Dapagliflozin improves cardiovascular risk factors in Emirati patients with T2DM

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Abstract

Background: Dapagliflozin is a sodium–glucose co-transporter-2 inhibitor that proved efficacy in reduction of blood glucose level through extrusion of glucose in urine. It is used in treatment of type 2 diabetes mellitus (T2DM). It also has reported cardiovascular and renal benefits in patients with T2DM. Data are very limited about its effects in Emirati patients with diabetes. Our aim was to evaluate dapagliflozin treatment in Emirati patients with T2DM.

Patients and methods: This is a retrospective study involving 89 diabetes patients who were using dapagliflozin 10 mg once daily as add-on therapy for 12 months. All patients had T2DM, aged over 18 years and had an estimated glomerular filtration rate (eGFR) over 60 ml/min/1.73 m². Body weight, height, body mass index, sitting blood pressure and heart rate were collected. Fasting plasma glucose, glycosylated hemoglobin (HbA1c), lipid profile and other available biochemical parameters, for example, creatinine, blood urea nitrogen, and urine albumin/creatinine ratio were traced from medical records and eGFR was calculated.

Results: Patients were aged 62.3 ± 9.4 years with a median duration of diabetes of 15 (10–20) years. Data were analyzed before, at 6 months and 12 months of treatment. Fasting plasma glucose, HbA1c, body mass index, systolic and diastolic blood pressure significantly decreased (p = 0.002, p < 0.0005, p < 0.002, p < 0.0005, p < 0.0005, respectively). The median reduction of HbA1c was 0.7% (0.2–1.2) and 0.9% (0.5–1.8) at 6 and 12 months, respectively. Systolic blood pressure decreased by a median of 7 mmHg (4–20 mmHg) and 9 mmHg (1–10 mmHg) on the 6th and 12th month of treatment, respectively, while the diastolic decreased by a median of 3 mmHg (4 to 10 mmHg) and 6 mmHg (1–10 mmHg); without increase in heart rate (p = 0.188). A significant reduction of body mass index, C-reactive protein and rate pressure product was noticed (p = 0.002, p = 0.001, p < 0.0005, respectively). No decline in eGFR or microalbuminuria was noticed. Stage I chronic kidney disease with eGFR < 90 ml/min/1.73 m² showed continuous progressive reduction of HbA1c without a significant change in other variables.

Conclusion: Our data indicate improved cardiovascular risk profile in dapagliflozin-treated Emirati patients with T2DM.

Keywords: cardiovascular, CKD, dapagliflozin, HbA1c, microalbuminuria, SGL2i

Introduction

Approximately 180 grams of glucose is filtered daily through the renal glomeruli. Most of this amount (~99.9%) is reabsorbed to the circulation by sodium-coupled transport in the proximal tubules; 90% or more of the filtered glucose is reabsorbed by the sodium glucose transporter-2 (SGLT2) in the proximal part of the proximal convoluted tubule. The rest of filtered glucose is reabsorbed by sodium–glucose transporter-1 (SGLT1) in the distal part of the proximal tubule. So, only a minimal amount of the filtered glucose (<0.1 g) passes into urine.¹ Use of SGLT2 inhibitors (SGL2i) aims at reducing the tubular capacity to reabsorb glucose, so glucose is lost in urine. This improves glycemic control and relieves glucotoxicity.² In patients with type 2 diabetes (T2DM), renal threshold for glycosuria is
elevated so that glucose appears in urine at plasma glucose $\geq 15$ mmol/L. The expression and activity of apical SGLT$_2$ and basolateral glucose transporter proteins may explain the elevated renal threshold for glycosuria in T2DM.$^3$ Dapagliflozin selectively inhibits the SGLT$_2$. Loss of glucose in urine induced by dapagliflozin treatment leads to reduction of blood glucose, irrespective of insulin sensitivity or $\beta$-cell function.$^4$

Up to 50% of patients with T2DM are obese. Weight loss improves insulin sensitivity and glycemic control.$^{2,5}$ Around 5–10% weight loss helps control of blood glucose, as well as other cardiovascular risk factors and comorbidities.$^{1,6,7}$ Dapagliflozin reduces body weight. Positive cardiovascular and renal outcomes of SGL2i, including dapagliflozin use, were demonstrated in several studies.$^{8-10}$

None of the available oral antidiabetic medications in common use reduce body weight. Metformin may and may not provide modest weight loss. Sulfonylureas and thiazolidinediones increase body weight. On the other hand, dipeptidyl peptidase-4 inhibitors are neutral in this respect.$^7$

The efficacy of dapagliflozin has been evaluated in many studies.$^{11,12}$ However, data are limited about the use of dapagliflozin in Emirati patients with T2DM. In the present study, we investigated the hypoglycemic effect of dapagliflozin, as well as its effects on body weight, blood pressure and other possible cardiovascular risk factors in a sample of this population.

**Materials and methods**

This is a retrospective observational study analyzing data of patients with T2DM who received dapagliflozin (10 mg tablet) as add-on therapy for 12 months.

The study proposal has been reviewed and approved by the MOHAP Research Ethics Committee, Sharjah (research Approval Reference No. MOHAP/DXB-REC/OON/No. 42 2019). All methods were performed in accordance with the relevant guidelines and regulations of Zulekha Hospital, Sharjah (ZHS). The ethics committee waived the need to obtain informed consent for this study.

Two hundred files of patients with diabetes who visited the endocrinology clinic at ZHS from May 2018 to May 2019 were screened. Eighty-nine patients were eligible for the study. All patients had T2DM, aged over 18 years and were using dapagliflozin 10 mg tablet as add-on therapy for the recent 12 months. We confirmed there was no change in other antidiabetic medications and there was a stable lifestyle pattern throughout the study period.

The study is a retrospective one in which dapagliflozin was prescribed per the US Food and Drug Administration (FDA), American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and international guidelines. All patients had estimated glomerular filtration rate (eGFR) $> 60$ ml/min/1.73 m$^2$. Patient exclusion was done if data were not enough, there was a change or adjustment in medication, or there was any condition that may affect the assessed variables. Insulin treatment was an exclusion criterion.

Body weight, height, body mass index (BMI), sitting blood pressure, and heart rate were collected from patient records. Fasting plasma glucose (FPG), HbA1c, lipid profile and other biochemical parameters, for example, creatinine, blood urea nitrogen, and urine albumin/creatinine ratio were traced from medical records of the patients. The Modification of Diet in Renal Disease study (MDRD) formula was used for calculation of eGFR.$^{13}$

Reviewing the protocols and methodology usually followed in our laboratory during biochemical tests revealed that blood samples were collected from all participants after 8–10h fasting, using plain ethylenediaminetetra-acetic acid and lithium heparin Vacutainers. Sera were separated by centrifuging blood at 3500 rpm for 10 min and all samples were immediately processed. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) were measured by Cobas 6000, Roche Diagnostics, modular autoanalyzer using an enzymatic colorimetric method.$^{14,15}$ Low-density lipoprotein cholesterol (LDL-C) was directly measured.$^{16}$ Blood glucose, C-reactive protein (CRP), urine albumin, and urine creatinine were determined on the same instrument by enzymatic hexokinase, turbidimetric, immunoturbidimetric, and kinetic Jaffe methods, respectively.$^{17}$ HbA1c was measured by turbidimetric inhibition immunoassay using the COBAS INTEGRA 400 plus machine, Roche Diagnostics. The final result was expressed as
HbA1c percent and is calculated from the HbA1c/hemoglobin (Hb) ratio as follows: HbA1c% = (HbA1c/Hb) × 91.5 + 2.15. Erythrocyte sedimentation rate was measured using Westergren method on Vesmatic 20, Diesse, Italy.

Statistical analysis was done for collected clinical and biochemical data. Any adverse events that occurred during the study were recorded. Two of the screened patients stopped dapagliflozin because of recurrent urinary-tract infection despite enough treatment by antibiotics according to culture and sensitivity studies. Both cases were postmenopausal females with uncontrolled diabetic state. Five patients dropped their follow up in our clinic.

Primary end points were effect on HbA1c and fasting plasma glucose. Secondary end points were effect on body weight, blood pressure, heart rate, rate pressure product (RPP), eGFR, microalbuminuria, lipid profile, and CRP.

**Statistical analysis**

Sample size: using repeated-measures analysis of variance (ANOVA) with an expected moderate effect size for HbA1c (f=0.25), a sample size of 43 participants achieves 95% power with an α-error probability of 5% and a correlation among repeated measures of 0.5. For cardiovascular risk factors, a smaller effect size (f=0.18) is suggested with an increase in the required sample size to 81 participants. Calculation was made by G*Power software program (version 3.1.9.7) written by Franz Faul (Universitat Kiel, Germany).

Data were entered and analyzed using IBM-SPSS software (version 25). Qualitative data were expressed as frequency and percentage. Quantitative data were initially tested for normality using Shapiro–Wilk’s test with data being normally distributed if p>0.050. Quantitative data were expressed as mean± standard deviation (SD) if normally distributed, or median and interquartile range (IQR) if not. Quantitative data between two groups were compared by independent-samples t test if normally distributed, or by Mann–Whitney U test if not. Paired quantitative data were compared by Wilcoxon’s test. Repeated measures were compared by repeated-measures ANOVA if normally distributed or Friedman’s test if not. Spearman’s correlation test was used to find out the association between quantitative data which were not normally distributed. For any of the used tests, results were considered as statistically significant if p≤0.05. Appropriate charts were used to graphically present the results whenever needed.

This study included 89 cases; 46 males (51.7%) and 43 females (48.3%). Our study population had a mean age of 62.3 ± 9.4 years and a median duration of diabetes of 15 (10-20) years. Median HbA1c at the start of the study for the whole group was 8.7% (7.8-10.2). Baseline characteristics are shown in Table 1.

Both clinical and biochemical parameters were analysed before and at 6 and 12 months of dapagliflozin treatment. Our analysis showed a significant reduction in fasting plasma glucose (FPG), HbA1c, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) (p= 0.002, <0.0005, 0.002, <0.0005, <0.0005 respectively) (Table 2).

The median reduction of HbA1c was 0.7 % (0.2-1.2) and 0.9 % (0.5-1.8) at 6 and 12 months, respectively. The median reduction in FPG was 1.65 mmol/l (0.18-3.38) and 2.4 mmol/l (0.58-5.63) at 6 and 12 months of treatment (Table 3). Reduction of HbA1c directly and positively correlated with baseline HbA1c (p<0.0005) (Figures 1 and 2). The reduction of these parameters was progressive all through the study time (Tables 2 and 3).

SBP decreased by a median of 7 mmHg (4-20) and 9 mmHg (2-20) on the 6th and 12th month of treatment, respectively, while the diastolic decreased by a median of 3 (4-10) and 6 (1-10) mmHg respectively. The reduction of body weight was at an average of 0.9 kg (0.74-2.38) at 6 months and 0.75 kg (1-3.08) at 12 months. Table 3 There was no decline in eGFR and no significant change in lipid profile during the study period.

Our cohort was subdivided into two groups according to the results of basal eGFR; CKD group with eGFR < 90 ml/min (n=23) and no CKD group with eGFR ≥ 90 ml/min (n=44). CKD group has statistically significant older age (65.6 ± versus 59.7 ± 7.4 years, p = 0.01) but there was no significant difference in sex distribution; male/female = 14/9 in CKD group and 21/23 in no CKD group (X²=1.046, p=0.307).
### Table 1. Baseline characteristics of the study group.

| Characteristic               | Total          | Male          | Female         | p value |
|-----------------------------|----------------|---------------|----------------|---------|
| **Sex**                     |                |               |                |         |
| Age, years ± SD             | 62.3 ± 9.4     | 63.8 ± 8.2    | 60.7 ± 10.4    | 0.119   |
| Duration of DM, years       | 15 (10–20)     | 15 (10–20)    | 12 (8–17)      | 0.204   |
| BMI, kg/m²                  | 29.4 (26.8–32.7)| 15 (10–20)    | 12 (8–17)      | 0.204   |
| FPG, mmol/dl                | 10.2 (7.9–13.2)| 10.3 (8–13.2) | 9.9 (7.6–13.1) | 0.665   |
| HbA1c%                      | 8.7 (7.8–10.2) | 9.3 (8.25–10.35) | 8.35 (7.5–9.9) | 0.013   |
| Creatinine, mmol/dl ± SD    | 79 (64.5–91.25)| 77.6 ± 20     | 83.97 ± 23.6   | 0.226   |
| SBP, mmHg                   | 131 (119.5–145)| 130 (118.5–139.25) | 138 (122–149) | 0.072   |
| DBP, mmHg                   | 77 (72–82.5)   | 78 (72.75–80) | 76 (70–85)     | 0.915   |
| Urea, mmol/dl               | 5.4 (4.1–8.4)  | 6.8 (4.1–8.6) | 4.9 (3.8–6.35) | 0.0165  |
| ACR mg/gm                   | 13 (5.1–24.5)  | 8.7 (5.4–20.1)| 14.7 (5–45.1)  | 0.117   |

Data expressed as median (25th percentile–75th percentile).

ACR, albumin creatinine ratio; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure; SD, standard deviation.

### Table 2. Changes in baseline characteristics after 6 months and 12 months dapagliflozin as add on therapy.

| Variable          | Baseline          | After 6 months    | After 12 months   | p value |
|-------------------|-------------------|-------------------|-------------------|---------|
| BMI, kg/m²        | 29.5 (26.4–32.8)  | 29.15 (26.85–32.93) | 29.05 (26.1–33.55) | 0.002   |
| FPG, mmol/dl      | 10 (7.85–13.05)   | 8 (6.5–10.1)      | 7.5 (6.3–9.6)     | 0.002   |
| Creatinine, mmol/dl | 78.5 (63.5–89) | 74 (62–92)        | 72.5 (62.5–90.75) | 0.995   |
| SBP, mmHg         | 132.8 ± 16.2      | 126.1 ± 14        | 124.1 ± 14.9      | <0.0005 |
| DBP, mmHg         | 78 (72–83)        | 75 (70–80)        | 72 (66–79)        | <0.0005 |
| Pulse, b.p.m.     | 82 (74–94)        | 82 (75–91)        | 80 (74–90)        | 0.188   |
| Blood urea, mmol/dl | 5.4 (4.1–8.4) | 6.1 (4–7.5)       | 4.8 (3.9–7.3)     | 0.361   |
| ACR, mg/gm        | 13 (5.1–24.5)     | 12.5 [5.6–28.9]   | 8 (4.2–18.1)      | 0.174   |
| HbA1c%*           | 8.7 (7.8–10.2)    | 7.8 [7.1–9.2]     | 7.6 (6.9–8.4)     | <0.0005 |
| T-C, mmol/dl      | 4 (3.25–4.9)      | 3.8 [3.3–4.7]     | 3.9 [3.3–5.1]     | 0.990   |
| eGFR, ml/min/1.73 m² ± SD | 102.4 ± 41.2 | 104.4 ± 39       | 105 ± 45.8        | 0.606   |
| LDL-C, mmol/dl    | 2.24 (1.76–2.88)  | 2.10 (1.65–2.8)   | 2.21 (1.67–3.3)   | 0.964   |
| HDL-C, mmol/dl ± SD | 1.18 ± 0.27   | 1.26 ± 0.35       | 1.26 ± 0.30       | 0.063   |
| TG, mmol/dl       | 1.21 (0.88–1.7)   | 1.26 (0.86–1.7)   | 1.25 (0.8–1.82)   | 0.728   |

Bold numerals indicate statistical significance.

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beat per minute; ACR, albumin creatinine ratio; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; T-C, total cholesterol; TG, triglycerides.
Continuous progressive reduction of HbA1c was observed in patients with stage I chronic kidney disease (eGFR < 90 ml/min/1.73m²). No significant change in other parameters in this group as regard to BMI, eGFR or serum creatinine (Table 4).

There was an observable decline in microalbuminuria and urine albumin/creatinine ratio particularly at 12-months, but this did not reach a statistical significance \( (p=0.174) \). However, the marked reduction in microalbuminuria was observed in 3 patients of the study group who had significantly high urinary microalbumin at the start of the study.

Most interestingly is the significant reduction of C-reactive protein (CRP) at 12 months, in patients who had high level at the start of treatment \( (p=0.011) \) (Figure 3).

Rate Pressure Product, was also significantly and progressively reduced all through our study period \( (p<0.0005) \) (Table 2).

**Discussion**

Dapagliflozin causes a urinary loss of 60–80 grams of glucose per day. This equates to a negative energy balance of 240–320 calories per day, or 0.9–1.3 kg weight loss per month.\(^7\),\(^19\) It leads to reduction of blood glucose with recovery from glucotoxicity, improvement of insulin sensitivity and increased insulin-mediated skeletal muscle glucose disposal.\(^20\) Reduced hyperinsulinemia protects many organs from abnormal vasoreactivity, angiogenesis, and fibrogenesis.\(^21\),\(^22\),\(^23\)

In our study, the reduction in HbA1c was greater than that mentioned by Vasilakou et al. \( (0.7\% \text{ versus } 0.61\% \text{ and } 0.9\% \text{ versus } 0.52\% \text{ at } 6 \text{ months and } 12 \text{ months, respectively}) \).\(^24\)

Efficacy of dapagliflozin in Qatari patients with type 2 diabetes was tested by Al Adawi et al.\(^25\) The study period was 12 months, and patients had a mean age of 57.0 ± 9.0 years and a mean baseline HbA1c of 9.0 ± 1.4%. In her study, dapagliflozin decreased HbA1c by 0.8% after 6 months, and by 1.5% after 12 months. More reduction of HbA1c in the Qatari population can be explained by different patient criteria, including higher baseline HbA1c. In our study, the degree of reduction of HbA1c was directly proportionate to the baseline level.

Weight loss was noticed in patients with T2DM treated by dapagliflozin and other SGL2i, by several authors.\(^26\),\(^27\) Bolinder et al. explained weight loss by reduced total body fat mass, visceral and
subcutaneous. Weight loss in Bolinder’s study was in the range of 1–2 kg over a period of 6 months. In Cai’s study, the mean weight loss induced by dapagliflozin 10 mg daily was 1.79 kg. In Manuel’s study, body weight decreased by 1.7 kg with the 5 mg dapagliflozin, and 2.2 kg with the 10 mg dose, compared with placebo.

Here, we report a median weight loss of 0.9 kg after 6 months and 0.75 kg at 1 year (Table 3).

Table 3. The median changes in clinico-laboratory variables at 6 months and 12 months of treatment.

| Variable | Change in 6 months | Change in 12 months |
|----------|--------------------|---------------------|
| FPG      | 1.65 (0.18–3.38)   | 2.4 (0.58–5.63)     |
| HbA1c    | 0.7 (0.2–1.2)      | 0.9 (0.5–1.8)       |
| SBP      | 7 (4–20)           | 9 (2–20)            |
| DBP      | 3 (4–10)           | 6 (1–10)            |
| Weight   | 0.90 (0.74–2.38)   | 0.75 (1–3.08)       |
| BMI      | 0.30 (0.2–0.9)     | 0.35 (0.4–1.38)     |
| eGFR     | 0.42 (10.2–11.5)   | 1.41 (15–16.9)      |

Data expressed as median (25th percentile–75th percentile).
BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; SD, standard deviation.

Inability to lose more weight may be explained by the sedentary lifestyle and dietary habits of patients at this age and in this region with high prevalence of diabetes. Weight loss further improves insulin sensitivity and decreases blood glucose and HbA1c.

The blood-pressure-lowering effect of dapagliflozin may be explained by the significant reduction of tissue sodium content as demonstrated by Karg et al. Decrease in body sodium is of special significance in patients with T2DM who are known to retain more sodium in their bodies. Sodium retention increases the risk of cardiovascular complications.

SGLT2 inhibition blocks both glucose and sodium reabsorption in the proximal tubular cells. This leads to osmotic diuresis and natriuresis with reduction of SBP and DBP, and weight loss as well. Reduction of blood pressure may be also attributed to weight loss.

In agreement with previous studies, the use of dapagliflozin in our population was associated with a significant reduction of both SBP (7 mmHg and 9 mmHg at 6 months and 12 months, respectively, \( p < 0.0005 \)) and DBP (3 mmHg and 6 mmHg at 6 months and 12 months, respectively, \( p < 0.0005 \)), Tables 2 and 3.

However, similar to our study, Heerspink et al. reported changes in HbA1c, SBP, and body weight of 0.5% (0.7–0.3%), 3.5 mmHg (5.9–1.0 mmHg) and 0.76 kg (1.2–0.26 kg), respectively.
It is worthwhile mentioning that reduction of blood pressure in our patients was not associated with increase in heart rate ($p = 0.188$). Glucose-lowering treatments that reduce body weight and SBP without affecting heart rate are of special value in diabetes patients.37 This is particularly important in patients with CKD. Studies indicate that higher resting heart rate is a risk factor for end-stage renal disease and CKD-related hospitalizations.38

We also report a significant reduction in the RPP at 6 months and 12 months of treatment ($p < 0.0005$). RPP is used to determine the myocardial energy requirement and oxygen consumption.37,38 Reduction in RPP indicates decreased cardiac work and oxygen consumption at rest. This may explain the improved quality of life and decreased hospitalization of heart failure patients and reduced incidence of type 2 myocardial infarction in patients using dapagliflozin, as mentioned in the DEFINE and DECLARE-TIMI 58 studies.40–42

Dapagliflozin treatment was found to suppress atherogenic small dense LDL-C and increase HDL-C.43 In our study, we did not notice a significant effect of dapagliflozin on lipid profile.

Different studies reported improved endothelial function, reduction of arterial stiffness and renal resistive index in T2DM patients with use of dapagliflozin.44–46 Improvement of endothelial function and improved parameters of early vascular remodeling may be interpreted in our study by the significant reduction in CRP in patients who initially had a high level before starting treatment, Figure 3.

Approximately 30–40% of diabetes patients have CKD and so drug safety in this group of patients is important during management of diabetes.47

Heerspink et al.36 reported a significant reduction of microalbuminuria. Heerspink et al. found a reduction by at least 30% in 50% of patients with microalbuminuria. In our study, marked reduction was observed in few patients who already had significantly high microalbumin in urine, but the change in the whole study group did not reach a statistical significance.

Similar to our observation, Manuel et al.29 showed no significant difference in eGFR or microalbuminuria at 24 weeks of treatment. The same observation was also demonstrated by Fioretto et al.48

Most studies which explored the efficacy and safety of SGLT2i in patients with impaired kidney function have predominantly included patients with stage 3 CKD (eGFR 30–60 ml/min/1.73 m²), and have demonstrated that the glucose-lowering efficacy of SGLT2i in these patients is diminished compared with patients with normal kidney function.48,49 Claire et al. did not find a significant change in HbA1c in patients with T2DM having stages 3b–4 CKD, but there was a decrease in urinary albumin, blood pressure and body weight, to a clinically significant extent.50–54

In our study, in patients with eGFR $<90$ ml/min/1.73 m² (stage I CKD), dapagliflozin reduced HbA1c over a period of 1 year without further deterioration of eGFR ($p = 0.806$), Table 4.
Few side effects were reported in our study subjects such as constipation and abdominal distension. Only two patients stopped the medicine because of recurrent urinary-tract infection. Both were post-menopausal females above 60 years of age with high blood glucose.

Our study has several limitations including its retrospective design, small sample size, and lack of more informative metabolic parameters for obesity, insulin resistance, and β-cell function.

**Conclusion**
In conclusion, our data indicate improved cardiovascular risk factor profile in the form of reduction of body weight, BMI, blood pressure, RPP, FPG, HbA1c, and CRP.

**Author’s note**
Aml Mohamed Nada is also affiliated with Mansoura Medical School, Egypt.

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**Author contribution**
Dr AM Nada, the corresponding author, contributed to the study design, data collection and analysis, manuscript writing, and review and submission process. Dr M Younan contributed to the study design and laboratory work. She contributed to writing the manuscript with certain emphasis on the laboratory aspect, and strictly revised the manuscript.

**Conflict of interest statement**
The authors declare that there is no conflict of interest.

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