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Association Between IL-18 and Carotid Intima-Media Thickness in Patients with Type II Diabetic Nephropathy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CD 1 Yuanyuan Zhang
EF 2 Haomiao Feng
ABG 3 Zhiyong Wei

1 Department of Endocrinology, Linyi People's Hospital, Linyi, Shandong, P.R. China
2 Department of General Surgery, Linyi People's Hospital, Linyi, Shandong, P.R. China
3 Department of Pathology, Linyi People's Hospital, Linyi, Shandong, P.R. China

Corresponding Author: Zhiyong Wei, e-mail: zhiyongweivip@yeah.net
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Background: We specifically designed this study to determine the relationship between levels of IL-8 and carotid intima-media thickness (cIMT) in patients with type 2 diabetes mellitus (T2DM).

Material/Methods: A total of 149 diabetic patients at different stages of diabetic nephropathy and 72 matched controls were recruited in this study. A wide range of parameters were measured: IL-18 (by ELISA), urinary albumin excretion rates (UAER), and carotid intima-media thickness (cIMT, by pulse wave velocity [PWV]). All the diabetic patients were treated by alprostadil.

Results: ELISA indicated that the level of IL-18 in the patient group was significantly higher compared with that in the control group. The level of IL-18 apparently increased in the higher cIMT group in T2DM patients. Serum IL-18 levels were positively correlated with cIMT in patients with T2DM, the level of IL-18 was negatively correlated with cIMT, and IL-18 levels were positively correlated to age. Moreover, IMT was positively correlated with hemoglobin A1C (HbA1C) and IL-18 levels were significantly associated with cIMT (all $P<0.05$).

Conclusions: IL-18 levels were positively correlated with atherosclerotic burden in patients with T2DM and it may be considered as a significant therapeutic target.

MeSH Keywords: Alprostadil • Atherosclerosis • Carotid Intima-Media Thickness • Diabetic Nephropathies • Receptors, Interleukin-18

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Background

Diabetes mellitus (DM), a chronic non-communicable disease, has spread around the world, with a prevalence of 9.7% [1]. Diabetic nephropathy (DN) is a major cause of chronic kidney disease and has become a leading cause of end-stage renal disease (ESRD) [2]. DN is a major microvascular complication from diabetes and the prevalence of DN is constantly increasing [3]. The pathology of DN includes glomerular basement membrane thickening, and a large number of basement membrane-like substances are observed in the mesangial area [4]. The main manifestations of DN include irreversible persistent proteinuria, progressive deterioration of renal functions, a gradual increase in the creatinine serum level, and the onset of ESRD [2]. DN accompanied by its major complications have caused a large number of deaths in diabetes patients. Researchers are puzzled by the pathogenesis of DN and they suspected that lipid disorders, hemodynamic abnormality, micro-inflammation, oxidative stress, and glomerular filtration barrier play significant roles in DN [5].

A growing number of studies have started to investigate interleukin 18 (IL-18), which is believed to be linked with DN. IL-18 is a single-chain protein of about 20.8kb size and it is a precursor polypeptide of active IL-18 [6]. Reports have revealed that IL-18 has been detected in a variety of human organs and cells [7]. However, the expression level of IL-18 in cells remains stable in the low range, but it is significantly increased during crises [8]. Studies also demonstrated that higher concentration and higher protein content of IL-18 were observed in urine [9] and the plasma IL-18 levels in DN patients were significantly increased. Researchers also obtained evidence that the serum IL-18 expression levels were positively correlated with urine protein, blood urea nitrogen, and creatinine levels [10, 11]. As suggested by Aso et al., patients with carotid intima-media thickness (cIMT) exhibited a higher level of IL-18 in the serum; therefore, IL-18 may have a relationship with cIMT [11].

CIMT indicates the thickness of the carotid artery intima and smooth muscle layer [12]. As suggested by Doppler, high-resolution color was adopted to measure the vertical distance between the endometrial upper edge and the upper edge of the outer membrane at the carotid artery intima posterior wall. Then the average value of the left and right sides were calculated as the cIMT [12]. A cIMT >1 mm not only provides evidence for thickening but also predicts cardiovascular diseases [13]. Macrovascular diseases resulting from diabetes are major causes of type 2 diabetes mellitus (T2DM) and the main pathology of T2DM is atherosclerosis [14]. As suggested by previous studies, cIMT is an independent predictor of cardiovascular diseases in which atherosclerosis can be diagnosed at early stages [15]. Apart from that, chronic hyperglycemia has been proven to play a pivotal role in atherosclerosis and research found that the level of glycosylated hemoglobin was independently correlated with cIMT. Therefore, glycosylated hemoglobin can be used to predict the risk of stroke in both diabetic and non-diabetic patients [16]. Hu et al. indicated that a significant increase in postprandial plasma glucose was an independent predictor of cIMT [17]. As a result, identifying potential risk factors that are associated with diabetes and cIMT thickening is critical to treating cardiovascular diseases related to diabetes.

In this study, we explored the correlation between IL-18 and cIMT in patients with T2DM in order to discover alternative therapeutic strategies that can be used to treat cardiovascular diseases resulting from diabetes.

Material and Methods

Subjects

We had recruited 221 subjects who consulted in the Endocrine Department of our hospital from January 2015 to January 2016: 149 T2DM patients (DN group) and 72 controls (Control group). The criteria for selecting T2DM patients was set by the American Diabetes Association (ADA) [18]. Subjects in the control group were qualified by physical examination, as well as biochemical and radiological examination. The following exclusion criteria were used: subjects who had been given clinical treatments, hyperglycemia of subjects was controlled by medication, and diet or non-insulin intake. T2DM patients were divided into 2 groups: the increased IMT group and normal IMT group. This study was approved by the Institutional Ethics Committee of Linyi People's Hospital according to the Helsinki Declaration. Informed consents were obtained from patients prior to inclusion.

Sample collection and patient measurements

Urine and blood samples were collected after overnight fasting. Samples were stored immediately at –20°C until they were prepared for the corresponding analysis. Apart from that, all patient measurements were obtained at the same time.

Subject characteristics

Blood pressure (BP), height, and weight were measured using conventional methods. BP was assessed by using a desktop sphygmomanometer. All measurements were obtained after patients were abstained from smoking and drinking for a certain period of time. Repeated measurements were carried out every 2 min and BP was calculated as the average of the 3 repeated measurements. Patients abstained from high-fat

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diet and alcohol consumption before testing. Fasting was performed after dinner. Fasting blood glucose (FBG), fasting insulin (FINS), hemoglobin A1C (HbA1C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were all measured by using venous blood samples. Blood glucose was measured by using glucose oxidase and insulin was measured by electrochemical techniques. HbA1C was determined by using High Performance Liquid Chromatography (HPLC). Blood lipid was measured by an automatic biochemical analyzer (Medical Ltd, Beijing). All of these measurements were obtained by our clinical laboratory.

Measurement of serum IL-8

IL-18 was measured by using an enzyme-linked immunosorbent assay followed by humanized monoclonal antibody (Kainuo Bio Ltd, Beijing) and ELISA kit (Biomedical laboratory, Nagoya University, Japan). The concentration of IL-18 was 12.5 pg/ml and venous blood samples were collected at 6~8 a.m. After fasting for 10~12 h; we collected the 24-h urine volume, total urine volume, and microalbuminuria (mAlb, Roche, Germany) and the corresponding urinary albumin excretion rates (UAER) were calculated.

Treatment of alprostadil

All patients were treated with alprostadil (10 ug/Qd) dissolved in 10 ml of saline solution, whereas patients in the control group were injected with 10 ml of saline solution. Measurement of blood creatinine, urine creatinine, and UAER was performed as described.

Measurement of IMT

CIMT measurements of 221 patients were performed using color the Doppler ultrasound device Aplio XV (Toshiba Medical Systems Co., Ltd., Japan), with a 7.5 MHz transducer, inspected by a trained expert measuring the distance from the leading edge of the lumen-intima interface to the leading edge of the intima-adventitia interface, which is about 1 cm proximal to the bifurcation of the carotid artery. Three measurements were made and the mean cIMT was calculated. The mean cIMT was considered normal if its value was <0.90 mm; thickening was defined if cIMT was 0.9–1.2 mm. Atherosclerosis was suggested by the whole wall of the carotid artery and a focal increase. Plaque was diagnosed if cIMT was >1.2 mm, and regular assessment of cIMT was conducted during the period of alprostadil treatment.

Formula

Body Mass Index (BMI)=weight (kg)/height^2 (m^2)

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 19.0, Illinois, USA). Measurement data are presented as mean ± standard deviation (SD). Comparisons were performed using the chi-square test. Spearman's correlation coefficient was used to analyze associations between quantitative variables and the corresponding correlation index was calculated. A *P*-value <0.05 was considered statistically significant.

Results

Subject characteristics

As shown in Table 1, the DN group (149 patients) included a total of 81 males and 68 females with an average age of 59.4±10.2 years. The control group included a total of 38 males and 34 females with an average of 61.2±10.1 years. Differences in age, sex ratio, body mass index, blood pressure, smoking, and drug consumption between the 2 groups were not significant ($P>0.05$). Significant differences in FBG, FINS, HBA1C, TG, TC, and LDL-C were observed between the 2 groups ($P<0.05$) and these figures in the DN group were significantly higher than those in the control group ($P<0.05$). Moreover, the levels of IL-18 and IMT were higher in the DN group compared with those in the control group ($P<0.05$).

Measurement of cIMT

Carotid artery ultrasonography was performed and cIMT was calculated as the average of bilateral carotid arteries (Figure 1). Localized thickening was diagnosed when IMT was ≥0.9 mm. Patients were divided into 2 groups – the IMT-thickened group (IMT ≥0.9 mm) and the IMT-normal group (IMT <0.9 mm) – based on the corresponding results of carotid artery ultrasonography.

The characteristics of the 2 groups are presented in Table 2. The IMT-thickened group had significantly higher cIMT levels than the control group ($P<0.05$) whereas age, BMI, blood pressure, and TC did not differ significantly between the 2 groups ($P>0.05$).

Differential expression of IL-18

The levels of IL-18 are demonstrated in Figure 2. Serum IL-18 level in the DN group was significantly higher than in the control group ($P<0.05$). In T2DM patients, serum IL-18 level in the IMT-thickened group was significantly different from those in the IMT-normal and control group ($P<0.05$).

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Table 1. The clinical and biochemical characteristics of patients in case group and control group.

Index	Case n=149	Control n=72	*P* value
Age	59.4±10.2	61.2±10.1	0.219
Gender			0.825
Male	81	38	
Female	68	34	
Smoker			1.000
Yes	40	20	
No	104	52	
Drug			0.598
Yes	76	34	
No	73	38	
BMI	23.5±3.3	22.9±2.8	0.185
SBP (mm Hg)	127.87±10.0	128.12±10.3	0.863
DBP (mm Hg)	76.45±7.4	76.62±8.1	0.877
FBG (mmol/L)	10.02±2.58	4.80±0.75	<0.001
FINS (mu/L)	14.43±5.35	8.17±3.20	<0.001
HBA1C (%)	8.47±1.59	4.76±0.64	<0.001
CHO (mmol/L)	4.21±0.90	4.07±0.63	0.237
TG (mmol/L)	2.08±0.58	1.30±0.64	<0.001
TC (mmol/L)	4.88±1.24	4.50±0.83	0.019
LDL-C(mmol/L)	3.24±0.41	2.10±0.52	<0.001
HDL-C (mmol/L)	1.23±0.44	1.49±0.55	<0.001
IL-18 (pg/ml)	270.3±57.3	173.9±50.6	<0.001
IMT (mm)	1.1±0.2	0.6±0.1	<0.001

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FBG – fasting blood glucose; FINS – fasting insulin; HBA1C – glycosylated hemoglobin; CHO – cholesterol; TG – triglyceride; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; IL-18 – interleukin -18; IMT – intima-media thickness. *P* value less than 0.05 represents statistical difference.

Biochemical characteristics of patients after treatment

The level of blood creatinine and blood urea nitrogen decreased significantly ($P<0.05$) after treatment. The level of 24-h UAER and creatinine clearance (Ccr) showed significant difference after treatment was applied to patients. The concentration of IL-18 and cIMT decreased significantly ($P<0.01$, Table 3).

Correlation analysis

Correlations between IL-18 and clinical characteristics in the DN group were assessed using Spearman's correlation coefficients. As shown in Tables 4, 5 and Figures 3–5, the level of IL-18 was positively correlated with age ($P<0.05$) and it appeared that IL-18 exhibited a positive correlation with HbA1C ($P=0.002$). Apart from that, positive correlations between IL-18 and cIMT was observed in the DN group (r=0.269 and $P=0.001$). Moreover, serum IL-18 and cIMT increased consistently with the deterioration of renal function (Figure 6).

Discussion

As one of the most important microvascular complications, DN occurs in 20–40% of all patients with diabetes mellitus and it affects both the morbidity and mortality of diabetics [19]. IL-18,

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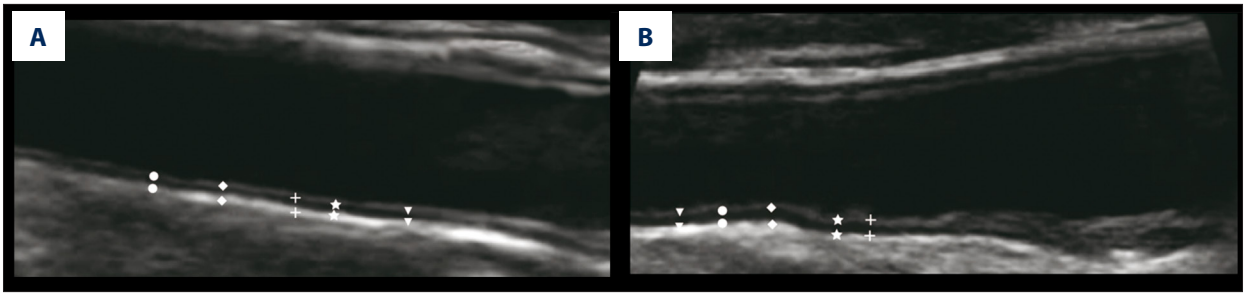

Figure 1. CIMT in the patient group (**A**) and control group (**B**) inspected by ultrasound contrast. CIMT – carotid intima-media thickness.

Table 2. The basic characteristics patients in increased IMT group and normal ITM group.

Index	Increased IMT group n=79	Normal ITM group n=70	*P* value
Age	60.3±9.9	58.4±10.3	0.254
Gender			0.728
Male	44	37	
Female	35	33	
Smoker			0.939
Yes	21	19	
No	58	51	
Drug			0.671
Yes	39	37	
No	40	33	
BMI	23.8±3.8	23.2±2.8	0.28
SBP (mm Hg)	127.62±10.3	128.12±9.6	0.761
DBP (mm Hg)	76.28±7.3	76.62±7.5	0.78
FBG (mmol/L)	10.07±2.66	9.97±2.53	0.815
FINS (mu/L)	16.09±5.79	12.76±4.90	<0.001
HBA1C (%)	8.57±1.76	8.37±1.41	0.449
CHO (mmol/L)	4.24±0.94	4.18±0.86	0.686
TG (mmol/L)	2.16±0.59	2.00±0.56	0.093
TC (mmol/L)	4.93±1.34	4.83±1.14	0.627
LDL-C(mmol/L)	3.28±0.40	3.17±0.42	0.104
HDL-C (mmol/L)	1.20±0.49	1.26±0.39	0.414
IL-18 (pg/ml)	309.3±63.9	230.6±50.7	<0.001
IMT (mm)	1.2±0.2	1.0±0.15	<0.001

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FBG – fasting blood glucose; FINS – fasting insulin; HBA1C – glycosylated hemoglobin; CHO – cholesterol; TG – triglyceride; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; IL-18 – interleukin -18; IMT – intima-media thickness. *P* value less than 0.05 represents statistical difference.

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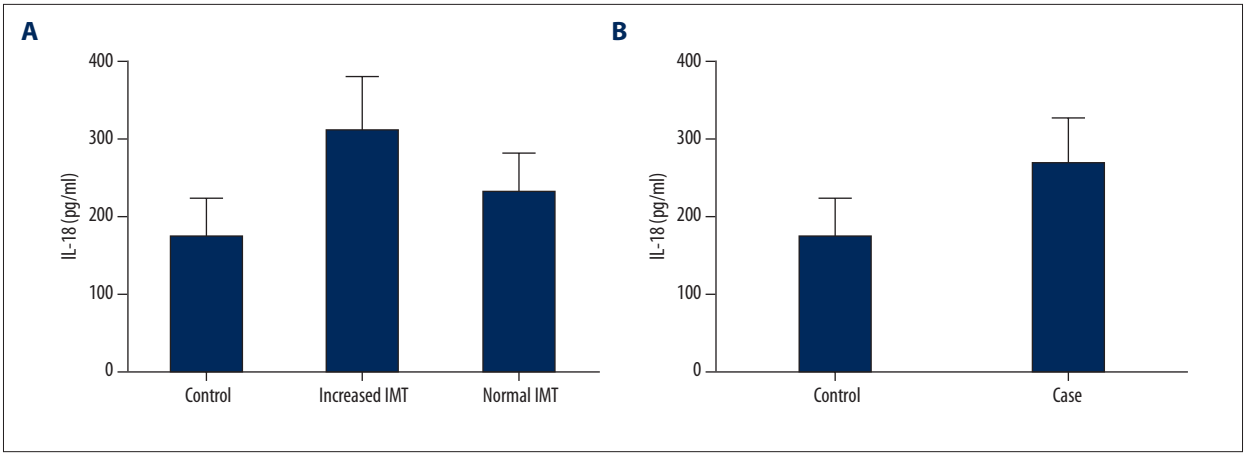

Figure 2. The expression level of IL-18 in different groups. Data were presented as mean ±SD.

Table 3. Comparison on the indexes of T2DM patients before and after therapy.

Index	Before n=149	After n=149	*P* value
24 h-urinary proteins (mg)	3.15±0.99	1.90±0.77	<0.001
Scr (μmol/L)	181.96±30.38	132.95±26.89	<0.001
BUN (mmol/L)	12.37±2.63	10.03±2.64	<0.001
UAER (mL/min)	31.64±7.85	46.59±7.75	<0.001
IL-18 (pg/mL)	403.94±43.03	271.83±62.36	<0.001
IMT (mm)	2.05±0.23	1.49±0.15	<0.001

T2DM – type 2 diabetes mellitus; IL-18 – interleukin-18; IMT – intima-media thickness; BUN – blood urea nitrogen; UAER – urinary albumin excretion rate; Scr – serum creatinine. *P* value less than 0.05 represents statistical difference.

Table 4. The analysis on the association between IL-18 and clinical information in case group.

Variable	IL-18	
	Coefficient of association	*P* value
Age	0.425	<0.001
BMI	0.089	0.278
FBG	–0.031	0.706
HBA1C	0.101	0.220
TC	0.057	0.494
TG	0.089	0.282
HDL-C	–0.117	0.156
LDL-C	–0.026	0.751

IL-18 – interleukin-18; BMI – body mass index; FBG – fasting blood glucose; HBA1C – glycosylated hemoglobin; TG – triglyceride; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol. *P* value less than 0.05 represents statistical difference.

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Table 5. The analysis on the association between IMT and clinical information in case group.

Variable	IMT	
	Coefficient of association	*P* value
Age	0.132	0.108
BMI	0.042	0.609
FBG	–0.068	0.407
HBA1C	0.162	0.048
TC	0.030	0.714
TG	0.050	0.540
HDL-C	-0.026	0.752
LDL-C	0.078	0.346

IMT – intima-media thickness; BMI – body mass index; FBG – fasting blood glucose; HBA1C – glycosylated hemoglobin; TG – triglyceride; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol. *P* value less than 0.05 represents statistical difference.

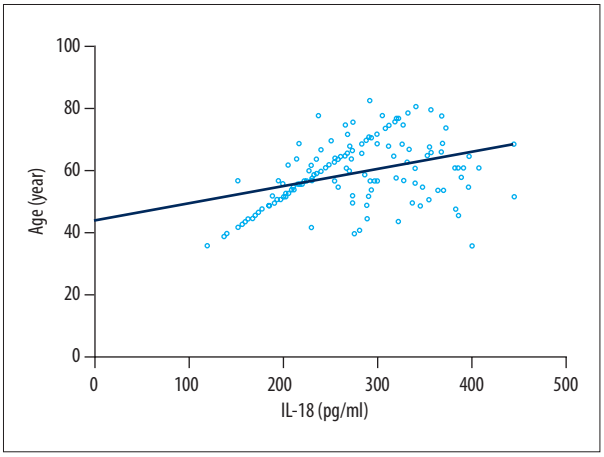

Figure 3. The correlation between age and IL-18 expression.

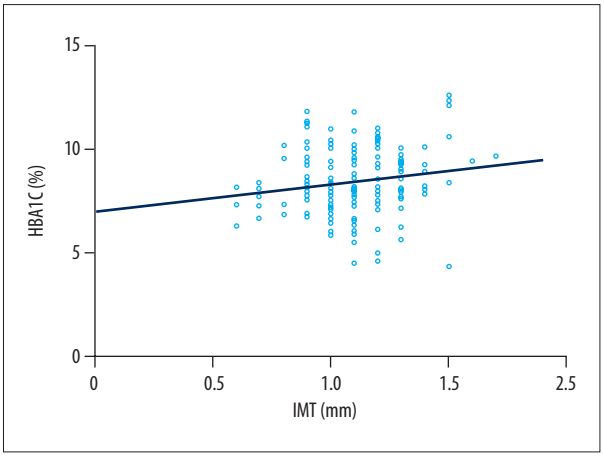

Figure 4. The correlation between IMT and HBA1C. HBA1C – hemoglobin A1C.

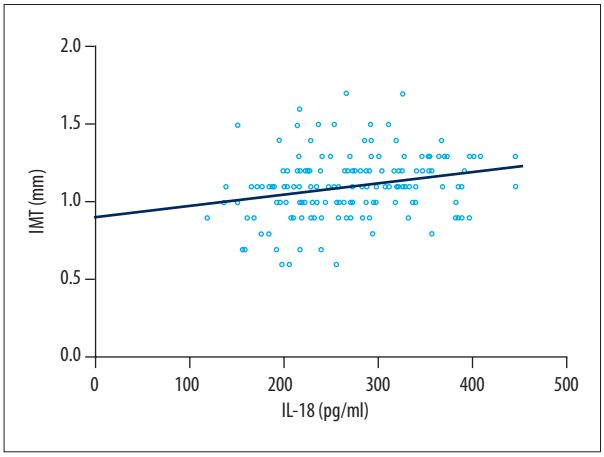

Figure 5. The correlation between IMT and IL-18 expression.

known as the precursor molecules of IL-1 family cytokines, is expected to be related with renal interstitial inflammation in the kidneys [20]. Alleviating the inflammatory condition could provide another solution to reduce the complications resulting from diabetic kidney disease [20]. Previous studies have already reported that there is an elevated serum level of IL-18 within type one diabetes mellitus (T1DM) patients [21–24], while the connection between IL-18 and T2DM has been illustrated by a few studies [25]. Although there are some suggestions that IL-18 is a marker of diabetic kidney disease in T2DM patients, its predictive power remains uncertain [26].

Recently, effective techniques have been developed to estimate the lesions in DN. CIMT is an available marker of diabetic macroangiopathy and coronary artery disease, particularly for those who experience renal function impairment [27]. Therefore, cIMT may indicate the severity of T2DM. As suggested by previous studies, no significant differences in clinical characteristics were observed between the control and T2DM group [28–30],

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but significant differences in FBG, FINS, HBA1C, TG, LDL-C, and HDL-C between the 2 groups have been demonstrated by several studies [31–33]. Our research showed significant differences in the serum level of IL-18 between the control group and case group. The levels of serum creatinine (Scr) and urea nitrogen in T2DM patients were significantly decreased after the treatment was applied to patients. Furthermore, a tremendous decrease in 24-h urine protein and Scr was discovered in T2DM patients. Surprisingly, there was a significant decrease in the serum concentration of IL-18 after the treatment.

We found that the concentrations of IL-18 and FINS in the increased IMT group were remarkably higher compared to that in the normal IMT group. Once the treatment was introduced to patients, cIMT was thinner together with a decrease in IL-18. Thus, we concluded that there is a positive relationship between IL-18 and cIMT. Another study also revealed that cIMT in patients with high levels of serum IL-18 exhibited a significantly thicker pattern [11]. In addition, cIMT is a useful tool for assessing cardiovascular diseases in diabetes [34]. Therefore, we suspected that IL-18 has a significant association with cIMT in patients with coronary artery disease (CAD).

Another interesting trend shown from our study is that the level of serum IL-18 was positively correlated with age in T2DM patients. Older patients exhibited a higher level in serum of IL-18 compared with young T2DM patients. Recent reports indicate that the expression level of IL-18 is likely to increase due to aging [35,36]. Thus, we also suspected that aging is another factor that is related to IL-18. Our results also suggested a positive correlation between cIMT and HBA1C. Since HBA1C is the only glucometabolic factor, it has been reported to be associated with the severity of CAD [37]. As suggested by an epidemiological study, HBA1C may induce cardiovascular diseases in patients with diabetes [38]. Therefore, higher levels of HBA1C may be associated with increased risk of cardiovascular diseases.

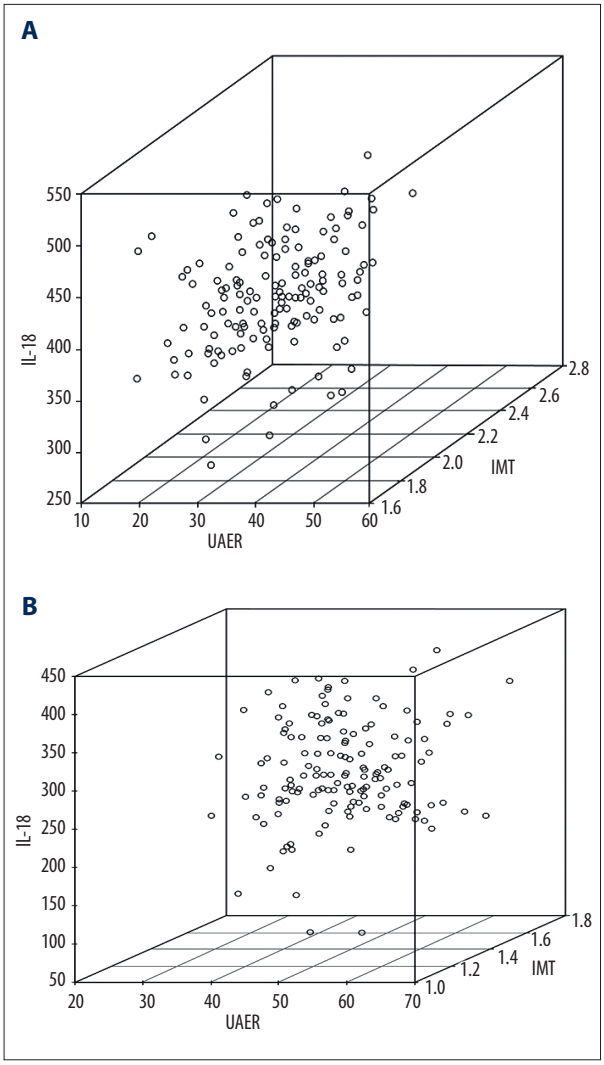

Figure 6. The correlation among UAER, IMT and IL-18 expression before (**A**) and after (**B**) alprostadil treatment. UAER – urinary albumin excretion rates.

Conclusions

There are some drawbacks within our study; for instance, it is still unclear how IL-18 is linked with T2DM, and further research on this topic is needed. Moreover, the therapy used in this research was limited to alprostadil injection, which is not able to represent the wide range of therapeutic approaches that are used in clinical practice, and future research needs to investigate other treatments in order to reach a convincing conclusion. Overall, our study illustrated that the level of serum IL-18 was much higher among T2DM patients compared to those in the control group. We found a positive correlation between the level of serum IL-18 and cIMT, which may provide clinicians with information useful in diagnosis and prognosis of T2DM.

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