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Could MOTS-c Levels in Children with Type 1 Diabetes Mellitus Be an Indicator for Early Diabetic Kidney Disease?

İlknur Girişgen[1], Selda Ayça Altıncık[2], Esin Avcı[3], Murat Öcal[4], Tülay Becerir[1], Gaye Malaş Öztekin[3], Bayram Özhan[2], Selçuk Yüksel[5]

[1]Pamukkale University Faculty of Medicine, Department of Pediatric Nephrology, Denizli, Türkiye
[2]Pamukkale University Faculty of Medicine, Department of Pediatric Endocrinology, Denizli, Türkiye
[3]Pamukkale University Faculty of Medicine, Department of Biochemistry, Denizli, Türkiye
[4]Batman State Hospital, Clinic of Pediatric Endocrinology, Batman, Türkiye
[5]Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Pediatric Nephrology and Rheumatology, Çanakkale, Türkiye

What is already known on this topic?

Vascular complications associated with diabetes are not commonly observed in children and young people. However, structural abnormalities may manifest a few years after the onset of the disease, usually starting from age 11 years with between two and five years of diabetes duration. Intensive education and treatment during childhood can help prevent or delay the onset and progression of diabetic complications, including diabetic kidney disease (DKD), retinopathy, and neuropathy. Renal failure and hypertension may develop due to DKD. Hyperglycemia in diabetic patients leads to an increase in reactive oxygen species (ROS). This increase in oxidative stress and ROS is a critical factor in the development of diabetic vascular complications.

What this study adds?

The findings of this study suggest that the onset of oxidative damage and mitochondrial dysfunction in type 1 diabetes mellitus is independent of DKD. Furthermore, the results suggest that levels of glycated hemoglobin A1c, commonly used as a pragmatic marker of glycemic control in patients with diabetes, and duration of disease are significant risk factors for oxidative stress and tissue damage, while changes in estimated glomerular filtration rate and microalbuminuria continue to serve as indicators for DKD.

Abstract

Objective: To compare serum mitochondrial open reading frame of 12S rRNA-c (MOTS-c) levels, a new potential biomarker for oxidative stress, in children with type 1 diabetes mellitus (T1DM) and healthy children. A further aim was to investigate serum MOTS-c levels as a potential early indicator of diabetic kidney disease (DKD) by correlating levels with changes in glomerular filtration and microalbuminuria.

Methods: Patients with a diagnosis of T1DM and healthy controls were recruited. MOTS-c, urinary albumin excretion, estimated glomerular filtration rate (eGFR), and hemoglobin A1c (HbA1c) were evaluated and clinical features and anthropometric measurements were collected. Patients were stratified according to diabetes duration, presence of albuminuria, glomerular hyperfiltration, eGFR decline and metabolic control.

Results: The T1DM group included 82 [female:male (F:M) 1:1.64] patients while the controls numbered 61 (F:M 1:0.97), with respective mean ages of 14.3 ± 3.3 and 10.6 ± 4.2 years ($p < 0.01$). MOTS-c levels were significantly lower in the T1DM group than controls (76.2 ± 1.3 vs 105.2 ± 7.0, $p < 0.001$). No difference was found in MOTS-c levels between patient subgroups categorized by diabetes duration, obesity, metabolic control, hypertension, hyperlipidemia, glomerular hyperfiltration, decline in eGFR, and presence of microalbuminuria. Simple linear regression indicated that MOTS-c was not predictive for DKD.

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Address for Correspondence: İlknur Girişgen MD, Pamukkale University Faculty of Medicine, Department of Pediatric Nephrology, Denizli, Türkiye
E-mail: igirisgen78@hotmail.com **ORCID:** orcid.org/0000-0003-2617-4466

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Conclusion: MOTS-c levels were lower in children with T1DM than in healthy children. However, the lack of association of MOTS-c with renal biomarkers suggested that it is not an effective early marker for DKD. However, this finding suggests that the onset of oxidative damage and mitochondrial dysfunction in T1DM is independent of DKD. In addition, the results suggests that HbA1c and duration of diabetes are significant risk factors for development of microalbuminuria, while changes in eGFR and microalbuminuria continue to serve as indicators of DKD.
Keywords: Children, diabetes mellitus, diabetic kidney disease, MOTS-c, oxidative stress

Introduction

Vascular complications associated with diabetes are not commonly observed in children and young people. However, structural abnormalities may manifest a few years after the onset of the disease, usually starting from the age of around 11 years and between two and five years of diabetes duration (1). Intensive education and treatment during childhood may help prevent or delay the onset and progression of diabetic complications, including diabetic kidney disease (DKD) retinopathy, and neuropathy. Renal failure and hypertension may develop due to DKD (2). Risk factors for the development of DKD in children and adolescents include poor metabolic control, long-term diabetes, dyslipidemia, obesity, smoking, and family history of DKD (3). Urinary albumin excretion (UAE) and changes in glomerular filtration rate (GFR) remain important diagnostic tools for DKD (4). However, indicators that detect DKD earlier, before albuminuria develops and GFR declines, are needed.

Many structural and functional changes in DKD are believed to be due to a chronic inflammatory insult to the kidney. Chronic inflammation activates apoptosis, causes podocyte foot-process effacement, alters glomerular hemodynamics, increases vascular endothelial permeability leading to glomerular sclerosis, tubulointerstitial fibrosis and increased oxidative stress (5). Hyperglycemia in diabetic patients leads to an increase in reactive oxygen species (ROS). This increase in oxidative stress and ROS is a critical factor in the development of diabetic vascular complications (6,7,8,9,10).

Mitochondria are organelles that play a key role in regulating cellular metabolism and are sensitive to oxidative stress. Oxidative stress can cause damage to mitochondrial DNA, lipids, and proteins, leading to mitochondrial damage and apoptosis. Mitochondrial-derived peptides (MDPs) are a family of peptides encoded by the mitochondrial genome that regulate mitochondrial function, gene expression and metabolic homeostasis in the body (8). A new member of the MDPs, mitochondrial open reading frame of 12S rRNA-c (MOTS-c), is a peptide hormone that has been shown to exert positive effects on obesity, improve muscle function, promote bone metabolism, enhance immune regulation, inhibit inflammation, block cellular apoptosis, delay aging and reduces aging related disorders (9,11). MOTS-c is present in skeletal muscle and in organs, such as the brain, testis, kidney, liver and circulates in plasma, but MOTS-c levels decline with age. Under oxidative stress MOTS-c translocates to the nucleus, stimulating antioxidant pathways by interacting with nuclear factor erythroid 2-related factor 2, inhibits mitochondrial oxidative stress, promotes the clearance of damaged mitochondria, and improves mitochondrial biogenesis (12). MOTS-c has been shown to regulate metabolic homeostasis through AMP-activated protein kinase (AMPK) and thus modify glutathione production, prevent insulin resistance, and have favorable effects in diabetes mellitus (9,11). It has been suggested that the reduction in MOTS-c may also exert an effect on age-related diseases, such as Alzheimer's, cardiovascular disease, osteoporosis and diabetes, and experimental studies continue to investigate the benefits of MOTS-c treatment for these diseases (9,11).

The aim of the present study was to compare serum MOTS-c levels in children with type 1 diabetes mellitus (T1DM) to those of healthy children. Considering that the increase in oxidative stress and ROS, as well as mitochondrial dysfunction, are likely related to the development of diabetic vascular complications, the second aim was to investigate whether MOTS-c has a potential role in diabetic nephropathy. There have been several studies on type 2 diabetes mellitus (T2DM), but we believe our study is the first to investigate the association of DKD with serum MOTS-c levels in children and youth with T1DM.

Methods

Study Design, Subjects, and Definitions

A prospective, cross-sectional study involving children with T1DM was conducted in 2021-2022 at a tertiary care referral hospital. Patients who were being treated for insulin-dependent diabetes at the outpatient pediatric endocrinology clinic were eligible for inclusion. The study involved patients who were at puberty or at least 11 years old, whichever came first, and with 2-5 years diabetes duration. A group of normotensive children with normal body mass index (BMI) who visited the outpatient pediatric clinic for minor issues were enrolled as the control group.

Patients with chronic inflammatory diseases, chronic kidney disease, hypertension and, acute infection, as well as those taking medication other than insulin, were excluded.

Weight (kg), height (cm) and manual blood pressure were measured, and BMI was calculated. The standardized method of Tanner staging was used to assess pubertal status (13). Standard techniques were used to measure systolic blood pressure and diastolic blood pressure. BP was calculated in accordance with the National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Children and Adolescents (14). Demographic and clinical data including age, sex, diabetes duration and diabetes treatment were collected from patients' medical records.

Laboratory Assessments

Serum creatinine, cystatin C, triglyceride and lipid levels were measured using the electrochemiluminescence method on the Cobas 702 systems (Roche Diagnostics, Mannheim, Germany). Hemoglobin A1c (HbA1c) was measured by high-pressure liquid chromatography using Tosoh G8 instruments (Tosoh Bioscience, Japan).

Blood and urine samples were collected on the same day following an overnight fast. Urinary albumin was measured using a solid-phase competitive chemiluminescent immunoassay on Cobas 702 systems (Roche Diagnostics, Mannheim, Germany). To measure of MOTS-c in human serum, approximately 5 mLs of venous blood was collected into a serum separator tube. The samples were allowed to stand at room temperature for approximately 15 minutes and then centrifuged at 3500 rpm for 10 minutes. Human MOTS-c levels were measured using commercial kits from BT Lab (Bioassay Technology Laboratory, Shanghai, China) using an enzyme-linked immunosorbent assay. Values for MOTS-c levels are given in ng/mL.

Mean HbA1c levels above 7% during follow-up were taken to indicate poor metabolic control (15). The averages of at least three HbA1c levels in the previous year for all patients were used. Patients with ≤2 HbA1c results within the preceding year were excluded from the metabolic control subgroup.

The degree of albuminuria was expressed as urinary albumin-to-creatinine ratio in mg/g or UAE in mg/L. ACR values of less than 30 mg/g was defined as normal, and 30 to 299 mg/g were defined as microalbuminuria (16). Patients with albumin excretion >30 mg/g at baseline had two additional samples repeated over 3-6 months to ensure albuminuria was persistent (1). Patients without albuminuria at baseline were asked to provide a urine sample every six months. The GFR was calculated using creatinine-based estimated GFR (eGFR) ($eGFR_{cr}$) (17). The eGFR of the T1DM group at the start of the study was recorded and compared with the data from at least 1 year of follow-up. The formula [(baseline eGFR - final eGFR) x 100 / baseline eGFR] was used to calculate the estimated percentage change in GFR. Progressive decline was defined as an eGFR decline of 3.3% (+1 standard deviation) or more per year (18). Glomerular hyperfiltration was defined as an eGFR of more than 120 mL/min per 1.73 m^2 (19).

Patients were categorized into five subgroups according to the presence of microalbuminuria, glomerular hyperfiltration, eGFR decline, metabolic control, and diabetes duration.

Statistical Analysis

As there was no similar published study to use as a reference, we conducted the power analysis in line with the expectations and information obtained from the literature. Assuming that the effect size of the difference between the groups was moderate (d = 0.5), it was calculated that 80% power could be obtained with a 95% confidence level when at least 128 people (at least 64 people for each group) were included.

The Kolmogorov-Smirnov analysis was used to test central tendency and variability in data. If the data were normally distributed, mean and standard deviation are given. Continuous variables without normal distribution are presented as medians and interquartile range (Q1-Q3, 25^{th}-75^{th} percentile values). Categorical variables are expressed as numbers and percentages. The independent samples t-test was used for comparisons between groups when parametric test conditions were met. The Mann-Whitney U test was used for comparisons between groups when parametric test conditions were not met. Chi-squared analysis was used to investigate differences between categorical variables. The ANOVA test was used to determine differences between three or more unrelated samples or groups. Simple linear regression analysis was used to investigate whether MOTS-c predicted DKD. The Statistical Package for Social Sciences (SPSS) for Windows, version 27.0 (SPSS Corp., Chicago, IL, USA) was used for statistical analysis. A $p < 0.05$ was considered statistically significant.

Results

There were 82 participants with T1DM (31 girls and 51 boys) and 61 healthy children (31 girls and 30 boys) in the T1DM and control groups, respectively. In terms of gender distribution, there was no difference between the groups ($p = 0.12$). However, the T1DM group's mean age was 14.3 ± 3.3 (5.5-20) years, significantly older than the control

group with a mean age of 10.6 ± 4.2 years (p < 0.01). Table 1 presents the descriptive data and laboratory results of the patient group. Eight (9.8%) patients were obese, and 16 (19.5%) had hyperlipidemia.

Nine (11%) patients were prepubertal and 73 were pubertal. Upon comparing the pubertal and prepubertal patients, no significant differences were found between the two groups in terms of HbA1c levels, MOTS-c levels, eGFR decline, frequency of hyperfiltration, or the presence of microalbuminuria.

Based on mean HbA1c available in 72 (87.8%) of the T1DM group, 12 (16.7%) patients had good metabolic control and 60 (83.3%) had poor metabolic control. No significant differences were found between these two groups in terms of laboratory data and MOTS-c levels (Tables 2, 3). However, mean HbA1c was correlated with UAE and $eGFR_{cr}$ decline (Table 4).

The duration of diabetes was less than 5 years in 23 (28%) patients and more than 5 years in 59 (72%) patients. Diabetes duration was correlated with UAE (Table 4).

Twenty (24.4%) had microalbuminuria and 62 (75.6%) had normal albumin excretion. There were no significant differences in age, duration of diabetes, HbA1c levels, eGFR decline or MOTS-c levels between patients with and without microalbuminuria (Tables 2, 3). Moreover, no significant differences were found between these two groups in terms of eGFR, lipid levels, creatinine, or cystatin-C levels.

Hyperfiltration was detected in 25 (30.9%) patients based on $eGFR_{cr}$. When the groups with and without glomerular hyperfiltration ($eGFR_{cr}$) were compared, the duration of

Table 1. The descriptive data and laboratory results of patients with T1DM

Age (years)	14.3 ± 3.4
Pre-pubertal/pubertal	9/73
Height (cm) Height SDS	157 ± 15.48 -0.04 ± 1.03
Weight (kg) Weight SDS	53.12 ± 15.71 0.02 ± 1.16
Body mass index Body mass index SDS	20.98 ± 4.03 0.04 ± 1.3
Diabetes duration (years)	6.4 ± 3.1
Insulin dose (IU/kg/day)	1.0 ± 0.3
Mean HbA1c (%)	8.53 ± 1.65
Triglyceride (mg/dL)	112.0 ± 82.7
HDL cholesterol (mg/dL)	57.5 ± 12.6
Total cholesterol (mg/dL)	167.3 ± 36.1
LDL cholesterol (mg/dL)	89.6 ± 27.4
Creatinine (mg/dL)	0.6 ± 0.1
$eGFR_{cr}$ (mL/min/1.73 m^2)	112.0 ± 20.5
Cystatin-C (mg/dL)	0.85 ± 0.11
UAE (mg/L) median (IQ) UACR (mg/g) median (IQ) MOTS-c (mg/dL)	9.9 (4.3-22.9) 9 (5-21.7) 76.3 ± 12.2

SDS: standard deviation score, UAE: urinary albumin excretion, UACR: urinary albumin creatinine ratio, $eGFR_{cr}$: creatinine based estimated glomerular filtration rate, T1DM: type 1 diabetes mellitus, HbA1c: hemoglobin A1c

Table 2. Comparison of HbA1c and markers of diabetic kidney disease in subgroups of patients with T1DM

Subgroups		Age	Diabetes duration	Mean HbA1c	UAE (mg/L)	UACR (mg/g)	$eGFR_{cr}$ decline
Metabolic control	Good (n = 12)	14.3 ± 2.7	5.0 ± 3.1	6.8 ± 0.4	10 (5.7-20.9)	11.3 (5.7-12)	9.8 (-4.4-14.0)
	Poor (n = 60)	13.3 ± 3.1	6.4 ± 3.0	8.8 ± 1.5	7.2 (3.8-18.8)	8.1 (4.8-16.4)	4.03 (-5.4-10.3)
	p	0.1	0.5	0.04	0.15	0.18	0.72
Diabetes duration	< 5 years (n = 23)	13.8 ± 2.9	3.0 ± 0.8	8.2 ± 1.0	6.3 (3-18.6)	9 (5.2-15.7)	5.2 (-7.5-12.3)
	≥5 years (n = 59)	13.2 ± 3.1	6.7 ± 1.4	8.6 ± 2.1	11.3 (5.9-29.3)	11.3 (4.8-24)	3.4 (-4.3-9.8)
	p	0.5	< 0.001	0.48	0.08	0.17	0.96
Microalbuminuria	Present (n = 20)	14.1 ± 3.1	6.9 ± 3.2	9.3 ± 2.3	48(32.1-86)	59 (37.3-142)	6.7 (-11.6-11.3)
	Absent (n = 62)	13.7 ± 2.9	6.2 ± 2.7	8.2 ± 1.3	6.6 (3.3-13.6)	7.2 (4.7-11.6)	5.1 (-5-12)
	p	0.61	0.33	0.13	< 0.001	< 0.001	0.68
Hyperfiltration ($eGFR_{cr}$)	Present (n = 25)	13.9 ± 3.0	5.2 ± 2.1	8.2 ± 1.5	13.8 (3.9-28.7)	10.9 (4.9-20.8)	10 (2.4-15.8)
	Absent (n = 57)	13.2 ± 3.1	6.7 ± 3.2	8.6 ± 1.8	7.4 (4.2-22.9)	9.9 (5.3-23.7)	0.4 (-7.4-8.6)
	p	0.33	**0.01**	0.35	0.51	0.27	**0.006**
$eGFR_{cr}$ decline	Present (n = 38)	14 ± 3.6	8.7 ± 3.5	9.0 ± 1.4	7.2 (3.2-9.7)	7.5 (4.6-14.6)	10.4 (8.2-15.6)
	Absent (n = 30)	12.4 ± 3.4	5.2 ± 2.5	8.8 ± 2.5	31 (2.7-55.6)	19.7 (4.8-99)	-6.5 [-15.1-(-)6.5]
	p	0.37	**0.03**	0.83	0.66	0.28	< 0.00

HbA1c: hemoglobin A1c, T1DM: type 1 diabetes mellitus, UAE: urinary albumin excretion, UACR: urinary albumin creatinine ratio, $eGFR_{cr}$: creatinine based estimated glomerular filtration rate

Table 3. Comparison of MOTS-c levels in subgroups of patients with T1DM

Subgroups of patients	MOTS-c (mg/dL)	p
Duration of diabetes		
> 5 year (n = 59)	75.6 ± 12.7	0.2
< 5 year (n = 23)	78.7 ± 10.5	
Obese (n = 9)	75.9 ± 9.3	0.9
Normal weight patient (n = 73)	76.3 ± 12.6	
Good metabolic control (n = 12)	74.4 ± 11.4	0.4
Poor metabolic control (n = 60)	76.2 ± 12.6	
Hyperlipidemia		
Yes (n = 16)	76.6 ± 14.1	0.9
No (n = 66)	76.2 ± 11.6	
Glomerular hyperfiltration ($eGFR_{cre}$)		
Yes (n = 25)	80.0 ± 10.2	0.07
No (n = 57)	74.7 ± 12.8	
$eGFR_{cre}$ decline		
Yes (n = 38)	74.1 ± 12.5	
No (n = 30)	77.0 ± 11.7	0.3
Microalbuminuria		
Yes (n = 20)	74.1 ± 9.7	0.4
No (n = 62)	76.7 ± 12.8	
Puberty (n = 73)	75.3 ± 12.4	0.051
Prepubertal (n = 9)	83.8 ± 6.8	

T1DM: type 1 diabetes mellitus, $eGFR_{cr}$: creatinine based estimated glomerular filtration rate, MOTS-c: mitochondrial open reading frame of 12S rRNA-c

Table 4. Correlation of MOTS-c with HbA1c and markers of diabetic kidney disease

		$eGFR_{cr}$ decline	UAE (mg/L)	UACR (mg/g)	Mean HbA1c	Diabetes duration
MOTS-c	r	-0.0	-0.15	-0.06	0.123	-0.13
	p	0.94	0.180	0.593	0.30	0.24
$eGFR_{cr}$ decline	r		0.04	-0.01	-0.26	0.08
	p		0.69	0.93	**0.03**	0.49
UAE (mg/L)	r			0.788	0.27	0.241
	p			**< 0.001**	**0.02**	**0.03**
UACR (mg/g)	r				0.11	0.18
	p				0.33	0.10
Mean HbA1c	r					0.15
	p					0.19

*Correlation was significant at the 0.05 level (2-tailed).
UAE: urinary albumin excretion, UACR: urinary albumin creatinine ratio, $eGFR_{cr}$: creatinine based estimated glomerular filtration rate, HbA1c: hemoglobin A1c, MOTS-c: mitochondrial open reading frame of 12S rRNA-c

diabetes was shorter in patients with hyperfiltration but the duration of diabetes in these patients.

GFR_{cr} monitoring was performed in 68 (82.9%) patients. Of these 38 (55.9%) experienced a decline in eGFRcr greater than 3.3%, while the remaining 30 (44.1%) did not experience any decline. Upon comparison of these two groups, there was no significant difference in terms of age, creatinine, cystatin-C, UAE, or MOTS-c levels (Tables 2, 3). The $eGFR_{cr}$ decline was greater in patients with hyperfiltration than without hyperfiltration (p = 0.006) (Table 2). Patients with GFRcr decline had a significantly longer duration of diabetes (Table 2).

Mean serum MOTS-c levels were significantly lower in the T1DM group (76.2 ± 12.2 mg/dL) than in the control group (105.2 ± 54.6 mg/dL, p < 0.01) (Figure 1). The association between serum MOTS-c levels and baseline clinical and biochemical factors was evaluated. MOTS-c levels were not correlated with baseline age, body weight, height, or BMI. Furthermore, there was no correlation between MOTS-c levels and total cholesterol, low density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, HbA1c levels, serum creatinine, cystatin-C, eGFRcr, ACR, or UAE (Table 4).

No significant difference in MOTS-c levels was found among the T1DM subgroups categorized by diabetes

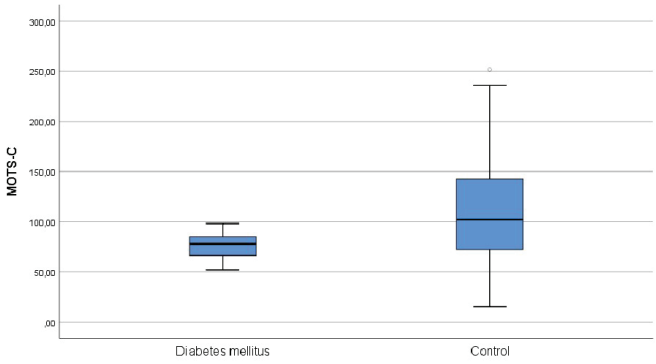

Figure 1. MOTS-c serum levels in type 1 diabetes mellitus and the healthy control group

MOTS-c: mitochondrial open reading frame of 12S rRNA-c

duration, obesity, metabolic control, hyperlipidemia, glomerular hyperfiltration, decline of eGFR, or presence of microalbuminuria (Table 3). The simple linear regression analysis results indicated that MOTS-c was not predictive for GFR decline, hyperfiltration, or microalbuminuria.

Discussion

In recent years, studies have shown the relationship between MOTS-c and adult T1DM and T2DM, childhood obesity, insulin resistance and related vascular complications (20,21,22,23). We found that MOTS-c levels were lower in the T1DM group than the control group. However, there was no correlation between MOTS-c levels and UAE or, eGFR. Although MOTS-c levels were lower in T1DM patients than in controls, there was no association between MOTS-c and indicators of diabetic nephropathy. This finding suggests that the onset of oxidative damage in T1DM is independent of diabetic nephropathy.

DKD is a significant cause of morbidity and mortality among T1DM patients, that can lead to chronic renal failure and require renal replacement therapy. Changes in the kidneys of people with diabetes generally occur in five stages (24,25). Hyperfiltration is the first stage of DKD, and the third stage is associated with the development of microalbuminuria. Hyperfiltration and microalbuminuria are believed to be strong predictors of DKD progression (4). Studies have shown that the prevalence of glomerular hyperfiltration in the pediatric population with T1DM varies between 13% and 52% (26). In the present study, 30.9% of patients had glomerular hyperfiltration, 24% had microalbuminuria, and 55% had $eGFR_{cr}$ decline. At the end of one year, the decline in $eGFR_{cr}$ was greater in patients with hyperfiltration compared to those without.

In children with T1DM, microalbuminuria is frequently detected during puberty, with a prevalence of around 10-25% after 5-10 years of diabetes duration (24,27,28,29). The development and progression of microvascular complications are influenced by puberty and duration of diabetes (24). We found that the mean diabetes duration was 7.9 ± 4.0 years and duration of diabetes was correlated with UAE and eGFR decline. Hyperfiltration was significantly more pronounced in older patients. Seventy-three patients were pubertal, and there was no difference in the frequency of microalbuminuria, GFR decline, or hyperfiltration between the pubertal and prepubertal patient groups. Poor glycemic control is well-known to be associated with the development of vascular complications. In the present study, 83% of patients had poor metabolic control and HbA1c was correlated with UAE and $eGFR_{cr}$ decline. However, there was no increase in the number of patients with glomerular hyperfiltration or microalbuminuria in the poor metabolic control group compared to the good metabolic control group.

The novel bioactive peptide, MOTS-c, has recently attracted attention as a potential prevention or therapeutic option for obesity and T2DM (20). Experimental studies have suggested that MOTS-c may serve as a new metabolic regulator and a potential therapeutic target in T2DM (8,11,30). In addition to experimental studies, studies on people with obesity and T2DM, particularly children, continue to be conducted. Du et al. (20) demonstrated that levels of circulating MOTS-c are decreased in obese male children and adolescents, and a negative correlation existed between circulating MOTS-c levels and BMI, fasting insulin levels, insulin resistance measured by homeostasis model assessment-insulin resistance (HOMA-IR) and HbA1c levels. They suggested that decreased MOTS-c concentration might be a biomarker of insulin resistance in childhood obesity. Ramanjaneya et al. (23) demonstrated that levels of circulating mitochondrial derived peptides, MOTS-c and humanin, were reduced in individuals with T2DM and significantly related to HbA1c. This study revealed that levels of MDPs were lower in people with poorly controlled T2DM compared to those with well-controlled T2DM. Luo et al. (21) showed that serum MOTS-c levels were decreased in obese children, which may be associated with impaired vascular endothelial function. Luo et al. (21) also showed that MOTS-c levels were positively correlated with HDL levels and negatively correlated with BMI, total triglycerides, and HOMA-IR. We found that there were no significant differences in MOTS-c levels between children with diabetes who had good metabolic control and those who had poor metabolic control. There was no statistically significant correlation between MOTS-c levels and BMI, HbA1c levels, or lipid levels.

Kong et al. (22) reported that adult patients with T1DM (n = 10) had significantly lower circulating MOTS-c levels than healthy controls and suggested a relationship between circulating mitochondrial-encoded peptides and the pathogenesis of autoimmune diabetes. They also demonstrated that MOTS-c treatment prevented T cell-mediated autoimmune destruction of pancreatic beta cells and autoimmune diabetes in non-obese diabetic mice. Similar to the findings of Kong et al. (22), we also found low MOTS-c levels in children with childhood T1DM. This suggests that mitochondrial damage starts in T1DM in childhood. There was no correlation between MOTS-c levels in the T1DM group and serum creatinine, cystatine-C, eGFRcr, ACR, or UAE. In addition, the absence of a significant difference in MOTS-c levels among subgroups categorized according to the presence of glomerular hyperfiltration, eGFR decrease and microalbuminuria suggests that MOTS-C is not an early indicator of DKD.

Study Limitations

The control group was younger than anticipated, which is a significant limitation. The correlation of MOTS-c with age was analysed, and no correlation was found. MOTS-c levels are known to decrease in relation to age-related illnesses (geriatric disease) and old age, but our study and control groups were children, and we do not think that the significant difference in the mean ages of the T1DM and control group affected the findings.

Conclusion

There are a limited number of published studies in patients with T2DM and a single study in adult patients with T1DM that have shown low MOTS-c levels. In the present study, MOTS-c was lower in the T1DM group than in healthy children. However, the lack of association with microalbuminuria, hyperfiltration, and eGFR decline suggested that MOTS-c is not an early marker of DKD. Moreover, the results suggest that HbA1c and duration of diabetes are significant risk factors for the development of DKD, while changes in eGFR and microalbuminuria continue to serve as indicators of DKD.

Ethics

Ethics Committee Approval: The study was approved by the Pamukkale University Local Ethics Committee (number: 10.150.1.90-106832, date: 05.01.2021).

Informed Consent: The patients along with their caregivers gave their written consent to participate in the study.

Footnotes

Authorship Contributions

Concept: İlknur Girişgen, Design: İlknur Girişgen, Tülay Becerir, Data Collection or Processing: Selda Ayça Altıncık, Murat Öcal, Gaye Malaş Öztekin, Bayram Özhan, Analysis or Interpretation: İlknur Girişgen, Esin Avcı, Murat Öcal, Gaye Malaş Öztekin, Literature Search: İlknur Girişgen, Selda Ayça Altıncık, Tülay Becerir, Bayram Özhan, Selçuk Yüksel, Writing: İlknur Girişgen, Selda Ayça Altıncık, Esin Avcı, Tülay Becerir, Selçuk Yüksel.

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