Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a predicting factor in patients with Diabetic Nephropathy

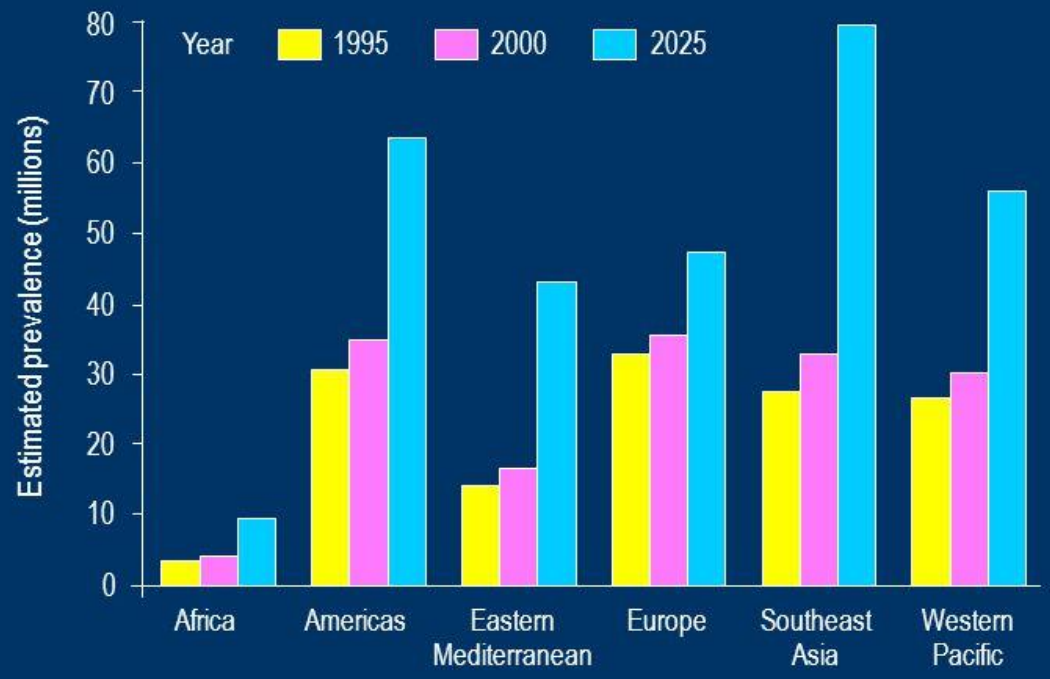
Atefeh Amouzegar, MD
Assistand prof. of Nephrology
Firoozgar Hospital, IUMS, Tehran, Iran
Nov 21 2019

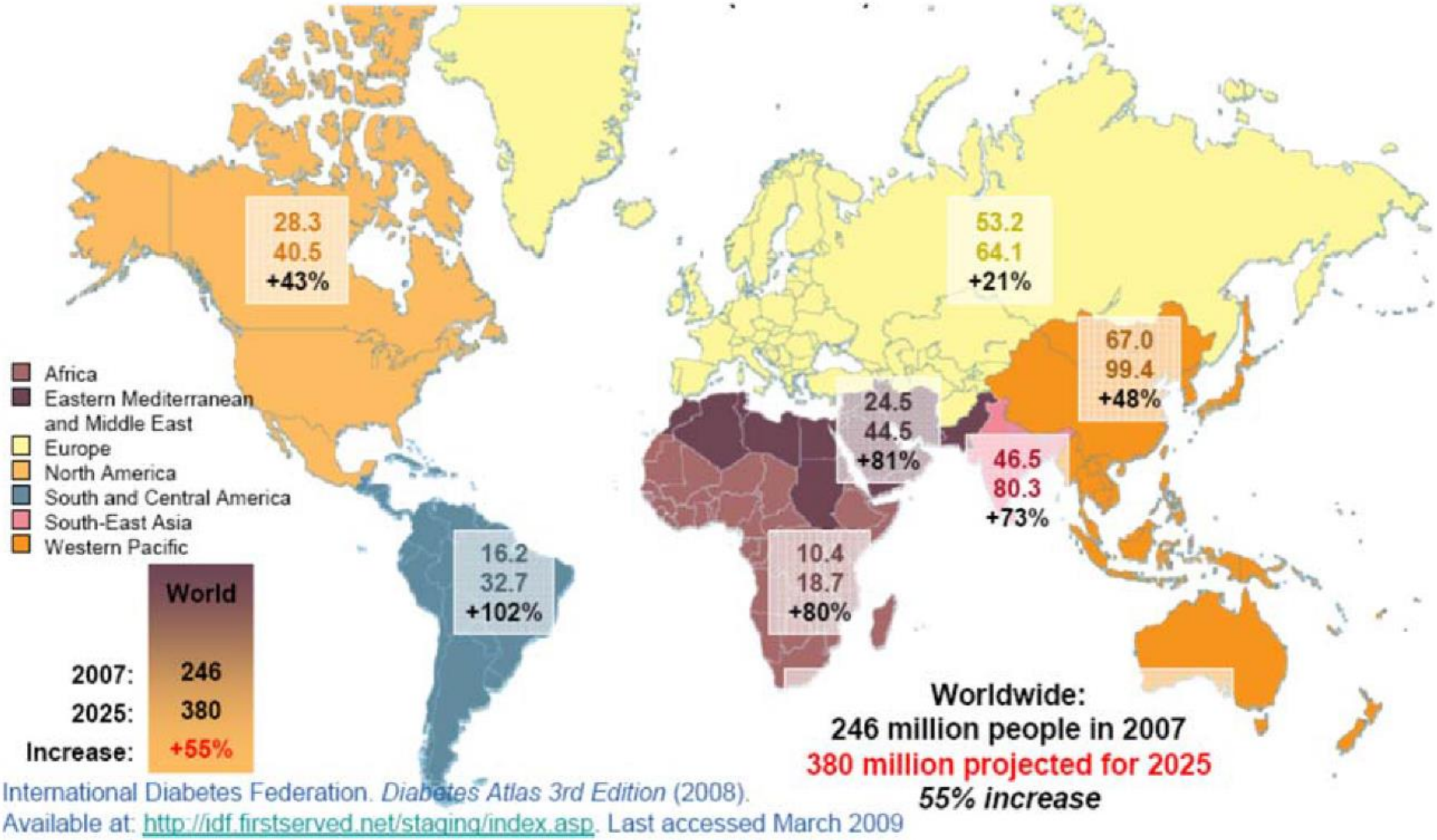
Introduction

- Diabetes mellitus (DM) is a chronic disease and one of the most important and problematic health issues.
- Diabetic nephropathy which develops in 30–40% of diabetic patients is one of the major microvascular complication of diabetes mellitus.

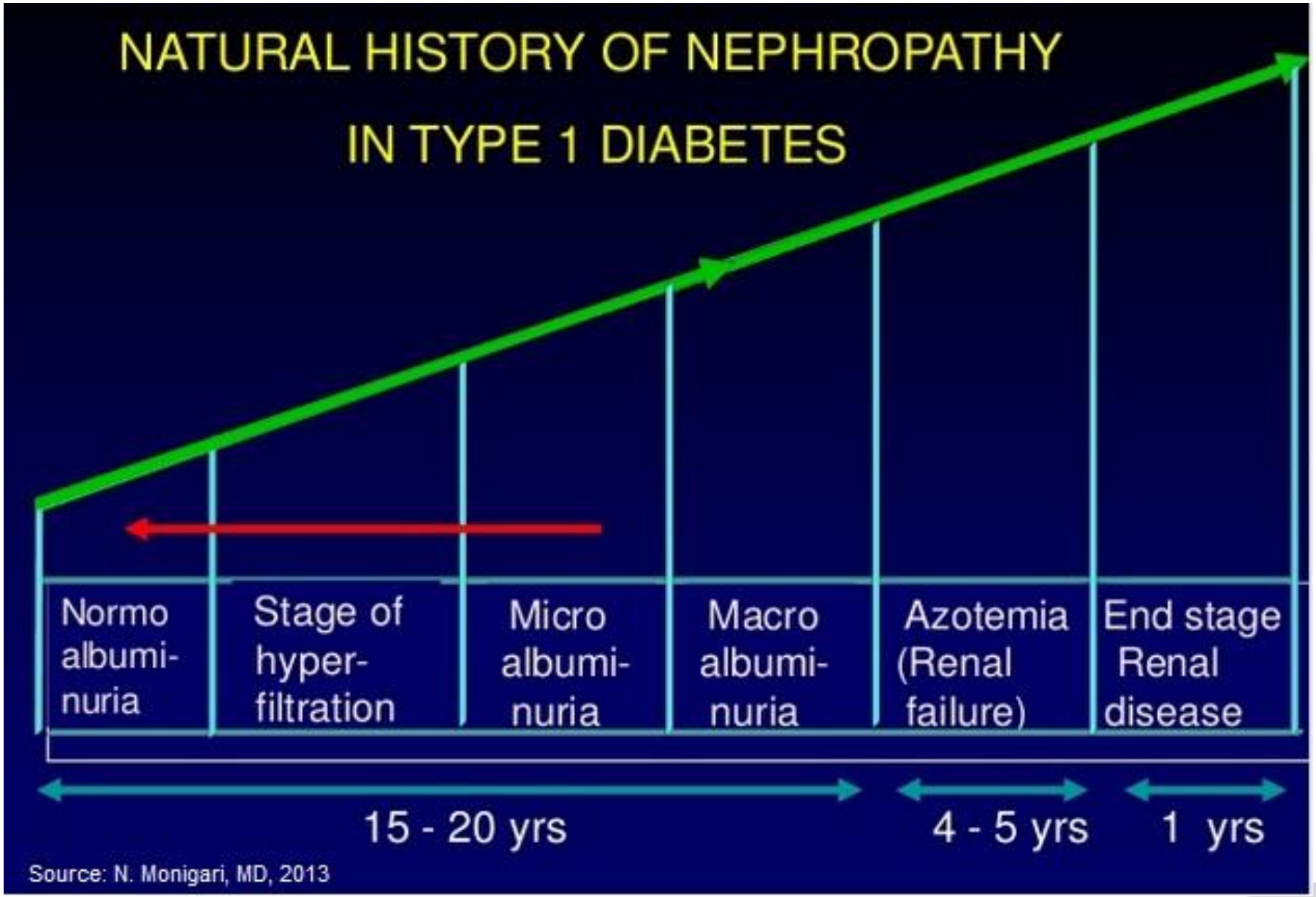
Incidence of Diabetes

Worldwide Data





International Diabetes Federation. *Diabetes Atlas 3rd Edition* (2008).
Available at: http://idf.firstserved.net/staging/index.asp. Last accessed March 2009


NATURAL HISTORY OF NEPHROPATHY
IN TYPE 1 DIABETES
Normo albumi-nuria
Stage of hyper-filtration
Micro albumi-nuria
Macro albumi-nuria
Azotemia (Renal failure)
End stage Renal disease
15 - 20 yrs
4 - 5 yrs
1 yrs
Source: N. Monigari, MD, 2013

Introduction

The presence of **albuminuria** designates the most common sign of early renal involvement which can be detected clinically in diabetic subjects.

Introduction

Albuminuria is mainly a consequence of glomerular damage but defective tubular reabsorption of albumin might also contribute equally in the genesis of diabetic nephropathy.

Introduction

- NGAL is a small protein which belongs to the superfamily of ‘lipocalins’.
- Experimentally NGAL is overproduced by renal tubules within few hours of an ischemic or toxic injury.

Introduction

In the present study we aimed at evaluating the serum and urine level of NGAL in diabetic patients at different stages of albuminuria as a predictive factor of disease severity in diabetic nephropathy and thereby contributing to preventive and treatment options in proper time.

Material and methods

Patient and Control Groups

This cross-sectional study was conducted on type 2 diabetic patients who were referred to Endocrine Research center, Iran University of Medical Sciences, Tehran, Iran between Jan, 2017 and Jan, 2019.

One hundred and ninety eight subjects were enrolled in this study including **50 normal** individuals, and 148 diabetics consisting of **50** diabetics without albuminuria (**normoalbuminuria**), **58** diabetics with **microalbuminuria** and **40** diabetics with **macro-albuminuria**.

Patients who were using Diltiazem, Angiotensin II converting enzyme inhibitors (ACEI), Angiotensin Receptor Blockers (ARBs) or had creatinine level ≥ 1.5 mg/dl or GFR< 60 ml/min were excluded from the study

Macroalbuminuric patients were also selected from those patients who had not been treated with any of the above mentioned medications before and were referred to clinic for the first time.

ELISA NGAL Assay

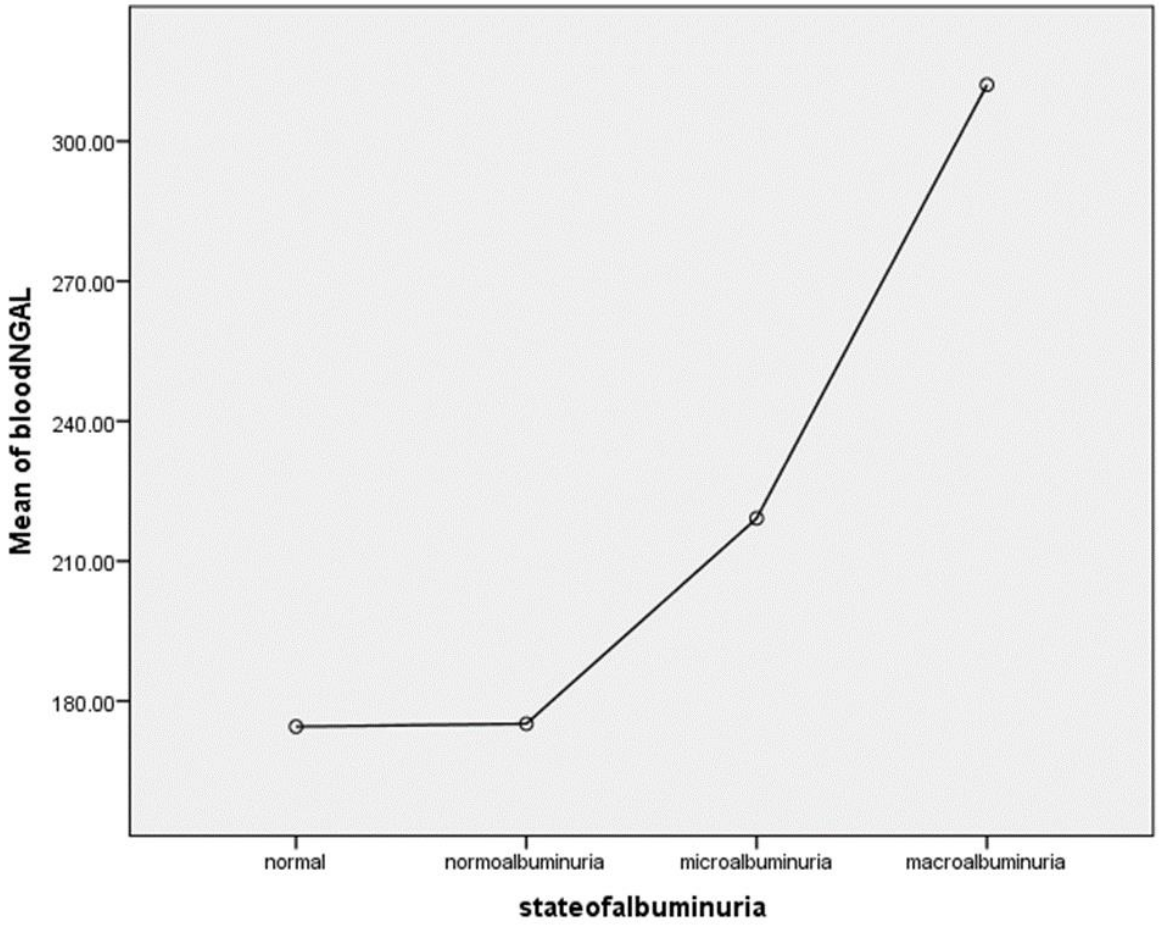
For the evaluation of sNGAL level, 5 milliliters of venous blood was drawn and the isolated serum was stored in -80 ° C after centrifusion and for evaluation of uNGAL 20 ml of urine, was collected and stored at -70˚c After collection of all samples the NGAL was measured using “Human NGAL ELISA kit”, BIOPORTO diagnostics, Denmark.

Results

The main characteristics of patients and controls

	Control group	Normoalbuminuric	Microalbuminuric	Macroalbuminuric	**P value For trend**
n (male/female)	50 (24/26)	50 (21/29)	58 (32/26)	40 (24/16)	0.19
Age	39.6 ± 15	55.8 ± 9.3	54.8 ± 9.5	56.6 ± 9.3	0.63
Duration of disease (year)	_	9.2 ± 6.4	9.0 ± 5.1	10.0 ± 5.0	0.66
FBS (mg/dl)	_	160 ± 91	173 ± 76	169 ± 62	0.67
BS2hpp[a] (mg/dl)	99 ± 15	223 ± 108	251 ± 117	235 ± 81	-
HGBA1C[b]	_	8.1 ± 2	8.3 ± 2	8.1 ± 1	0.11
Creatinine (mg/dl)	0.8 ± 0.15	0.97 ± 0.18	0.99 ± 0.17	1 ± 0.16	0.18
eGFR[c] (cc/min)	94.7 ± 20	75 ± 15	76.8 ± 16	70 ± 9.2	0.23
Serum NGAL(*ng/mL*)	174.9 ± 75.9	175.1 ± 117.8	219 ± 107.1	312 ± 150.9	**0.001**
Urine NGAL (*ng/mL*)	44.6(30.2-76)	48(19-102)	43(21-98)	98.5(46.7-157)	0.06

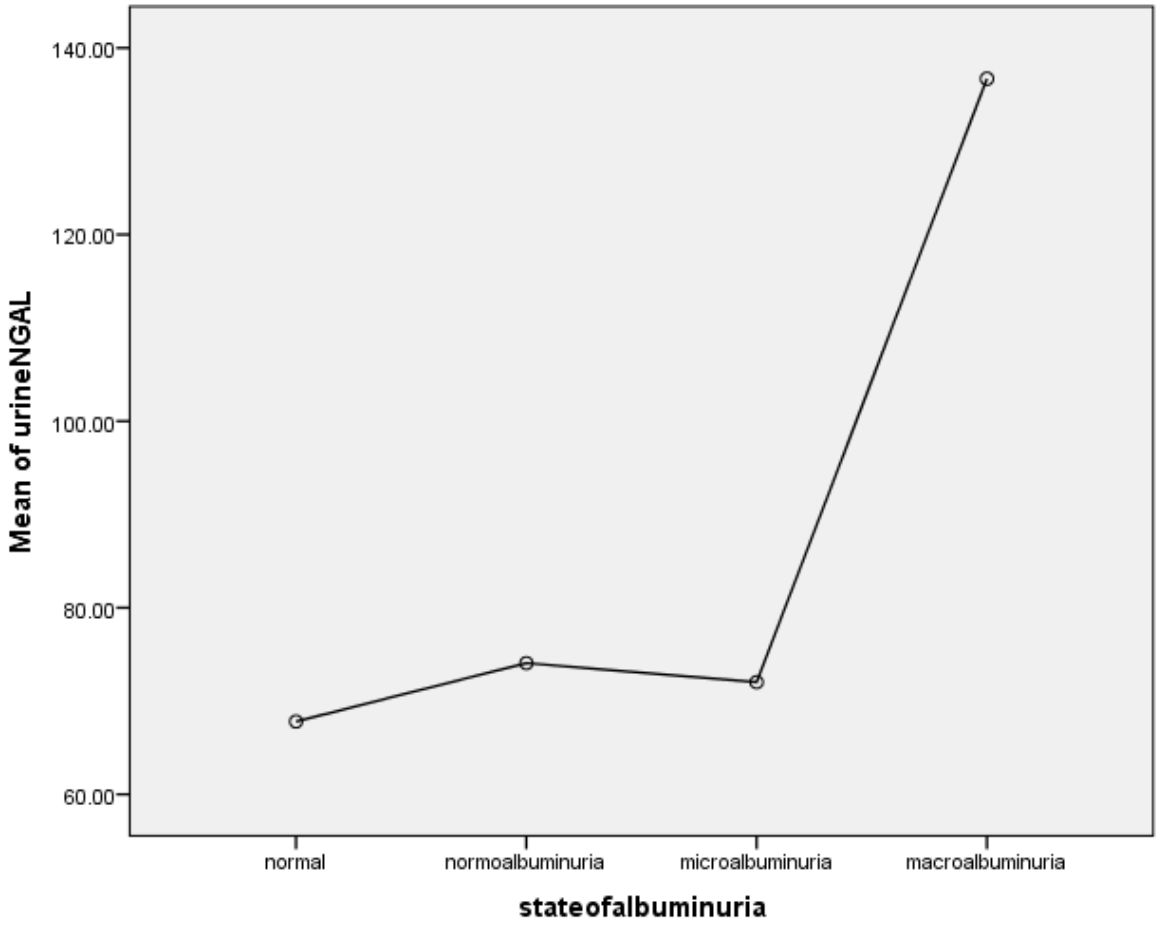
The relationship between sNGAL and State of Albuminuria



The mean difference of sNGAL in four groups

(I)State of albuminuria	(J) State of albuminuria	Mean difference (I-J)	Std. Error	Sig.
Normal	normoalbuminuric	-0.61	21.28	0.97
	microalbuminuric	-44.66	20.53	0.031
	Macroalbuminuric	-137.5	22.57	0.000
Normoalbuminuric	normal	-0.61	21.28	0.97
	microalbuminuric	-44.04	20.53	0.033
	Macroalbuminuric	-136.96	20.57	0.000
Microalbuminuric	normal	44.66	20.53	0.031
	normoalbuminuric	44.07	20.53	0.033
	Macroalbuminuric	-92.92	21.87	0.000
Macroalbuminuric	normal	137.58	22.57	0.000
	normoalbuminuric	136.96	22.57	0.000
	microalbuminuric	92.92	21.87	0.000

The best cut-off point of sNGAL for macroalbuminuric state was 225.8 ng/ml with a specificity of 74 % and sensitivity of 70%.


140.00
120.00
100.00
80.00
60.00
Mean of urineNGAL
normal
normoalbuminuria
microalbuminuria
macroalbuminuria
stateofalbuminuria

The best cut off point of uNGAL for macroalbuminuric state was 71.4 ng/ml with a sensitivity of 60% and specificity of 72%.

Dicussion

The Result Of Our Study Revealed That

All diabetic patients with albuminuria had elevated sNGAL values compared with diabetics without albuminuria (normoalbuminurics) and control healthy group.

Additionally, a significant drift was observed in macroalbuminuric state, and sNGAL values increased in parallel with increasing severity of albuminuria and renal involvement, approaching higher levels in patients with overt proteinuria ($p<0.001$).

Original Article: Complications

Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Kidney Injury Molecule 1 (KIM1) in patients with diabetic nephropathy: a cross-sectional study and the effects of lisinopril

S. E. Nielsen, K. J. Schjoedt, A. S. Astrup, L. Tarnow, M. Lajer, P. R. Hansen*, H.-H. Parving† and P. Rossing

Results Urine-NGAL levels were [geometric mean (95% CI)]: control subjects 74 (52–104) (pg/mmol creatinine), normoalbuminuric 146 (97–221), microalbuminuric 222 (158–312) and macroalbuminuric group 261 (175–390). Urine-NGAL increased significantly from the normo- to the micro- and further to the macroalbuminuric group ($P < 0.05$). Urine-NGAL was higher in normoalbuminuric vs. control subjects ($P < 0.01$). Plasma-NGAL was significantly higher in the normoalbuminuric and macroalbuminuric groups than in the control group. Urine-KIM1 was higher in all diabetic groups than in the control group ($P < 0.001$), with no difference between diabetic groups. During lisinopril treatment, urine-NGAL was reduced (95% CI) 17% (11–50) (not significant).

DIABETICMedicine 2010

Although we couldn’t show statistically significant increase in sNGAL in normoalbuminuric group in the current study, it was found that sNGAL increases with the appearance of albuminuria and it could be claimed that sNGAL has a sensitivity of 98% for diagnosis of **microalbuminuria**.

In another recently published study, the sNGAL was significantly higher in diabetic individuals as compare to the control group by means of significant difference between the groups ($P < 0.05$).

This study reveals that tubular injury might occur in advance of glomerular injury in diabetic individuals, and sNGAL can be used as a biomarker to detect diabetic nephropathy even before overt nephropathy.

Neutrophil Gelatinase-Associated Lipocalin as an Early Biomarker of Nephropathy in Diabetic Patients

Davide Bolignano[a] Antonio Lacquaniti[a] Giuseppe Coppolino[a]
Valentina Donato[a] Maria Rosaria Fazio[a] Giacomo Nicocia[b] Michele Buemi[a]

Results: All groups showed increased NGAL values with respect to controls; interestingly, increased NGAL levels were already found in diabetic patients without early signs of glomerular damage (normoalbuminuric). Both sNGAL and uNGAL increased in parallel with the severity of renal disease, reaching higher levels in patients with manifest diabetic nephropathy. The assessment of Pearson coefficient evidenced significant relationships between sNGAL and, respectively, uNGAL, serum creatinine and GFR (inversely) and between uNGAL and, respectively, serum creatinine, proteinuria, albuminuria, serum albumin and GFR (both inverse-

Kidney Blood Press Res 2009;32:91–98

The Result Of Our Study Revealed That

Urine NGAL shows significantly elevated level **only** in diabetics with **macroalbuminuria** compared to other diabetics and control subjects (P=0.06).

REVIEW Open Access

Urinary biomarkers for early diabetic nephropathy in type 2 diabetic patients

Temesgen Fiseha

Cystatin C, alpha-1 microglobulin, immunoglobulin G or M, type IV collagen, nephrin, angiotensinogen and liver type fatty acid–binding protein (L-FABP) associated with early DN in type 2 diabetic patients. Our search identified a total of 42 studies that have been published to date. Urinary levels of these biomarkers were elevated in type 2 diabetic patients compared with non-diabetic controls, including in patients who had no signs indicating nephropathy (without microalbuminuria), and showed positive correlation with albuminuria. Despite the promise of these new urinary biomarkers, further large, multicenter prospective studies are still needed to confirm their clinical utility as a screening tool for early type 2 DN in every day practice.

Fiseha Biomarker Research (2015)

ORIGINAL ARTICLE

Evaluation of Neutrophil Gelatinase Associated Lipocalin, As A Biomarker of Renal Injury in Type 2 Diabetic Patients

MAHNOOR KHAN, NAKHSHAB CHOUDHRY[1], MUHAMMAD FAHIM UL HAQ[3], *SHAHJAHAN[2], SADIA MAHMOOD[3], SANA SARMAD, [1] RIFFAT YASMIN[2]*

Results: The diabetic group showed highly increased levels of uNGAL (male diabetics mean=212.8±45.3 ng/ml, male controls mean=5.36±0.55 ng/ml and female diabetics mean=158.2±28.7 ng/ml, female controls mean=7.85±1.45 ng/ml).These levels increased in parallel

P J M H S Vol. 8, NO. 3, JUL – SEP 2014

conclusions

Serum NGAL increases in diabetic patients with the appearance of albumin in urine, so that its level clearly correlates with severity of DN, while uNGAL increment is observed only in overt albuminuria.

conclusions

Furthermore Serum and urine NGAL measurement could be a useful, noninvasive, easily available test for the evaluation of renal involvement in the course of diabetes.