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Research Article

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

Girisgen İ et al. MOTS-C Levels in Children with Type 1 Diabetes Mellitus

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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 2-5 years of diabetes duration. Intensive education and treatment during childhood can help prevent or delay the onset and progression of diabetic complications such as, 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?
This finding suggests that the onset of oxidative damage and mitochondrial dysfunction in T1DM is independent of diabetic kidney disease. Additionally, the study suggests that HBA1C and duration of diabetes are significant risk factors, while changes in eGFR and microalbuminuria continue to serve as indicators of diabetic kidney disease.

Abstract
Objective: The aim of our study was to compare serum MOTS-c levels in children with Type 1 diabetes mellitus (T1DM) to those of healthy children. We also aimed to examine whether serum MOTS-c levels could be used as an early indicator of DKD by correlating with changes in GFR and microalbuminuria.
Methods:We recruited 82 patients who were being treated for insulin-dependent diabetes at the outpatient pediatric endocrinology clinic. At study MOTS-c, urinary albümin excretion, eGFR, HbA1c were evaluated and diabetes-related clinical features and anthropometric measurements were collected. Patients were divided into subgroups according to diabetes duration, precence of albuminuria, glomerular hyperfiltration, eGFR decline and metabolic control.
Results:The levels of MOTS-C were significantly lower in the Tip1DM group (76.2±1.3mg/dl) than in the control group (105.2±7.0, p=0.00). No significant difference in MOTS-c levels was found among the subgroups categorized by diabetes duration, obesity, metabolic control, hypertension and hyperlipidemia, glomerular hyperfiltration, decline in eGFR, and presence of microalbuminuria. The simple linear regression analysis results indicated that MOTS-C was not predictive for marker of diabetic kidney disease.
Conclusions: In current study, MOTS-c was lower in the type 1DM 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 in diabetic kidney disease. This finding suggests that the onset of oxidative damage and mitochondrial dysfunction in T1DM is independent of diabetic kidney disease. Additionally, the study suggests that HBA1C and duration of diabetes are significant risk factors, while changes in eGFR and microalbuminuria continue to serve as indicators of diabetic kidney disease.
Keywords: Children, diabetes mellitus, diabetic kidney disease, Mots-c, oxidative stress

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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 age 11 years with 2-5 years of diabetes duration (1). Intensive education and treatment during childhood can help prevent or delay the onset and progression of diabetic complications such as, 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 caused by a chronic inflammatory insult to the kidney. Chronic inflammation activates apoptosis, causes podocyte foot-process effacement, alters glomerular hemodynamics, increases vascular endothelial permeability, leads 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 (6-10). 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 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 plasma but the levels decline with age. Under oxidative stress

MOTS-c translocates to the nucleus, stimulates antioxidant pathways by interacting with nuclear factor erythroid 2-related factor 2 (NRF2), inhibits mitochondrial oxidative stress, promotes the clearance of damaged mitochondria, and improves mitochondrial biogenesis (12). MOTS-c has been shown to regulate metabolic homeostasis via AMP-activated protein kinase (AMPK) reduce glutation, prevent insulin resistance, and have favorable effects on diabetes mellitus (9, 11). It has been suggested that the reduction in MOTS-c may affect 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 our 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 related to the development of diabetic vascular complications, the second aim of our study was to investigate whether MOTS-c has a potential role in diabetic nephropathy. There have been several studies on T2DM, but 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. We recruited 82 patients who were being treated for insulin-dependent diabetes at the outpatient pediatric endocrinology clinic. The study involved patients who were at puberty or at least 11 years old, whichever came first, with 2-5 years diabetes duration. A group of 61 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 were excluded.

Weight (kg), height (cm) and manual blood pressure were measured, and BMI was calculated. The standardized method of Tanner stages was used to assess pubertal status (13). Standard techniques were used to measure systolic and diastolic blood pressure (SBP and DBP, respectively). 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). 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 Cobas 702 systems (Roche Diagnostics, Mannheim, Germany). 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 cc 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 studied using commercial kits from BT Lab (Bioassay Technology Laboratory, Shanghai, China) using an enzyme-linked immunosorbent assay (ELISA). Values found are MOTS-c levels in ng/ml units.

Mean HbA1c levels above 7% during follow-up indicate poor metabolic control (15). The averages of at least 3 HbA1c levels in the previous year for all patients were used. Patients with ≤ 2 HbA1c data within 1 year were excluded from the metabolic control subgroup.

The degree of albuminuria was expressed as albumin-to-creatinine ratio (ACR, mg/g) or UAE (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 >30mg/g at baseline had 2 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 6 months. The GFR was calculated using creatinine-based eGFR ($eGFR_{cr}$) (17). The eGFR of the study 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% (+1SD) or more per year (18). Glomerular hyperfiltration was defined as an eGFR of more than 120ml/min per 1.73 m^2 (19).

Patients were categorized into 5 subgroups according to the presence of microalbuminuria, glomerular hyperfiltration, eGFR decline, metabolic control, and diabetes duration.

Statistical evaluation

Because there was no study similar to ours 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 a 95% confidence level when at least 128 people (at least 64 people for each group) were included in the study. The Kolmogorov-Smirnov analysis was used to test central tendency and variability in data. If the data are normally distributed, mean and standard deviation are given. Continuous variables without normal distribution were presented as medians (Q1-Q3, 25th-75th 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 3 or more unrelated samples or groups. Simple linear regression analysis was used to investigate whether MOTS-c predicts DKD. All statistical analyses were performed using SPSS 24.0, and a P value less than 0.05 was considered statistically significant.

Results

We enrolled 82 participants with T1DM (31 girls and 51 boys) and 61 healthy children (31 girls and 30 boys). In terms of gender distribution, there was no statistically significant difference between the 2 groups (p=0.12). The T1DM group's mean age was 14.3±3.3 (5.5-20) years, which was statistically higher than the control group's mean age of 10.6±4.2 years (p=0.00). Table 1 presents the descriptive data and laboratory results of the patient group. Eight patients were obese, and 16 had hyperlipidemia.

Nine patients were prepubertal and 73 were pubertal. Upon comparing the pubertal and prepubertal patients, no significant differences were found between the 2 groups in terms of HbA1c levels, MOTS-c levels, eGFR decline, frequency of hyperfiltration, and the presence of microalbuminuria (p>0.05).

According to the mean HbA1c, 12 patients had good metabolic control and 60 had poor metabolic control. No significant differences were found between the 2 groups in terms of laboratory data and MOTS-c levels (Tables 2-3). Mean HbA1c was correlated with UAE and $eGFR_{cr}$ decline (Table 4).

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

Twenty patients had microalbuminuria and 62 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). Additionally, no significant differences were found between the 2 groups in terms of eGFR, lipid levels, creatinine, or cystatin-C levels.

Hyperfiltration was detected in 25 (30.9%) patients according to $eGFR_{cr.}$ When the groups with and without glomerular hyperfiltration ($eGFR_{cr}$) were compared, the duration of diabetes was shorter in patients with hyperfiltration but the duration of diabetes in these patients was over 5 years.

GFR_{cr} monitoring was performed in 68 patients. Of these 38 experienced a decline in eGFRcr (55%) greater than 3.3%, while the remaining 30 did not experience any decline. Upon comparison of the 2 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).
MOTS-c levels were significantly lower in the T1DM group (76.2±12.2mg/dl) than in the control group (105.2±54.6, p=0.00) (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 body mass index. There was no statistically significant correlation between MOTS-c levels and total cholesterol, LDL cholesterol, 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 subgroups categorized by diabetes duration, obesity, metabolic control and 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 T1 and T2DM, childhood obesity, insulin resistance and related vascular complications (20-23). 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 diabetic nephropathy indicators. 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 5 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 this study, 30.9% of patients had glomerular ($eGFR_{cr}$) hyperfiltration, 24% had microalbuminuria, and 55% had eGFRcr decline. At the end of 1 year, the decline in eGFRcr 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, 27-29). 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 higher 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 associated with the development of vascular complications. In our study, 83% of patients had poor metabolic control. 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.
A novel bioactive peptide, mitochondrial-derived 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 for 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. demonstrated that levels of circulating MOTS-c are decreased in obese male children and adolescents, and a negative correlation exists among circulating MOTS-c levels and body mass index, fasting insulin levels, HOMA-IR, and HbA1c levels. They suggested that decreased MOTS-c concentration might be a biomarker of insulin resistance in childhood obesity (20). Ramanjaneya et al. demonstrated that circulating MDPs (MOTS-c and humanin) were reduced in individuals with T2DM and significantly related to HbA1c. The study revealed that levels of MDPs were lower in people with poorly controlled T2DM compared to those with well-controlled T2DM (23). Luo et al. (21) showed that serum MOTS-c levels decrease in obese children, which may be associated with impaired vascular endothelial function. The study also revealed that MOTS-c levels were positively correlated with HDL levels and negatively correlated with BMI, TG, and HOMA-insulin resistance (21). 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 among 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. Like the only study conducted in adult patients with T1DM, 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 statistically significant correlation among MOTS-c levels 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 it would be affected in childhood.

Conclusions

In the literature, a limited number of studies in patients with T2DM and a single study in adult patients with T1DM have shown low MOTS-c levels. In our 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. Additionally, the study suggests that HBA1C and duration of diabetes are significant risk factors, while changes in eGFR and microalbuminuria continue to serve as indicators of DKD.

Ethics

Ethics Committee Approval The study was approved by the local Ethics Committee (date: 05.01.2021, number:10.150.1.90-106832).
Informed Consent The patients along with their caregivers gave their written consent to participate in the study.
Competing interests The authors declare no competing interests.
Authorship contributions Concept: İlknur Girişgen. Data collection: Selda Ayça Altıncık, Murat Öcal, Bayram Özhan, Gaye Malaş Öztekin. Design: İlknur Girişgen, Tülay Becerir. Analysis: İlknur Girişgen, Esin Avcı, Gaye Malaş Öztekin, Murat Öcal Writing: İlknur Girişgen, Selda Ayça Altıncık, Esin Avcı, Selçuk Yüksel, Tülay Becerir. Literature Search: İlknur Girişgen, Selda Ayça Altıncık, Selçuk Yüksel, Tülay Becerir, Bayram Özhan
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Figure 1.

Figure 1. MOTS-C levels of Tip1DM and control groups.

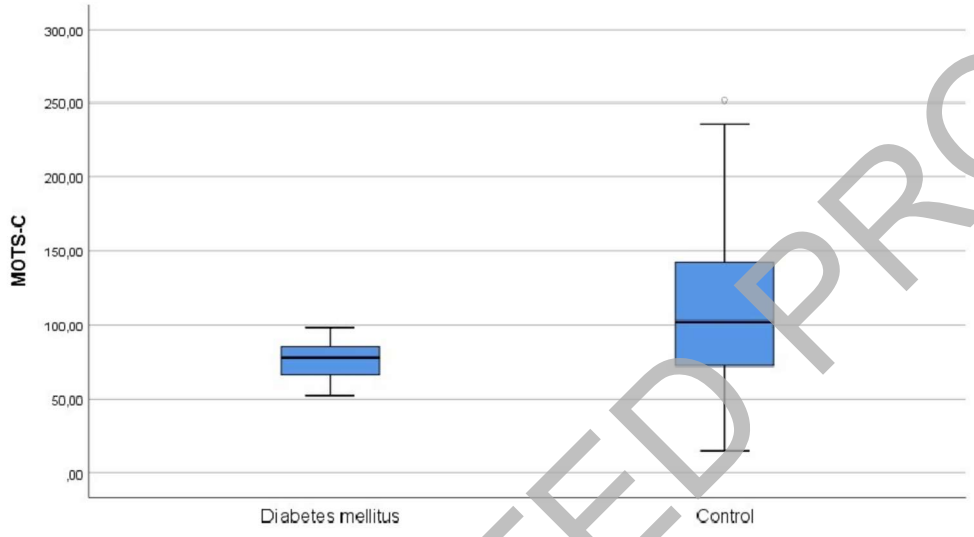

Table 1. The descriptive data and laboratory results of patients with T1DM

Age (year)	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 (year)	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/1.73m^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 eGFR

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

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

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			.788	0.27	0.241
	p			**.000**	**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

UAE=urinary albümin excretion, UACR=urinary albümin creatinin ratio
*Correlation is significant at the 0.05 level (2-tailed).