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Atherogenic Indices in Disease Progression of Autosomal Dominant Polycystic Kidney Disease (ADPKD): A Key Role or Stand By

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Abstract

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the formation of numerous fluid-filled cysts that lead to progressive loss of functional nephrons. Lipids are fundamental building blocks of all cells and play important roles in the pathogenesis of different diseases. Lipid and atherogenic indices as a marker of progression risk has not been previously described in early ADPKD patients with relatively intact kidney function.

Objective: The aim of the study was to determine whether atherogenic indices are indicated for ADPKD progression.

Patients and Methods: A cross-sectional study included 85 ADPKD participants. The study was conducted at kidney diseases consultant of Imam Al-Hassan Al-Mujtaba teaching hospital in Kerbala, Iraq.

Results: The mean of triglycerides was 151.18 mg/dL which indicated a potentially elevated average in such cases. The mean levels of HDL, LDL, VLDL, Non-HDL-C, atherogenic coefficient (AC), and atherogenic index of plasma (AIP) were 38.69 mg/dL, 73.18 mg/dL, 30.32 mg/dL, 104.48 mg/dL, 2.80, and 0.57, respectively. The higher levels of AC and AIP indicate a greater risk of atherosclerosis. The mean level of Castelli I was 3.80 and the mean level of Castelli II was 1.97 with an 2SD of 1.01.

Conclusion: Abnormalities in basic lipid profile tend to be more frequent in ADPKD and it might constitute a major atherogenic risk factor for the development of other diseases.

مؤشرات الدهون الأثيرية في تطور مرض الكلى الكيسي الوراثي السائد (ADPKD) دور مهم أم مجرد وقوف

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الخلاصة

المقدمة: يتميز مرض الكلى الكيسي الوراثي السائد بتكوين العديد من الخراجات المملوءة بالسوائل التي تؤدي إلى فقدان تدريجي للنيفرون الوظيفي. الدهون هي اللبنات الأساسية لجميع الخلايا وتلعب أدوارا مهمة في التسبب في الأمراض المختلفة. لم يتم وصف مؤشرات الدهون والتصلب العصبي كعلامة على خطر التقدم من قبل في مرضى ADPKDالأوائل الذين يعانون من وظائف الكلى السليمة نسبيا.

الهدف: كان الهدف من الدراسة هو تحديد ما إذا كانت مؤشرات تصلب الشرايين موصوفة لتطور مرض الكلى الكيسي الوراثي السائد

المرضى وطرق العمل: شملت دراسة مقطعية 85 مشاركا تم تشخيص جميعهم بمرض ADPKD

وأجريت الدراسة في استشارية أمراض الكلى في مستشفى الإمام الحسن المجتبى التعليمي في مدينة كربلاء.

النتائج: متوسط مستوى الدهون الثلاثية كان 151.18 ملجم/ديسيلتر. يشير هذا إلى ارتفاع متوسط مستوى TG في مثل هذه الحالات. وكان متوسط مستوى البروتين الدهني عالي الكثافة 38.69 ملغم/ديسيلتر. في حين كان متوسط مستوى LDL 73.18 ملغم/ديسيلتر وكان متوسط مستوى 30.32 VLDLملغم/ديسيلتر. وكان متوسط مستوى الكوليسترول غير HDL 104.48 ملجم/ديسيلتر. كان متوسط معامل تصلب الشرايين (AC) 2.80 ، وكان متوسط مؤشر تصلب الشرايين لمستوى AIP في البلازما 0.57، ويشير ارتفاع AC و AIPإلى زيادة خطر الإصابة بتصلب الشرايين. كان متوسط مستوى كاستيلي الأول 3.80 وكان متوسط كاستيلي الثاني 1.97 مع 1.01 2SD.

الاستنتاج: تميل التشوهات في ملف الدهون الأساسي إلى أن تكون أكثر تواترا في ADPKD وقد تشكل عامل خطر رئيسي تصلب الشرايين لتطور أمراض أخرى.

1. Introduction

Chronic renal disease is characterized by elevated serum creatinine for more than three months or a decrease in glomerular filtration rate to less than 60 ml/minute. It is often irreversible (Kadhim et al., 2022). The development of many fluid-filled cysts, which eventually result in the loss of functioning nephrons, is a hallmark of autosomal dominant polycystic kidney disease (ADPKD). As of right now, there is a lack of early disease prognostic and diagnostic markers (Baliga et al., 2021). Two genes, polycystic kidney disease 1 (PKD1) and polycystic kidney disease 2 (PKD2), have been associated to ADPKD; 78% of patients had the former mutation, while 15% had the latter (Cornec-Le Gall et al., 2019). It appears that a PKD1/2 mutation is absent in about 7% of ADPKD patients (Audrézet et al., 2012; Reiterová and Tesař, 2022). The fact that polycystins are expressed in a variety of organs makes ADPKD a systemic illness. Affected organs include the liver, pancreas, and spleen; additional organs include the brain vessels and circulatory system. These manifestations of ADPKD's systemic and multiorgan nature include the development of cysts in these extrarenal organs (Patel et al., 2009). A characteristic feature of ADPKD is the unrelenting development of many fluid-filled kidney cysts, which eventually replace the healthy parenchyma and result in significant bilateral kidney enlargement and renal failure over many years (Neumann et al., 2013). ADPKD symptoms often appear in the fourth decade of life, however cystogenesis initiates focally in the tubule and typically begins in utero (Cornec-Le Gall et al., 2019). ADPKD is a degenerative disease that progresses over time, causing chronic kidney disease (CKD) and end-stage renal disease (ESRD). In up to 70% of ADPKD patients, ESRD requiring renal replacement therapy (RRT) appears by the age of 70 (Spithoven et al., 2014). Approximately 10% of patients involved in dialysis and transplant programs have ADPKD (Alsabbagh et al., 2024). Chronic renal failure (CRF) is a common and irreversible disease which is develops progressively. Based on the glomerular filtration rate GFR it is classified into five stages (Santos and Preta, 2018).

Lipids are essential components of all cells and are involved in the etiology of several illnesses, such as cancer, autoimmune disorders, neurodegeneration, and inflammation (Abdullah et al., 2020). Lipids, which are the body's most potent source of energy, are represented by total cholesterol, phospholipids, fatty acids, and triglycerides (TG). All of these lipids are involved in the creation of cell membranes, and some of them are the source of steroid hormones (Feingold, 2024). In comparison to healthy controls, ADPKD patients of all ages exhibited moderately elevated plasma triglycerides, low-density lipoprotein (LDL), and LDL, and around 50% lower levels of high-density lipoprotein (HDL), according to Southern Indian research (Veeramuthumari and Isabel, 2013). The 6-year cohort research conducted by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) discovered that baseline blood HDL-cholesterol levels were protective against faster reductions in GFR and greater kidney development (Torres et al., 2011). In another investigation, low density lipoprotein (LDL), inflammation, and insulin resistance were reported to be elevated in young ADPKD patients with normal renal function (Lai et al., 2017). In contrast to CKD, hypertriglyceridemia is not a characteristic of ADPKD (Barter, 2014). In conclusion, we have demonstrated that in ADPKD patients with normal kidney function, metabolites and lipids are present and strongly correlate with eGFR and ht-TKV. These lipids and metabolites may be helpful in identifying reprogramming and metabolic abnormalities, which seem to happen early in the course of illness. Measuring ht-TKV, the sole test that is now known to predict the pace of disease development, may not be as expensive as finding other predictors of early kidney impairment. These metabolites could make it possible to predict and categorize ADPKD patients into groups that proceed to ESRD more quickly or slowly (Menezes et al., 2016). Significant correlations between baseline ht-TKV readings in ADPKD patients and two big chain length

triglycerides were discovered. No prior research has found any correlation of this sort between certain triglycerides and a progression risk measure in early ADPKD patients with mostly intact kidney function. In animal models, lipid dysregulation—which includes decreased fatty acid oxidation in the kidney—is linked to ADPKD (Allen et al., 2006). and PKD-1 null kidneys' stimulation of apolipoprotein-related genes (Mallett et al., 2015).

2. Patients, Materials and Methodology

In cross-sectional research, there were 85 patients of ADPKD were categorized according to their GFR in order to identify any variations in the mean levels of Kidney Injury Molecule-1 (KIM-1), Neutrophil gelatinase-associated lipocalin (NGAL), and Chitinase-3-like protein 1 (CHI3L1).

The study protocol was approved by the ethical committee of Kerbala University College of Medicine. Furthermore, the Imam Al-Hassan Al Mujtaba Teaching Hospital's administrative and scientific associations reviewed and approved the study in writing before it could be carried out in Kerbala. Five measurement instruments were included in the study questionnaire: urea and creatinine level analysis, serum measurements of TG, HDL, LDL, and VLDL, monitoring for blood pressure measurement and ultrasound, and a series of questions on clinical and demographic characteristics. Data on clinical and demographic traits was also gathered. Ultrasonography is used to identify kidney cysts of greater size as well as the existence of cysts in other organs including the pancreas and liver, as well as to identify organomegaly.

2.1.Measurement of the Atherogenic Indices

2.1.1. Atherogenic Coefficient (AC)

It is the proportion of non-high-density lipoproteins cholesterol (non-HDL-C) to high-density lipoproteins cholesterol (HDL-C) (Olamoyegun et al., 2016). It is a diagnostic alternative method that has been applied to predict the possibility of suffering cardiovascular events.

$$AC = \text{non-HDL-C} / \text{HDL-C}$$

2.1.2. Atherogenic Index of Plasma (AIP)

An unusual lipid ratio that shows the logarithm of the TG to HDL-C molar ratio (Gómez-Álvarez et al., 2020). AIP is a significant predictive measure with a positive connection to CVD, according to accumulated evidences.

$$AIP = \log (\text{TG}/ \text{HDL-C})$$

2.1.3. Castelli's Risk Indexes (I & II)

Also called cardiac risk indexes, two lipid ratios that have been shown to have significant positive correlations with the risk of CVD: CRI-I is the ratio of TC to HDL-C, and CRI-II is the ratio of LDL-C to HDL-C (Igharo et al., 2020). Several studies evaluated and verified their favorable association with CVD(Tecer et al., 2019).

$$\text{CRI-I} = \text{TC}/ \text{HDL-C ratio}$$

$$\text{CRI-II} = \text{LDL-C} / \text{HDL-C ratio}$$

2.1.4. Cholesterol Index (C-Index)

an easy index that, compared to other indices, more accurately predicts the possibility of getting CAD (Ulusoy, 2013).

$$\text{C- index} = (\text{LDL-C}) – (\text{HDL-C})$$

3. Results

3.1.Demographics of patients group with Autosomal Dominant Polycystic Kidney Disease (ADPKD).

The population in the study group was middle-aged, with a little male predominance. According to body mass index (BMI) readings, the majority of the group may be obese or overweight. According to blood pressure results, some participants could be hypertensive. The research group's demographic characteristics were displayed in Table 1. There were 36 girls (42.4%) and 49 males (57.6%) in this research. The results indicated that the age range was 8 to 84 years old, with a median age of 60. It was 55.4 years old on mean age. The range of the BMI was 16.5 to 47.7, with a median of 29.06 and a mean of 29.7.

80 mmHg was the median diastolic blood pressure while 130 mmHg was the median systolic blood pressure.

Table 1: Demographic Characteristic of The Study Group.

Variable	Median	Minimum	Maximum	Mean ±SD
Age	60	8	84	55.4±19.2
BMI	29.06	16.5	47.7	29.7±6.68
Sys BP	130	80	180	128.7±19.7
Dys BP	80	50	110	81.2±13.5
Sex, No. (%)	Female	36 (42.4%)		
	Male	49 (57.6%)		

Table 2 presented the research group's medical history. About 65.9% of the subjects had a history of autosomal polycyst kidney in their families. Three quarters of the patients (36.5%) had at least one chronic illness identified. In regard to kidney function, around 16.5% of patients have had kidney surgery, which may have involved a nephrectomy, the removal of stones and cysts, or only stones. Just 8% had undergone prior dialysis.

10.6% of the participants reported having organomegaly (liver and spleen), while 18.8% reported having additional cysts in the pancreas and liver. Additionally, a significant percentage of the sample (71.8%) utilized anti-hypertensive medicine, which suggests that hypertension may be more common in this group. It's interesting to note that nine individuals (10.6%) were receiving treatment with the medicine Tolvaptan, which is intended to treat kidney cysts. It was demonstrated that Tolvaptan could be a viable course of treatment for some kidney cyst patients at this time.

Table 2: Medical History Among Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Variable	No n. (%)	Yes n. (%)
Family History	29 (34.1%)	56 (65.9%)
Anti-Hypertensive Therapy	24 (28.2%)	61 (71.8%)
Chronic Disease	54 (63.5%)	31 (36.5%)
Kidney Surgery	71 (83.5%)	14 (16.5%)
Previously Dialysis	78 (91.8%)	7 (8.2%)
Organomegaly	76 (89.4%)	9 (10.6%)
Other Cysts	69 (81.2%)	16 (18.8%)
Treated with Tolvaptan	63 (74.1%)	9 (10.6%)

3.2.Study the Lipid Profile among Autosomal Dominant Polycystic Kidney Disease (ADPKD)

The mean of many lipid profile indicators was shown in Table 3 and Fig.1 for a group of individuals suffering from Autosomal Dominant Polycystic Kidney Disease (ADPKD). Triglyceride mean level averaged 151.18 mg/dL. This suggested that under certain circumstances, the mean TG level may be higher. High-density

lipoprotein had a mean level of 38.69 mg/dL, indicating considerable variability. In contrast, the mean VLDL level was 30.32 mg/dL and the mean LDL level was 73.18 mg/dL. The mean amount of non-HDL cholesterol, which was also determined, was 104.48 mg/dL.

Table 3: Mean Differences of Lipid Profile Levels Among Patients' Group of Autosomal Dominant Polycystic Kidney Disease.

Mean ±SD	TG	HDL	LDL	VLDL	Non-HDL-c
	151.18±48.36	38.69±6.86	73.18±31.43	30.32±9.81	104.48±29.40

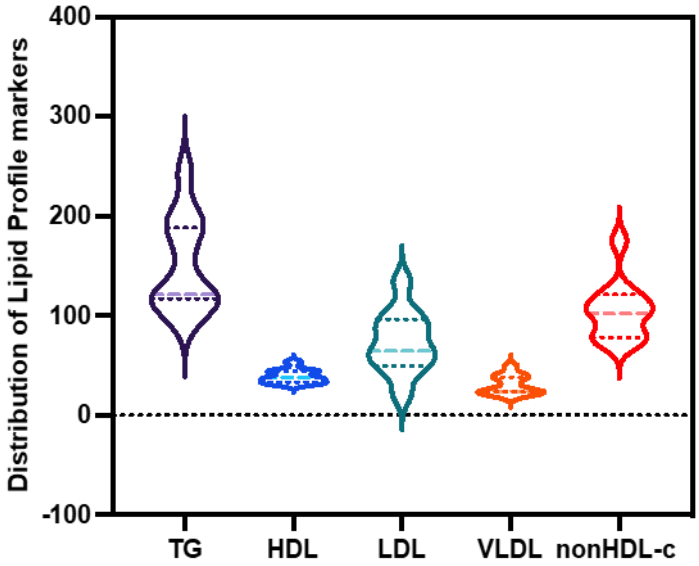

Figure 1: Violin Boxplot to Demonstrate the Density of Lipid Profile Levels Among Patients Group of Autosomal Dominant Polycystic Kidney Disease.

3.3.Study the Atherogenic Indices in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Autosomal Dominant Polycystic Kidney Disease (ADPKD) patients' mean values for a variety of atherogenic indices were compiled in Table 4 and Fig.2. The findings indicated that the plasma AIP level's mean Atherogenic Index was 0.57 and the mean Atherogenic Coefficient (AC) was 2.80. An increased risk of atherosclerosis is indicated by both a higher AC and AIP. Castelli Risk I and II, which are used to assess the 10-year risk of coronary heart disease, were also calculated. The means of Castelli I and II were 3.80 and 1.97, respectively, with a 2SD of 1.01.

Table 4: Mean differences of atherogenic indices Levels among patients' group of autosomal dominant polycystic kidney disease.

Mean ±SD	AC	AIP	Castelli's I	Castelli's II
	2.80±1.03	0.57±0.15	3.80±1.03	1.97±1.01

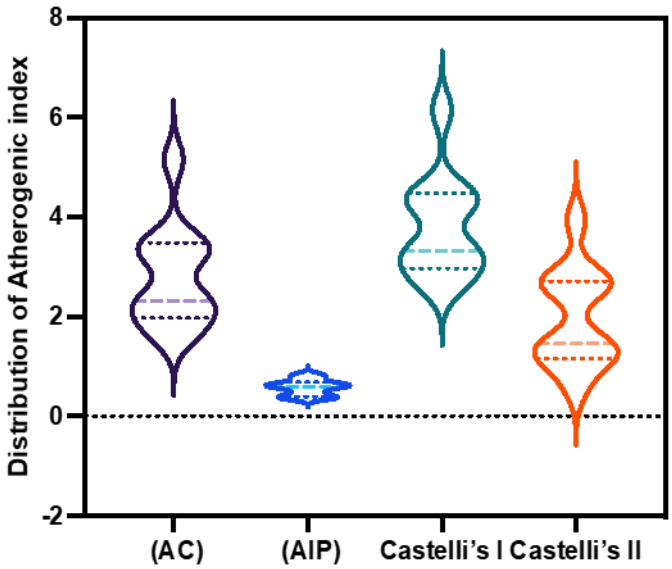

Figure 2: Violin Boxplot to Demonstrated the Density of Atherogenic Indices Among Patients Group of Autosomal Dominant Polycystic Kidney Disease.

4. Discussion

These findings supported earlier research demonstrating that dyslipidemia and ADPKD frequently coexist. In compliance with the KHA-CARI recommendations (Mallett et al., 2015) Especially in the early stages of the disease, controlling aberrant lipid levels may help to reduce the growth of cysts (Ecder, 2016). A significant relationship was found in the CRISP (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease) study between a higher increase in total kidney volume and a lower serum level of high-density lipoprotein (Torres et al., 2011). A previous study also revealed that, because metabolic dysregulation is closely linked to the progressive loss of kidney function, it may quicken the course of ADPKD (Fliszkiewicz et al., 2019).

Cardiovascular problems and ADPKD may progress more quickly in cases of metabolic disturbances. These irregularities have been shown to play a part in the acceleration of cyst formation through certain pathways. It is claimed that hypercholesterolemia and its impact on the advancement of ADPKD are related to KDIGO (Chapman et al., 2015) and KHA-CARI Guidelines (Mallett et al., 2015). Since 30% of APDKD patients exhibited hypercholesterolemia and hypertriglyceridemia compared to the non-ADPKD CKD group, where the frequency varied between 25 and 100% depending on the accompanying nephrotic syndrome, it was confirmed that there was disturbed lipid metabolism (Wanner et al., 2014). Few studies have examined the mean differences in atherogenic indices between kidney disease patient groups; however, none of them have discussed the function that these indices play in autosomal dominant polycystic kidney disease (Dennis et al., 2023).

According to Huang et al., 2020, AIP was also connected to a lipid-related consequence in instances of nephrotic syndrome. AIP is a predictor of subclinical renal impairment, which is defined as an eGFR between 30 and 60 mL/min/1.73 m2, according to a recent study (Huang et al., 2021)**.** Additionally, the ratio of non-high-density lipoprotein cholesterol (non-HDL-C) to high-density lipoprotein cholesterol (HDL-C) is known as the atherogenic coefficient (AC). It is an alternate diagnostic method that has been applied to forecast the likelihood of experiencing cardiovascular events (Olamoyegun et al., 2016)**.** Additionally, two lipid ratios known as Castelli's risk indices (I & II)—the CRI-I is the ratio of TC to HDL-C, and the CRI-II is the ratio of LDL-C to HDL-C—

have been shown to have significant positive correlations with cardiovascular disease (CVD) (Igharo et al., 2020). It was evaluated and found to be positively correlated with CVD earlier (Tecer et al., 2019). Conversely, the cholesterol index, or C-index, has been described as a straightforward indicator that more accurately predicts the possibility of developing CAD than any other indicator (Ulusoy, 2013). In general, it is still unknown how dyslipidemia can potentially accelerate the course of renal diseases. One theory is that dyslipidemia is linked to an increase in tubular epithelial cells' reabsorption of cholesterol and phospholipids.

Tissue damage, foam cell production, and tubulointerstitial inflammation may all be triggered by this reabsorption (Abrass, 2004). Furthermore, elevated lipoprotein levels may promote the production of proinflammatory cytokines, which would lead to glomerulosclerosis (Keane et al., 1993).

It was initially hypothesized that PKD progression and aberrant lipid metabolism were related, using rodent rat models. In a non-orthologous ADPKD model, eating a lot of fat increased the size of the kidneys and the scores for cysts and renal fluid (Jayapalan et al., 2000). Mice lacking Pkd1 and Pkd2 also show signs of aberrant lipid metabolism. Interestingly, apolipoprotein levels were elevated in cystic kidneys due to upregulation of genes governing apolipoprotein synthesis and transport; these modifications were linked to changes in the function of the nuclear hormone receptor, hepatocyte nuclear factor-4 (Allen et al., 2006). On the other hand, it was demonstrated that the polycystic kidneys had a markedly reduced level of apoA1, a critical component of the high-density lipoprotein complex (Yoo et al., 2009). Over a 6-year follow-up period, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort research revealed a clinically significant inverse association between blood HDL-cholesterol levels and the pace of kidney development as well as the drop-in glomerular filtration rate (GFR) (Torres et al., 2011). It is uncertain how having greater HDL levels provides protection. Because it plays a part in reverse cholesterol transfer, HDL has strong anti-atherogenic properties. By its recognized interactions with the spingosine-1-phosphate receptor family and the Class B Type 1 scavenger receptor, it may also have anti-inflammatory effects. Whatever the exact mechanism, HDL is a theoretically modifiable component that slows the growth of the kidney and the deterioration of renal function (Schrier and Levi, 2010). Significant oxidative stress is present in early stage ADPKD before renal function deteriorates and hypertension develops, according to a number of experimental and clinical investigations (Brookes et al., 2013). Increased oxidative stress may be linked to endothelial dysfunction, dysregulated lipid metabolism, and kidney injury. It is possible that the oxidative alteration of low-density lipoprotein (LDL) by a diseased kidney could directly lead to systemic vascular damage (Mao et al., 2015).

5. Conclusion

Physicians treating patients with ADPKD should be aware of the incidence of metabolic abnormalities in this disease. Abnormalities in basic lipid profile tend to be more frequent in ADPKD and it might constitute an essential atherogenic risk factor for the advancement of other diseases.

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