoing clinical trial called ‘Statin therapy in patients with early stage ADPKD’ to determine the efficacy and benefits of pravastatin on kidney volume, renal blood flow, and kidney function. Patients between 25 and 50 years old, diagnosed with ADPKD, with an estimated GFR above 60 mL/min/1.73 m^2, an HtTKV of more than 500 mL/m, and a blood pressure below 140/80 mmHg can participate in this trial. Participants will receive either 40 mg tablets of pravastatin or placebo every day for 6 weeks. When this dose is well tolerated, they have to take it every day for 2 years.

Curcumin in children and young adults—NCT02494141 (phase 4)

Curcumin, a polyphenol diferuloylmethane, is a yellow spice with antioxidant, anti-inflammatory, and antiproliferative properties. Curcumin has beneficial effects on the mammalian target of rapamycin (mTOR) signaling pathway [96] and on the signal transducer and activator of transcription 3 (STAT3) [97], which are both relevant to ADPKD [98]. Indeed, several studies have demonstrated that curcumin significantly inhibits cyst formation in cell cyst models as well as in a *Pkd1*-deletion mouse model [98, 99]. Furthermore, recent studies have shown that curcumin ameliorates kidney function and OS in rats with adenine-induced CKD and in a rat model of type 2 diabetic nephropathy, mainly via upregulation of nuclear factor erythroid 2-related factor 2 [100, 101].

The currently ongoing clinical trial called 'Curcumin therapy to treat vascular dysfunction in children and young adults with ADPKD' is recruiting 6- to 25-year-old ADPKD patients with an estimated GFR above 80 mL/min/1.73 m^2. Participants will receive either 25 mg/kg/day curcumin for 1 year or an equivalent placebo. This research will on the one hand determine the effectiveness of curcumin on the health and function of arteries in children and young adults with ADPKD and, on the other hand, will explore whether curcumin can slow kidney growth.

Metformin in adults—NCT02656017 (phase 2) and NCT02903511 (phase 2)

It has been shown that metformin attenuates diabetic nephropathy in rats through an increased expression of glutathione S-transferase-α mRNA and NADPH quinone oxidoreductase 1 mRNA and through the decrease of ROS levels and the increase of antioxidant levels [102, 103]. Moreover, metformin is the best known clinical activator of the AMPK signaling pathway. This pathway inhibits the mTOR pathway, thereby inhibiting cyst growth and expansion in both in vitro [104] and ex vivo ADPKD models [105]. In addition, administration of metformin significantly slows down cystogenesis in ADPKD mouse models [105] and in PC2-deficient zebrafish [106]. Despite the fact that no papers have been published about the effect of metformin on OS in ADPKD patients, the effects in diabetic nephropathy are promising. Therefore, different studies about metformin administration in ADPKD patients are ongoing.

According to a study of 111,781 veterans with diabetes and CKD (age 64.1 ± 10.3 years), the initiation of metformin significantly reduced the risk of mortality, even among individuals with moderately to severely reduced estimated GFR (30–44 mL/min/1.73 m^2). This finding suggests that metformin initiation may be beneficial among persons with even more severe CKD [107]. In line with this, 'Metformin as a novel therapy for ADPKD (NCT02656017)' is the title of the currently ongoing clinical trial to test if metformin is safe in adult ADPKD patients. Meanwhile, the effect on the progression of the disease, especially in the early stages, as well as kidney size and function will be investigated. Patients between 18 and 60 years old, with an estimated GFR above 50 mL/min/1.73 m^2, can participate in this trial. One group will start with a dose of 500 mg per day, which will be increased after 2, 4, and 6 weeks. Eventually, the dose given from the sixth week on will be constant until the end of the trial (26 months). The placebo group follows the same scheme.

In the meantime, another ongoing clinical trial (NCT02903511), which is called 'Feasibility study of metformin therapy in autosomal dominant polycystic kidney disease', is recruiting 30- to 60-year-old ADPKD patients to test whether metformin is safe and well tolerated by ADPKD individuals who are not diabetic and who have a slightly decreased kidney function. In addition, this study will also evaluate the effects of metformin on kidney growth and kidney function. Therefore, an eGFR of 50–80 mL/min/1.73 m^2 was one of the inclusion criteria. Patients in the experimental arm will start with one tablet of 500 mg metformin twice a day, while the placebo group will start with one tablet of 500 mg placebo twice a day. This dose will be increased by 500 mg every 2 weeks up to 1000 mg by mouth twice a day, as tolerated, for 12 months.

Pioglitazone in adults—NCT02697617 (phase 2)

Peroxisome proliferator-activated receptor-ɣ (PPAR-ɣ), a member of the ligand-dependent nuclear receptor family, is expressed in many tissues, including the kidney and liver. Pioglitazone is a PPAR-ɣ agonist, which is known to suppress the AKT/mTOR/S6 signaling pathway [108]. Supplementation of pioglitazone seems to ameliorate cardiac effects and limit cystogenesis in the embryos of $Pkd1^{-/-}$ mice models. In addition, treatment with pioglitazone increases the production of NO in adult $Pkd1^{\pm}$ mouse models, improving the endothelial function [109], and benefits renal failure through increasing antioxidants and reducing NADPH oxidases in a 5/6 nephrectomized rat model, which mimics CKD [110].

'Use of Low Dose Pioglitazone to Treat Autosomal Dominant Polycystic Kidney Disease (PIOPKD)' is a 2-year trial to test whether pioglitazone slows down cyst development in humans. ADPKD adults between 18 and 55 years, of whom the estimated GFR is greater than 50 mL/min/1.73 m^2, can participate in this trial. Patients will be randomized to placebo or 15 mg pioglitazone for 1 year, and then be crossed over to the other arm.

Conclusion

The PC1/PC2 complex is necessary for normal vascular development and is required for endothelial cilia to sense fluid shear stress through complex biochemical cascades involving many factors, including NO. Therefore, deficiency of either of these proteins causes a reduction in NO bioavailability, which, in turn, causes endothelial dysfunction. In addition, the presence of OS in early ADPKD, with reduced NO levels, may per se aggravate endothelial dysfunction. Eventually, endothelial dysfunction leads to cardiovascular events, including hypertension. Both OS and the cardiovascular events contribute to ADPKD progression. Several studies have already suggested that there is an increase in OS biomarker levels from the beginning of ADPKD, with further increases at advanced stages. To date, several clinical trials in ADPKD have been reported to either slow down the disease progression and/or to reduce OS. A few drugs have already been tested on humans and have shown promising results. Additional clinical trials are currently ongoing.

Key summary points

- The PC1/PC2 complex is necessary for normal vascular development.
- Hypertension is associated with the progression of renal disease and with an increased risk for development of cardiovascular disease and mortality in ADPKD patients.
- OS, endothelial dysfunction, and hypertension are already present in the early stages of ADPKD.
- The ongoing clinical trials of curcumin, metformin, and pioglitazone can have both a beneficial effect on disease progression and cyst development and a possible reduction in OS.

Questions (answers are provided following the reference list)

1. Did researchers find a significant difference in the occurrence of hypertension between male and female ADPKD patients?

   a) No, no differences were found
   b) Yes, there are differences between them in childhood
   c) Yes, between the ages of 20 and 40 years
   d) Yes, after they reach ESRD

2. With an average age of diagnosis of 30 years, hypertension affects

   a) 5–44% of the young ADPKD adults
   b) 90–95% of the young ADPKD adults
   c) 0–20% of the young ADPKD adults
   d) 60–75% of the young ADPKD adults

3. Which of the following statements about early ADPKD is correct?

   a) Plasma and urinary levels of ADMA are increased
   b) Plasma levels of ADMA are increased, but urinary levels are decreased
   c) Plasma levels of ADMA are decreased, but urinary levels are increased
   d) Plasma and urinary levels of ADMA are decreased

4. Which of the following markers of OS that are disturbed in CKD has not been elucidated yet in ADPKD?

   a) Increased ADMA levels
   b) Decreased SOD levels
   c) Increased MDA levels
   d) Increased NADPH oxidase activity

5. Which of the following is associated with an increased serum uric acid in ADPKD patients?

   a) Less risk of hypertension but an accelerated progression to ESRD
   b) More risk of hypertension and an accelerated progression to ESRD
   c) More risk of hypertension but a delayed progression to ESRD
   d) Less risk of hypertension and a delayed progression to ESRD

Compliance with ethical standards

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Answers:

1. c; 2. d; 3. a; 4. d; 5. b