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The Triglyceride-Glucose Index: A Cost-Effective Biomarker for Early Detection of Insulin Resistance in Autosomal Dominant Polycystic Kidney Disease

Trigliserid-Glukoz İndeksi: Otozomal Dominant Polikistik Böbrek Hastalığında İnsülin Direncinin Erken Tespiti İçin Maliyet Etkin Bir Biyobelirteç

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ABSTRACT

Objective: Autosomal dominant polycystic kidney disease (ADPKD) is a common hereditary cause of end-stage renal disease, often associated with metabolic disorders, including insulin resistance and diabetes mellitus (DM). The triglyceride-glucose (TyG) index has emerged as a cost-effective biomarker for predicting insulin resistance and metabolic dysfunction. This study evaluates the role of the TyG index in predicting DM development in ADPKD patients.

Methods: A retrospective analysis was conducted on 156 ADPKD patients followed at the Nephrology Clinic of Dokuz Eylül University since 2000. Patients with pre-existing DM, impaired fasting glucose, or undergoing lipid-lowering therapy were excluded. Demographic and laboratory data, including the annual TyG index, were recorded and compared between patients who developed DM (n=18) and those who did not (n=138). The TyG index was calculated using the formula based on fasting triglyceride levels and fasting glucose levels. Statistical analyses included repeated measures analysis of variance and chi-square tests, with a significance threshold of $p<0.05$.

Results: Among the cohort, 11.5% developed DM during follow-up. The TyG index was significantly higher in the DM group than in non-DM patients ($p<0.05$). Over time, the TyG index in the DM group showed a progressive increase, even before the detection of hyperglycemia ($p<0.05$).

Conclusion: The TyG index is a valuable, cost-effective tool for predicting DM in ADPKD patients. Its ability to detect diabetes risk before hyperglycemia highlights its potential for early intervention strategies. Prospective studies are needed to validate these findings and explore the role of the TyG index in clinical practice.

Keywords: Triglyceride, glucose, autosomal dominant polycystic kidney disease, insulin resistance, diabetes mellitus

ÖZ

Amaç: Otozomal dominant polikistik böbrek hastalığı (ADPKD) son dönem böbrek yetmezliğinin sık görülen kalıtsal bir nedenidir. Genellikle insülin direnci ve diyabetes mellitus (DM) gibi metabolik bozukluklarla ilişkilidir. Trigliserid-glukoz (TyG) indeksi, insülin direncini ve metabolik disfonksiyonu öngörmede maliyet-etkin bir biyobelirteç olarak öne çıkmıştır. Bu çalışma, ADPKD hastalarında DM gelişimini öngörmede TyG indeksinin rolünü değerlendirmektedir.

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Yöntem: 2000 yılından beri Dokuz Eylül Üniversitesi Nefroloji Polikliniği'nde takip edilen 156 ADPKD'li üzerinde retrospektif bir analiz gerçekleştirilmiştir. Daha önce DM tanısı konmuş, bozulmuş açlık glukozu bulunan veya lipid düşürücü tedavi gören hastalar çalışmaya dahil edilmemiştir. Demografik ve laboratuvar verileri, yıllık TyG indeksi dahil olmak üzere kaydedildi ve DM gelişen (n=18) ile gelişmeyen (n=138) hastalar karşılaştırıldı. TyG indeksi, açlık trigliserid seviyelerinin açlık kan glukoz seviyelerine bölünmesiyle hesaplandı. İstatistiksel analizlerde tekrarlayan ölçümler varyans analizi ve ki-kare testleri kullanıldı ve anlamlılık düzeyi p<0,05 olarak belirlendi.

Bulgular: Kohortta, takip sırasında %11,5 oranında DM geliştiği saptandı. DM grubunda TyG indeksinin, DM gelişmeyen hastalara kıyasla anlamlı derecede yüksek olduğu görüldü (p<0,05). DM grubunda TyG indeksinin, hiperglisemi tespit edilmeden önce zamanla progresif bir artış gösterdiği gözlendi (p<0,05).

Sonuç: TyG indeksi, otozomal dominant polikistik böbrek hastalarında DM gelişmesini öngörmede değerli, maliyet-etkin bir araçtır. Diyabet riskini hiperglisemi gelişmeden önce tespit etme yeteneği, erken müdahale stratejileri için potansiyelini vurgulamaktadır. Bu bulguları doğrulamak ve klinik uygulamalarda TyG indeksinin rolünü keşfetmek için prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Trigliserid, glukoz, otozomal dominant polikistik böbrek hastalığı, insulin direnci, diyabetes mellitus

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common hereditary causes of end-stage renal disease (ESRD).[1] Throughout the course of the disease, patients face risks such as hypertension, heart valve disorders, and progression to ESRD.[1] Two genes have been identified as responsible for this genetically inherited condition: *PKD1* and *PKD2*.[2,3] The product of the *PKD1* gene, polycystin-1, is a protein that facilitates cell-to-cell or cell-to-matrix communication.[2] Meanwhile, the *PKD2* gene encodes an integral membrane protein that functions similarly to calcium and sodium channels. These genetic products play crucial roles in maintaining cellular homeostasis, and disruptions in their functions contribute to the pathogenesis of ADPKD.[3] In a study conducted by Vareesangthip et al.,[4] abnormal protein and lipid organization of red blood cell and mononuclear cell membranes in patients with ADPKD were shown to increase membrane fluidity. This increase was found to affect the structural configuration of insulin receptors, impairing insulin function and leading to insulin resistance. Building on this work, Vareesangthip et al.[4] conducted a study in 1997 that confirmed the presence of insulin resistance in ADPKD patients.[5] These findings underscore the role of membrane abnormalities in the development of metabolic dysfunction in ADPKD, suggesting a link between cellular structure and systemic metabolic regulation.[5]

The triglyceride-glucose (TyG) index has recently emerged as a significant parameter. Numerous studies have demonstrated its association with cardiovascular diseases, depression, and chronic and acute kidney diseases.[6-9] Chamroonkiadtikun et al.,[10] in their 2020 study, highlighted the predictive value of elevated TyG ratios for the development of diabetes mellitus (DM). This finding has since been corroborated by several subsequent studies.[11]

Recognizing the risk of insulin resistance in ADPKD patients underscores the need for preventive measures to mitigate diabetes onset. In this context, the TyG index offers potential as an early indicator of risk. Our study retrospectively examined the relationship between TyG index levels and the development of DM in PKD patients under follow-up.

METHODS

This study retrospectively analyzed data from patients with ADPKD who were under follow-up at the nephrology clinic of Dokuz Eylül University since 2000. Patients included in the study were over the age of 18, had been diagnosed with PKD, had no prior diagnosis of DM, had at least five years of available laboratory data, and were not undergoing renal replacement therapy. The Non-Interventional Research Ethics Committee of Dokuz Eylül University Faculty of Medicine approved the study (decision no: 2025/02-12, date: 15.01.2025).

Exclusion criteria included patients with a known diagnosis of DM or impaired fasting glucose (IFG) at the time of ADPKD diagnosis and those using antilipidemic therapy regardless of whether they had a lipid profile disorder. Data from 193 ADPKD patients were reviewed. Of these, 23 patients with concurrent DM at the time of ADPKD diagnosis and 14 patients using antilipidemic therapy were excluded.

A total of 156 patients meeting the inclusion criteria were analyzed. Demographic data such as age, gender and additional comorbidities along with laboratory values, were recorded. Comparisons were made between patients who developed DM and those who did not during follow-up.

The diagnosis of ADPKD was based on the presence of unilateral or bilateral cysts according to age and family history. For individuals aged 15-39, the presence of three or more cysts was required. For those aged 40-59, at least two cysts in each kidney were necessary to confirm the diagnosis.[12]

DM was diagnosed based on fasting blood glucose levels exceeding 126 mg/dL, blood glucose levels above 200 mg/dL two hours after a 75-gram oral glucose tolerance test, or HbA1c levels greater than 6.5%.[13]

The TyG index was calculated by dividing the patient's annual triglyceride levels and their fasting blood glucose levels. The TyG indices of PKD patients who developed DM and those who did not were compared annually during the follow-up period.

Statistical Analysis

Numeric data is presented using means with standard deviations, as well as medians accompanied by ranges based on their distributions. Categorical variables are expressed as frequencies and percentages. Comparisons between categorical variables were conducted using the chi-square test when applicable. The independent samples t-test was utilized to compare data following a normal distribution, whereas the Wilcoxon test was applied for non-normally distributed data. To analyze changes in the annual TyG/glucose ratio and magnesium levels within and across groups, the repeated-measures analysis of variance test was employed. A p value of less than 0.05 was considered indicative of statistical significance, corresponding to a type 1 error rate of 5%. All statistical analyses were carried out using version 21.0 of the statistical package for social sciences (SPSS, Chicago, IL, USA) on a personal computer.

RESULTS

Among the 156 patients included in the study, 18 (11.5%) developed DM during follow-up. The ages of patients who developed DM and those who did not were similar (p=0.39). Of the patients who developed DM, 14 (77.7%) were female, compared to 80 (57%) in the group without DM (p=0.16). Body mass index values and hypertension history were comparable between the two groups (p=0.16, p=0.74). However, a statistically significant difference in the history of IFG was observed in the DM group (p<0.05). There was no difference between the groups in the use of renin-angiotensin receptor inhibitors or vasopressin 2 receptor antagonists (p=0.74). As shown in Table 1, glucose, triglyceride, blood urea nitrogen, creatinine, uric acid, albumin, sodium, potassium, calcium, and phosphorus levels were similar between the groups, except magnesium. Magnesium levels were significantly different in both groups (p=0.008). The cyst volume staging based on the Mayo Clinic classification was also similar between the groups. The demographic and laboratory characteristics are summarized in Table 1.

When comparing the groups with and without DM development over time, the TyG ratio was found to be significantly higher in the group that developed DM and was significantly higher than in the group that did not develop DM (p=0.01, p=0.013) (Table 2).

Regarding the annual TyG index, a statistically significant increase was observed in the DM group compared to the non-DM group (p<0.05, Figure 1).

DISCUSSION

This study evaluates the impact of the TyG index on insulin resistance and diabetes development in patients with ADPKD. An increase in the TyG index over time was associated with DM in patients, even before hyperglycemia was detected (p<0.05).

DM is a disease that develops as a result of insulin resistance and leads to significant morbidity and mortality.[14] One of the important characteristics of the disease is that if insulin resistance is detected early, the development of DM can be prevented through dietary regulation and lifestyle changes.[14,15] Therefore, if insulin resistance can be identified before blood sugar levels become elevated on their own, a more effective role can be taken in its prevention.[16]

The TyG index is known to reflect insulin resistance and effectively indicate disruptions in lipid-glucose metabolism.[17,18] In the literature, It has been validated as an important biomarker for detecting insulin resistance and predicting the development of DM. Studies conducted in various populations have demonstrated a strong correlation between elevated TyG index values and an increased risk of diabetes.[19-21]

The Prospective Urban Rural Epidemiology study examined the relationship between the TyG index, metabolic changes, and mortality, while also considering the economic status of the participating countries.[22] The TyG index has emerged as a valuable and cost-effective biomarker for predicting cardiovascular disease, mortality, and type 2 diabetes, particularly in low-and middle-income countries, where insulin resistance and metabolic disorders pose significant health concerns.[22]

Diabetes is known to accelerate the deterioration of kidney function in ADPKD patients. Diabetic ADPKD patients have been shown to have larger kidney volumes and earlier onset of hypertension.[21,23] Identifying and intervening in diabetes risk is critical to preventing the development of additional comorbidities before and during diagnosis, as well as during follow-up.

Although our data do not include post-transplant patients, the potential utility of the TyG index for early diagnosis in this population warrants further investigation. Diagnostic biomarkers that are both cost-effective and efficient play a critical role in patient care.[24,25] Among such tools, the TyG index has garnered significant attention for its potential as a low-cost diagnostic marker across various medical conditions. It is increasingly recognized as an important biomarker for understanding insulin resistance and associated metabolic disorders.[25]

Culliford et al.[26] conducted a study involving 1,560 non-diabetic renal transplant patients; finding a higher

Table 1. Demographic properties and baseline laboratory results			
	Developed DM n=138	**Not developed DM n=18**	**p**
Age, years, ±SD	49.05±12.03	54.67±12.34	0.39
Gender, female, %	80 (57.0)	14 (77.7)	0.11
BMI, kg/m^2, ±SD	27.10±5.16	27.99±3.30	0.16
Hypertension, n, %	115 (83.3)	16 (88.8)	0.74
ASKH, n, %	7 (5.07)	5 (27.78)	0.06
RAS bloker, n,%	106 (76.81)	14 (77.78)	0.76
V2 antagonist, n,%	25 (18.11)	2 (11.11)	0.74
BUN, mg/dL, ±SD	20.24±9.71	17.82±7.93	0.59
Creatinine, mg/dL, ±SD	1.24±0.69	1.16±0.47	0.58
Uric acid, mg/dL, ±SD	6.44±1.85	6.03±1.52	0.34
Albumin, g/dL, ±SD	4.34±0.28	4.30±0.25	0.36
Sodium, mEq/L, ±SD	139.87±2.60	140.25±1.67	0.39
Potassium, mEq/L, ±SD	4.40±0.42	4.50±0.56	0.60
Calcium, mEq/L, ±SD	9.60±0.44	9.83±0.50	0.49
Phosphorus, mEq/L, ±SD	3.35±0.57	3.53±0.58	0.87
Magnesium mEq/L, ±SD	0.85±0.07	0.73±0.17	0.008
Glucose mg/dL, ±SD	91 (±7.3)	89 (±8.4)	0.69
LDL gr/dL, ±SD	132±31	141±43	0.32
Triglyceride, gr/dL, ±SD	166.2 (±55.72)	136.14 (±77.84)	0.08
Triglyceride/glucose	1.46±0.85	1.55±0.53	0.013
Hemoglobin, gr/dL, ±SD	13.56±1.35	12.5±1.32	0.67
Mayo grade Grade 1A, n, % Grade 1B, n, % Grade 1C, n, % Grade 1D, n, % Grade 1E, n, %	 14 (10.14) 28 (20.29) 46 (33.33) 31 (22.46) 19 (13.76)	 3 (16.67) 4 (22.22) 7 (38.39) 3 (16.67) 1 (5.56)	0.70

DM: Diabetes mellitus, SD: Standard deviation, BMI: Body mass index, ASKH: Aterosklerotik kalp hastalığı, RAS: Renin angiotensin system, BUN: Blood urea nitrogen, LDL: Low-density lipoprotein

Table 2. Follow up of triglyceride/glucose index							
	Baseline	**1st year**	**2nd year**	**3rd year**	**4th year**	**p′**	**p″**
DM +	1.55±0.53	1.41±0.80	1.42±0.75	1.49±0.87	1.63±1.12	0.01	0.013
DM -	1.46±0.85	1.55±1.98	1.52±0.96	1.53±0.99	1.50±0.72	0.01	

p′: The statistical significance of triglyceride-glucose (TyG) change over five years, p″: The statistical difference in TyG variation between individuals who developed diabetes and those who did not, DM: Diabetes mellitus

incidence of post-transplant DM among those with a history of ADPKD. Their meta-analysis supported these findings, despite the underlying pathophysiological mechanisms remaining unclear.[26] Based on these results, we propose that the TyG index could be used as an early indicator of insulin resistance in ADPKD patients prone to developing DM.

Study Limitations

Our study is a retrospective case-control design, which inherently presents limitations. Additionally, post-transplant patients were not included in this analysis. Nevertheless, the TyG index emerges as a simple, cost-effective, and accessible tool for predicting diabetes development in ADPKD patients. Considering the impact

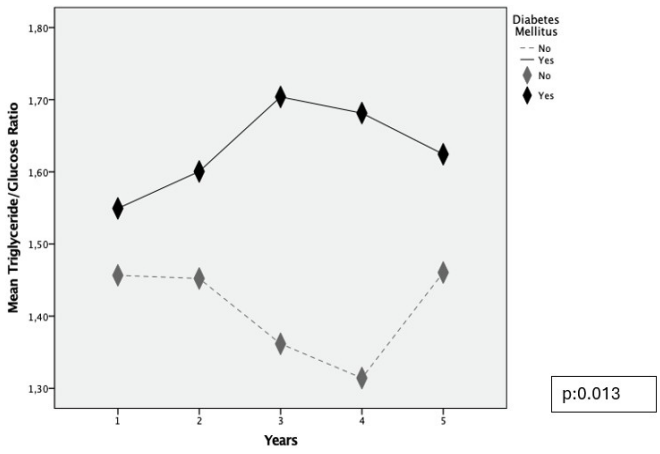

Figure 1. Diagram for follow up of triglyceride/glucose index

of ADPKD on diabetes-associated metabolic changes, screening and intervention strategies based on the TyG index could be critical for the early diagnosis and management of diabetes in this population. The ability to predict this risk before hyperglycemia develops is particularly important for preventing diabetes onset. Regular monitoring of triglyceride and glucose levels is essential for timely intervention.

CONCLUSION

Our findings indicate that in ADPKD patients, DM develops in those with elevated TyG index levels before any increase in blood glucose levels is detected. Given that ADPKD is one of the significant causes of ESRD, monitoring TyG ratios could prevent the development of comorbidities like DM during follow-up and reduce the risk of post-transplant DM. Further exploration of diabetes effects in ADPKD is necessary to develop new clinical strategies for this patient group. Future studies with larger, more comprehensive designs are needed to better understand this relationship in detail.

Ethics

Ethics Committee Approval: The Non-interventional Research Ethics Committee of Dokuz Eylül University Faculty of Medicine approved the study (decision no: 2025/02-12, date: 15.01.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: Y.D.B., B.K., C.Ç., Design: Y.D.B., B.K., S.M.D., Data Collection or Processing: D.C.G., İ.A., M.A.O., C.H., Analysis or Interpretation: Y.D.B., B.K., Literature Search: İ.A., M.A.O., C.H., C.Ç., Writing: Y.D.B., S.M.D.

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