Follow Up of Value of the Intrarenal Resistivity Indices and Different Renal Biomarkers for Early Identification of Diabetic Nephropathy in Type 1 Diabetic Patients

Soha M. Abd El Dayem∗, Abo El Magd El Bohy⊥, Mona Hamed‡, Solaf Ahmed§

1Pediatrics Department, National Research Centre, Cairo, Egypt; 2Radiology Department, Cairo University, Cairo, Egypt; 3Clinical Pathology Department, National Research Centre, Cairo, Egypt

Abstract

AIM: To evaluate intrarenal resistivity index (RI) and different biomarkers of diabetic nephropathy (DN) with clinical signs of DN and its progression over time as early detection of DN.

PATIENTS AND METHODS: This longitudinal study included 48 type 1 diabetic patients who were studied at baseline and after three years. A blood sample was taken for assessment of glycosylated haemoglobin (HbA1), lipid profile and a urine sample was taken for assessment of albumin/creatinine ratio, Neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid binding protein (L-FABP) and kidney injury molecule-1 (KIM-1) at baseline and after three years.

RESULTS: HbA1, waist/hip ratio, albumin/creatinine ratio, lipid profile, NGAL, KIM-1, L-FABP and resistivity index (RI) were significantly increased in follow-up. Twenty patients (41.7%) showed progression to albuminuria. RI showed a significant increase in follow-up study. ROC curve showed that RI and NGAL had the highest sensitivity (100%), followed by L-FABP (90%) and lastly KIM-1 (63.6%) in the prediction of DN.

CONCLUSION: High RI, NGAL, KIM-1 & L-FABP can be considered as early markers of diabetic nephropathy in type 1 diabetes and are associated with its progression over time, independent of albuminuria.

Introduction

As a result of rising prevalence of type 1 diabetes, its complications including diabetic nephropathy (DN) affect more patients, but these complications rarely present clinically in childhood and adolescence. However, early functional and structural abnormalities may be present a few years after the onset of the disease [1-4]. Consequently, early sensitive markers that reflect the stage and course of diabetic nephropathy are needed to prevent progression to end-stage renal disease and dialysis as 1 of 3 patients with diabetic nephropathy develops end-stage renal disease (ESRD) [5] and the cumulative incidence of ESRD is 8%, 30 years after onset of type 1 diabetes (T1D) [6].

Our previous study [4] and many other recent studies [7-9] have shown that intrarenal resistivity index (RI), Neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid binding protein (L-FABP) and kidney injury molecule-1 (KIM-1) are promising early highly sensitive and highly specific (especially NGAL) markers for diagnosis of DN even in pre albuminuric stage because it has been shown that renal tubular damage can precede microalbuminuria and consequently allow early detection of DN, offering a good chance for delaying or even preventing progression to end-stage renal disease. However, the role of these early markers in the progression of diabetic nephropathy needs further evaluation.

Previous studies including our previous study [4] have shown that urinary levels of the tubular markers NGAL and KIM-1 [9, 10] and urinary L-FABP [11, 12] are increased in type 1 diabetic (T1D) patients, even before they develop signs of glomerular damage, i.e. micro- or macroalbuminuria. Also, u-NGAL is increased in type 1 diabetic patients compared to healthy controls, and increases with increasing levels of albuminuria [4, 10], so NGAL
represents an early biomarker of ‘normoalbuminuric’ DN with a good sensitivity and specificity.

In the current work, we are aiming to explore and evaluate whether increased intrarenal resistivity index (RI) and increased different biomarkers of diabetic nephropathy (DN) are associated with clinical signs of DN and its progression over time i.e. predictors of progression thus representing important non-invasive tests to make precocious diagnosis of “normoalbuminuric” DN.

Patients and Methods

Patients

This longitudinal study included 48 type 1 diabetic patients among those attending to the endocrine clinic, National Research Centre, who were studied at baseline and after three years.

Inclusion criteria at baseline: Patients with duration of disease > 5 years, patients age > 14 and < 19 yrs old.

Exclusion criteria were as follows: Patients during acute diabetic complications e.g. diabetic ketoacidosis (DKA) or hypoglycemia, Patients suffering from cardiac diseases e.g. congenital, rheumatic heart, left ventricular dysfunction, Patients receiving drugs for cardiovascular disease.

Study design and protocol

It is a longitudinal study done after obtaining approval from the ethical committee of the National Research Centre, Cairo, Egypt. The registration number is 14058. It conforms to the provisions of the Declaration of Helsinki (as revised in Edinburgh 2000). Written informed consent was obtained from all patients, their parents and controls after a full discussion about the aim of the study. This study is a part of a project done at the National Research Centre in collaboration with Cairo University for evaluation of cardiac, vascular and endothelial function in adolescent type 1 diabetic patients.

All the studied patients were subjected to history taking including the age of patients, sex, the age of onset of diabetes, duration of diabetes, type and dose of insulin therapy, family history of diabetes. We asked about the presence of any symptoms of cardiac, renal, neurological affection or presence of any autonomic dysfunction. We also asked about the history of taking drugs other than insulin.

Patients were subjected, at baseline and after three years, for general, cardiac, chest and neurological examination.

Blood pressure was measured three times for patients after 5-minute rest in the sitting position on both upper limbs with the use of automatic manometer (Omron M4 Plus, Omron Health care Europe, Hoof drop, and Holland). The mean value of the second and the third measurement was calculated. The measurements taken on the dominant limb were analysed.

All patients underwent the following tests at baseline and after three years:

For cholesterol measurements, venous blood was sampled after 12 hr fast. Serum total cholesterol was determined by a commercial kit (Boehringer-Mannheim, Germany). High-density lipoprotein (HDL) cholesterol was separated from the serum by precipitation of the other lipoproteins with a heparin/manganese procedure [13]. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. The concentration of triglycerides was measured in a TechnoCon AutoAnalyzer II (TechnoCon Instruments, Tarrytown, New York).

Glycosylated haemoglobin (HbA1) was determined spectrophotometrically using commercially kit supplied by Stanbio, USA according to the method described by Trivelli et al. [14]. Glycosylated haemoglobin (HbA1) was done every three months, and the mean value was calculated from the four readings of the last year, at baseline and after three years.

Screening for microalbuminuria was assessed in fresh morning urine samples by measuring albumin/creatinine ratio by enzyme-linked immunosorbent assay (ELISA) kit provided by (Orgentec Diagnostika, Gmbh, Mainz, Germany) [15]. Freshly voided urine specimens were collected early in the morning from patients and controls. Urine samples were placed at 4°C and transported directly to the laboratory where they were centrifuged to remove sediment and frozen in aliquots at −80°C for further analysis. Urinary biomarkers levels were standardised to urine creatinine measured in the same spot urine and expressed related to mg Cr.

Urinary NGAL and KIM-1 were assessed by enzyme-linked immunosorbent assay (ELISA) using a kit from Quantikine; R & D Systems, Minneapolis; USA. L-FABP was measured with a commercially available ELISA kit according to manufacturer's protocol (Biovendor Laboratory Medicine, Brno, Czech Republic). The inter- and intraassay coefficients of variation for NGAL, KIM-1, and L-FABP were <10%. The measurements were made in duplicate and a blinded fashion.

Only 40 patients were subjected to renal colour duplex ultrasound scans at baseline & after three years, using 3-6 MHz convex array transducer (Toshiba, Xario ultrasound machine). Patients were
scanned in the supine position. The transducer was placed in longitudinal position just to the Lt. of the midline, recording colour flow & Doppler spectrum from the abdominal aorta where peak systolic velocity of the abdominal aorta was recorded. Then, the transducer was placed in transverse position just distal to the origin of superior mesenteric artery, to achieve transverse view of the aorta at the origins of both renal arteries where peak systolic velocity of both renal arteries was recorded, and renal artery stenosis was ruled out in all patients by tracing and examining different segments of both renal arteries form origin to renal hilum. Then, resistivity indices were recorded in the segmental, interlobar and arcuate arteries, on both sides.

### Statistical Analysis

T-test for dependent and independent variables was used for analysis of data. McNemar test was also used. ROC curve was used for detection of cut-off value for detection of best sensitivity and specificity of NGAL, KIM-1, L-FABP and RI.

### Results

This longitudinal study included 48 type 1 diabetic patients who were studied at baseline and after three years.

#### Table 1: Descriptive statistics of basal demographic, anthropometric and laboratory data of diabetic patients

| Variable                              | Basal Mean | SD | Basal Minimum | Basal Maximum |
|---------------------------------------|------------|----|---------------|---------------|
| Age (yrs)                             | 19.30      | 1.58 | 16.17         | 20.50         |
| Duration of disease (yrs)             | 5.00       | 1.97 | 13.60         | 16.90         |
| Insulin (U/l)                         | 0.77       | 0.32 | 0.23          | 1.38          |
| Systolic blood pressure (mmHg)        | 100.00     | 1.64 | 99.00         | 105.00        |
| Diastolic blood pressure (mmHg)       | 60.00      | 9.66 | 50.10         | 80.00         |
| Waist circumference (cm)              | 69.00      | 8.76 | 53.10         | 82.76         |
| Hip circumference (cm)                | 78.50      | 7.21 | 62.10         | 91.70         |
| Waist/hip ratio                       | 0.78       | 0.07 | 0.60          | 0.97          |
| Waist/hip ratio                       | 0.42       | 0.06 | 0.25          | 0.51          |
| BMI (SDS)                             | -1.10      | 0.89 | -4.20         | 2.70          |
| BMI (Kg/m²)                           | 19.20      | 2.61 | 13.40         | 24.30         |
| Hba1 (%)                              | 5.80       | 1.66 | 4.50          | 8.98          |
| Albumin/creatinine ratio (µg/l)       | 7.61       | 3.87 | 1.96          | 33.48         |
| Cholesterol (mg/dl)                   | 100.00     | 70.83 | 43.00        | 188.7         |
| Triglycerides (mg/dl)                 | 35.00      | 58.22 | 14.00         | 180.00        |
| HDL-c (mg/dl)                         | 21.00      | 22.99 | 13.60         | 51.68         |
| LDL-c (mg/dl)                         | 22.00      | 33.36 | 10.00         | 111.86        |
| OxLDL (mg/dl)                         | 8.70       | 7.16 | 4.00          | 18.35         |
| Urinary NGAL (g/l)                    | 57.00      | 62.73 | 17.50         | 178.00        |
| Urinary L-FABP (µg/g creatinine)      | 1.50       | 26.14 | 58.60         | 54.15         |
| Resistivity Index                     | 0.55       | 0.04 | 0.40          | 0.74          |

#### Table 2: Descriptive statistics of follow-up demographic, anthropometric and laboratory data of diabetic patients

| Variable                              | Follow-up Mean | SD | Follow-up Minimum | Follow-up Maximum |
|---------------------------------------|----------------|----|--------------------|-------------------|
| Age (yrs)                             | 17.00          | 1.52 | 19.46             | 14.96             |
| Duration of disease (yrs)             | 8.00           | 3.59 | 12.00             | 5.50              |
| Onset of disease (yrs)                | 1.50           | 7.34 | 17.50             | 14.70             |
| Systolic blood pressure (mmHg)        | 100.00         | 13.0 | 120.00            | 100.00            |
| Diastolic blood pressure (mmHg)       | 50.00          | 8.86 | 80.49             | 40.00             |
| Waist circumference (cm)              | 50.00          | 10.67 | 81.88            | 30.00             |
| Hip circumference (cm)                | 75.00          | 8.59 | 113.00            | 45.56             |
| Hba1 (%)                              | 6.00           | 1.84 | 15.00             | 9.51              |
| Albumin/creatinine ratio (µg/l)       | 11.00          | 103.0 | 400.00           | 39.90             |
| Cholesterol (mg/dl)                   | 420.00         | 74.60 | 200.00           | 87.00             |
| Triglycerides (mg/dl)                 | 36.00          | 58.46 | 288.00           | 116.63            |
| HDL-c (mg/dl)                         | 20.00          | 19.96 | 130.00           | 50.91             |
| LDL-c (mg/dl)                         | 38.00          | 39.90 | 231.00           | 117.56            |
| OxLDL (mg/dl)                         | 1.30           | 15.13 | 7.86             | 43.93             |
| Urinary NGAL (g/l)                    | 25.70          | 72.81 | 410.70           | 212.41            |
| Urinary KIM-1 (mg/g creatinine)       | 0.10           | 90.24 | 46.30            | 145.08            |
| Urinary L-FABP (µg/g creatinine)      | 2.00           | 28.96 | 120.00           | 20.19             |

#### Table 3: Comparison between demographic, laboratory data and renai Doppler at the beginning and after three years follow-up in type 1 diabetic patients (n = 48)

| Variable                              | Basal Mean | SD | Basal Minimum | Basal Maximum |
|---------------------------------------|------------|----|---------------|---------------|
| Demographic data:                     |            |    |               |               |
| Systolic blood pressure (mmHg)        | 119         | 0.7 | 13.64         | 120            |
| Diastolic blood pressure (mmHg)       | 76.95       | 0.04 | 10.66         | 80.49          |
| BMI (Kg/m²)                           | 24.47       | 0.7 | 3.81          | 24.67          |
| Waist/hip ratio                       | 0.87        | 0.02 | 0.09          | 0.97           |
| Waist/height ratio                    | 0.51        | 0.03 | 0.06          | 0.73           |
| Laboratory data:                      |            |    |               |               |
| Hba1 (%)                              | 8.98        | 0.003 | 1.84         | 9.51            |
| Albumin/creatinine ratio (µg/l)       | 25.64       | 0.007 | 45.94         | 87.00           |
| Cholesterol (mg/dl)                   | 188.7       | 0.002 | 70.83         | 208.8           |
| Triglycerides (mg/dl)                 | 96.63       | 0.002 | 58.22         | 116.83          |
| HDL-c (mg/dl)                         | 51.68       | 0.001 | 22.99         | 19.66           |
| LDL-c (mg/dl)                         | 116.6       | 0.002 | 33.66         | 117.56          |
| OxLDL (mg/dl)                         | 18.35       | 0.006 | 7.16          | 15.16           |
| Urinary NGAL (g/l)                    | 178.50      | 0.002 | 62.73         | 212.41          |
| Urinary KIM-1 (mg/g creatinine)       | 70.69       | 0.001 | 51.37         | 145.08          |
| Urinary L-FABP (µg/g creatinine)      | 15.41       | 0.001 | 26.14         | 20.19           |
| Resistivity Index                     | 0.60        | 0.03 | 0.46          | 0.66            |

Only 40 diabetic patients did renai Doppler, while all patients did all laboratory investigation, at baseline and after three years. Descriptive statistics of demographic, anthropometric and laboratory data (basal and after three years) of diabetic patients were shown in Tables 1 and 2. Comparison between demographic, laboratory data and resistivity index of patients at baseline and after three years, were shown in Table 3.

The studied group comprised of 26 females and 22 males, with a baseline mean age of 16.17 ± 1.58 years and duration of diabetes of 9.17 ± 2.87 years and a follow-up mean age of 19.46 ± 1.52 years and duration of diabetes of 12 ± 3.59 years. All diabetic patients were on intensive insulin therapy regimen.
Basal NGAL, KIM-1, L-FABP & R.I. were high in diabetic patients who progressed to albuminuria and noted in 80%, 55%, 45% & 30% respectively at baseline (Table 5).

Table 5: Frequency distribution of basal level of NEGAL, KIM-1, L-FABP and resistivity index in diabetic patients with progressive albuminuria (N=20)

| Variables       | Basal | Progressed |
|-----------------|-------|------------|
|                 | N     | %          |
| NGAL            |       |            |
| Normal          | 4     | 20         |
| Abnormal        | 16    | 80         |
| KIM-1           |       |            |
| Normal          | 9     | 45         |
| Abnormal        | 11    | 55         |
| L-FABP          |       |            |
| Normal          | 11    | 55         |
| Abnormal        | 9     | 45         |
| Resistivity Index|     |            |
| Normal          | 14    | 70         |
| Abnormal        | 6     | 30         |

NGAL, neutrophil gelatinase-associated lipocalin; L-FABP, liver-type fatty acid binding protein; Kim-1, urine levels of kidney injury molecule-1.

RI showed a significant increase in follow-up study where R.I. was abnormally increased in 9 patients (22.5%) at baseline while increased in 33 patients (82.5%) in the follow-up study after three years (P value = 0.0001) (Table 6).

Table 6: Comparison between resistivity index at the beginning and after three years follow-up (N = 40)

| Variables       | Basal | Follow-up |
|-----------------|-------|-----------|
|                 | N     | %         |
| NGAL (N = 31)   | 5     | 16.1      |
|                 |       | 26        |
|                 |       | 83.9      |
|                 |       | 0.0001    |
| Abnormal (N = 9)| 2     | 22.2      |
|                 |       | 7         |
|                 |       | 77.8      |

McNamara test was used for analysis of data. What abnormal resistivity index after three years follow-up was significantly higher in diabetic patients. The bold value in the table indicates significance.

ROC curve showed that RI and NGAL had the highest sensitivity (100%), followed by L-FABP (90%) and lastly was KIM-1 (63.6%) in the prediction of DN (Table 7).

Table 7: ROC curve of basal resistivity index, NEGAL, KIM-1 and L-FABP of diabetic patients

| Variables       | Cut off | Area under the curve | SE | 95% C.I. | Sensitivity | Specificity | PPV | NPV |
|-----------------|---------|----------------------|----|----------|-------------|-------------|-----|-----|
| RI              | 0.575   | 0.645                | 0.066 | 0.941 | 69.8 - 87.7 | 61.5 - 82.7 | 1.39 | 0.59 |
| NGAL            | >0.5    | >0.5                 | >0.5 | >0.5    | >0.5        | >0.5        | >0.5 | >0.5 |
| KIM-1           | >89     | >89                  | >89  | >89     | >89         | >89         | >89  | >89  |
| L-FABP          | >28.2   | 0.527 - 0.752        | 0.487 - 0.716 | 0.862 - 0.982 | 63.8 - 95.0 | 61.5 - 87.7 | 1.39 | 0.59 |

PPV = Positive predictive value; NPV = Negative predictive value; C.I. = Confidence interval; NGAL = neutrophil gelatinase associated lipocalin; L-FABP = liver-type fatty acid binding protein; Kim-1, urine levels of kidney injury molecule-1; RI = resistivity index.

Discussion

Early management of DN is very important to prevent progression to end-stage renal disease and dialysis, and the current commonly used parameter to diagnose DN is microalbuminuria which is a non-optional biomarker with low sensitivity and specificity, so there is a necessity to explore and evaluate whether increased intrarenal resistivity index (RI) and increased different biomarkers, like NGAL, KIM-1 and L-FABP are associated with clinical signs of DN and its progression over time i.e. predictors of progression.

In our previous cross-sectional study [4], we have found that R.I., NGAL, L-FABP & KIM-1 are increased in type 1 diabetic patients compared to normal controls, and increase with increasing levels of albuminuria. Being a cross-sectional study, it does not describe the time perspective or causality, so these findings inspired us to look at these markers in a longitudinal study.

The current longitudinal study revealed significantly increased HbA1, diastolic blood pressure, waist/hip ratio, albumin/creatinine ratio, lipid profile, NGAL, KIM-1, L-FABP and RI in the follow up after three years and twenty patients (41.7%) progressed to albuminuria while the remaining 28 patients (58.3%) showed stationary or regressed albuminuria.

The progressed group showed increased basal RI but not statistically significant (p = 0.09) as R.I. was increased in diabetic patients who progressed to albuminuria in 30% at baseline. RI showed a significant increase in follow-up a study where R.I. was abnormally increased in 9 patients (22.5%) at baseline while increased in 33 patients (82.5%) in the follow-up study after three years (P value = 0.0001). ROC curve revealed that RI showed a sensitivity of 100% in the prediction of DN. Our results are in agreement with the results seen in type 1 diabetic patients of many previous studies that demonstrated increased resistivity indices early in the course of DN in the pre-albuminuric stage [4, 16, 17]. Also, Masulli et al. [18] reported similar results but in type 2 diabetic patients as they found that high RI is associated with features of DN and its progression over time, independent of albuminuria.

In our study, the progressed group showed significantly high basal NGAL (p = 0.01), basal KIM-1 (p = 0.01) & basal L-FABP (p = 0.04) where basal NGAL, KIM-1, & L-FABP were high in diabetic patients who progressed to albuminuria in 80%, 55% & 45%, respectively at baseline. NGAL, KIM-1 & L-FABP showed significant increase in follow-up (P values = 0.002, 0.0001, and 0.01 respectively). ROC curve revealed that NGAL showed a sensitivity of 100%, followed by L-FABP (90%) and lastly is KIM-1 (63.6%) in the prediction of DN. Our results are
comparable with the previous studies on diabetic patients that found that the levels of NGAL, KIM-1 and L-FABP are increased in type 1 diabetic patients, even before they develop albuminuria and also found that their levels were increased with increasing levels of albuminuria [4, 9-12, 19]. We found that NGAL has the highest sensitivity (100%) in the prediction of DN in line with the previous study that found a positive correlation between uNGAL and albuminuria and concluded that NGAL measurement could be useful for the evaluation of early renal involvement in the course of diabetes [19].

We conclude that resistivity indices and renal tubular biomarkers are increased before the appearance of pathological albuminuria, which is the earlier measurable sign of renal diabetic involvement, supporting the hypothesis of a tubular phase of DN preceding the glomerular phase and consequently, the increase in R.I. and renal tubular biomarkers’ values could express the degree of subclinical tubular impairment preceding the classic glomerular signs. R.I. and these new tubular biomarkers offer an advantage to urinary albumin on early detection of DN. We recommend these non-invasive tests for monitoring type 1 diabetic patients to predict those at risk of diabetic nephropathy as this longitudinal study design allow us to conclude that RI and tubular biomarkers precede the development of diabetic nephropathy and microalbuminuria.

References

1. Chiarelli F, Ciullo F, Romano F, Tuminì S, Costantini F, et al. Increased circulating nitric oxide in young patients with type 1 diabetes and persistent microalbuminuria: relation to glomerular hyperfiltration. Diabetes. 2000;49:1258–63. https://doi.org/10.2337/diabetes.49.7.1258 PMid:10909986
2. Savino A, Pelliccia P, Schiavone C, Primavera A, Tuminì S, et al. Serum and urinary nitrates and nitrites and Doppler sonography in children with diabetes. Diabetes Care. 2006;29:2676–81. https://doi.org/10.2337/dc06-0348 PMid:17130204
3. Komers R, Anderson S. Paradoxes of nitric oxide in the diabetic kidney. Am J Physiol Renal Physiol. 2003;284:F1121–8. https://doi.org/10.1152/ajprenal.00265.2002 PMid:12736164
4. Abd El Dayem S, El Bohy A and El Shehaby A. Value of the intrarenal arterial resistivity indices and different renal biomarkers for early identification of diabetic nephropathy in type 1 diabetic patients. J Pediatr Endocrinol Metab. 2015; aop.
5. Parving HH, Jacobsen P, Rossing K, Smidt UM, Hommel E, et al. Benefits of long term antihypertensive treatment on prognosis in diabetic nephropathy. Kidney Int. 1996; 49: 1778–82. https://doi.org/10.1038/ki.1996.266 PMid:8743496
6. Finne P, Reunanen A, Stemman S, Groop PH, Gronhagen-Riska C: Incidence of end-stage renal disease in patients with type 1 diabetes. JAMA. 2005; 294: 1782–87.
7. Pfleiderer S, Zimmerhackl LB, Kinne R, Manz F, Schuler G, et al. Renal proximal and distal tubular function is attenuated in diabetes mellitus type 1 as determined by the renal excretion of alpha 1-microglobulin and Tamm-Horsfall protein. Clin Investig. 1993;71:972–7. https://doi.org/10.1038/BJ00189026 PMid:7510155
8. Yagoob M, McClelland P, Patrick AW, Stevenson A, Mason H, et al. Evidence of oxidant injury and tubular damage in early diabetic nephropathy. QJM. 1994;87:601–7. PMid:8787555
9. Lacomani A, Donato V, Pintaudi B, Vieste GD, Chirico V, et al. "Neramoalbuminuric" diabetic nephropathy: tubular damage and NGAL. Acta Diabetol. 2013;50:935–42. https://doi.org/10.1007/s00592-013-0485-7 PMid:23754672
10. Nielsen SE, Schjoedt KJ, Astrup AS, Tarnow L, Lajer M, et al. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) in patients with diabetic nephropathy: a cross-sectional study and the effects of lisinopril. Diabet Med. 2010;27:1144–50. https://doi.org/10.1111/j.1464-5491.2010.03083.x PMid:20854382
11. Nielsen SE, Sugaya T, Hofvin P, Baba T, Parving HH, et al. Urinary liver-type fatty acid-binding protein predicts progression to nephropathy in type 1 diabetic patients. Diabetes Care. 2010;33:1320–4. https://doi.org/10.2337/dc09-2242 PMid:20168572 PMCid:PMC2975447
12. Nielsen SE, Sugaya T, Tarnow L, Lajer M, Schjoedt KJ, et al. Tubular and glomerular injury in diabetes and the impact of ACE inhibition. Diabetes Care. 2009;32:1684–8. https://doi.org/10.2337/dc09-0429 PMid:19502542 PMCid:PMC2732168
13. Marques-Vidal P, Ferrario M, Kuulasmaa K, Grafnerd et al. Moltchanova V, for the WHO MONICA Project. Quality assessment of data on HDL cholesterol in the WHO MONICA Project (1999). Available from: URL:http://www.thl.fi/publications/monica/hdl/hdlqta.htm, URN:NBN:fi-fei19991137.
14. Trivelli LA, Ranney HM, Lai HT. Hemoglobin components in patients with diabetes mellitus. N Engl J Med. 1971;284:353–7. https://doi.org/10.1056/NEJM197102182840703 PMid:5359916
15. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med. 1984;310:356–60. https://doi.org/10.1056/NEJM198403103100605 PMid:6690964
16. Salf A, Soliman NA, Abdel-Hameed A. Early evaluation of renal hemodynamic alterations in type I diabetes mellitus with duplex ultrasound. Saudi J Kidney Dis Transpl. 2010;21:295–99. PMid:20228518
17. Pelliccia P, Savino A, Cacemore C, Primavera A, Schiavone G, Chiarelli F. Early changes in renal hemodynamics in children with diabetes: Doppler sonographic findings. J Clin Ultrasound. 2008;36(6):335-40. https://doi.org/10.1002/jcu.20457 PMid:18361467
18. Masoli M, Mancini M., Liuizi R., Daniele S., Mainenti P., Vergara E., Genovesi S., Salvatore M., Vaccaro O.: Measurement of the intrarenal arterial resistance index for the identification and prediction of diabetic nephropathy. Nutrition, Metabolism and Cardiovascular Diseases. 2009;25(5): 358–64. https://doi.org/10.1016/j.numecd.2008.07.003 PMid:18805683
19. Alter ML, Kretschmer A, Von Websky K, Tsuprykov O, Reichetzeder C, et al. Early urinary and plasma biomarkers for experimental diabetic nephropathy. Clin Lab. 2012;58:659–71. PMid:22997966

https://doi.org/10.1001/jama.294.14.1782 PMid:16219881
https://doi.org/10.1038/ki.1996.266
https://doi.org/10.1111/j.1464-5491.2010.03083.x
https://doi.org/10.2337/dc09-2242
https://doi.org/10.1056/NEJM197102182840703
https://doi.org/10.1002/jcu.20457