Intensive Medical Therapy is Associated with Increased Urinary Excretion of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Experimental Diabetic Nephropathy

Yeong Huei Desmond Chuah, Michaela Hutter, Mahmoud Abdelaal, Carel W le Roux, Neil G Docherty

UCD School of Medicine

UCD Diabetes Complication Research Centre

Assiut University Hospital, Egypt

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

- 25 kDa glycoprotein with 178 amino acids

- Belongs to the lipocalin superfamily

- Involves in innate antimicrobial defense mechanism

- Plays a protective role in epithelial injury by its anti-apoptotic effect.

- Upregulated in various organs in response to injury, including kidneys and liver.

NGAL as renal tubular injury marker

Plasma NGAL of pre-renal origin is freely filtered in the glomeruli

Glomerulus

NGAL expression is upregulated in distal nephron in kidney injury

Proximal tubule

Collecting duct

Filtered NGAL is reabsorbed in the proximal tubule.

Koyner, J. L. & Parikh, C. R. Clinical utility of biomarkers of AKI in cardiac surgery and critical illness. *Clin. J. Am. Soc. Nephrol.* **8**, 1034–1042 (2013).
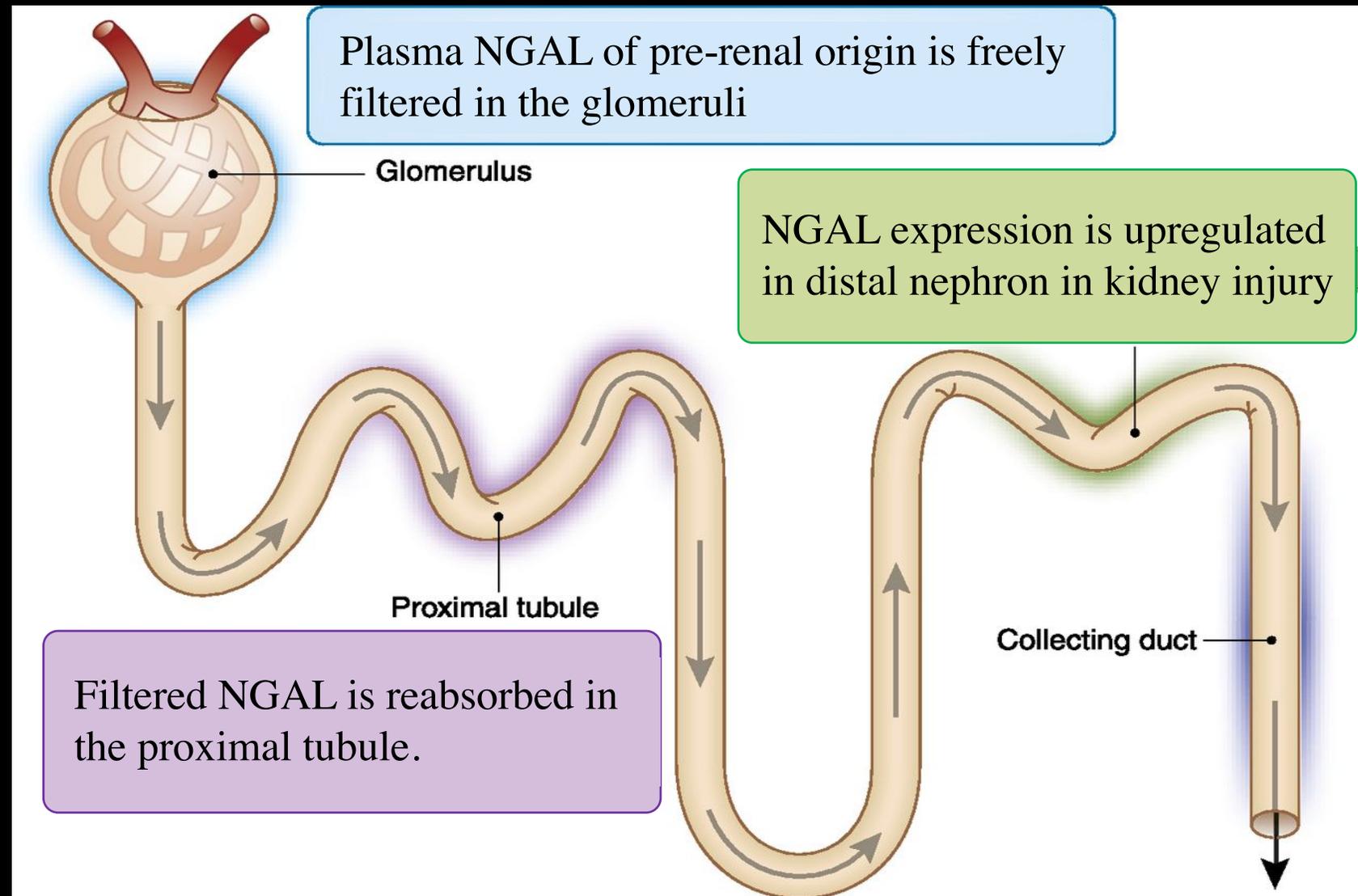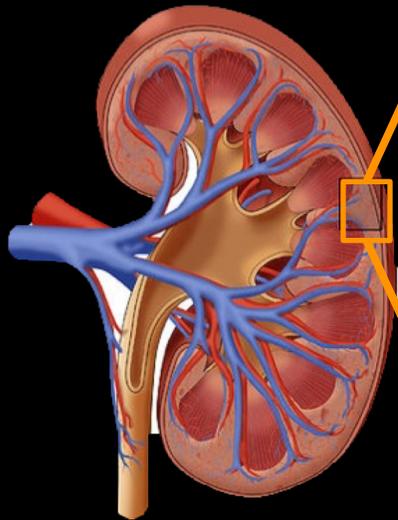
Urinary NGAL Excretion in Diabetic Nephropathy
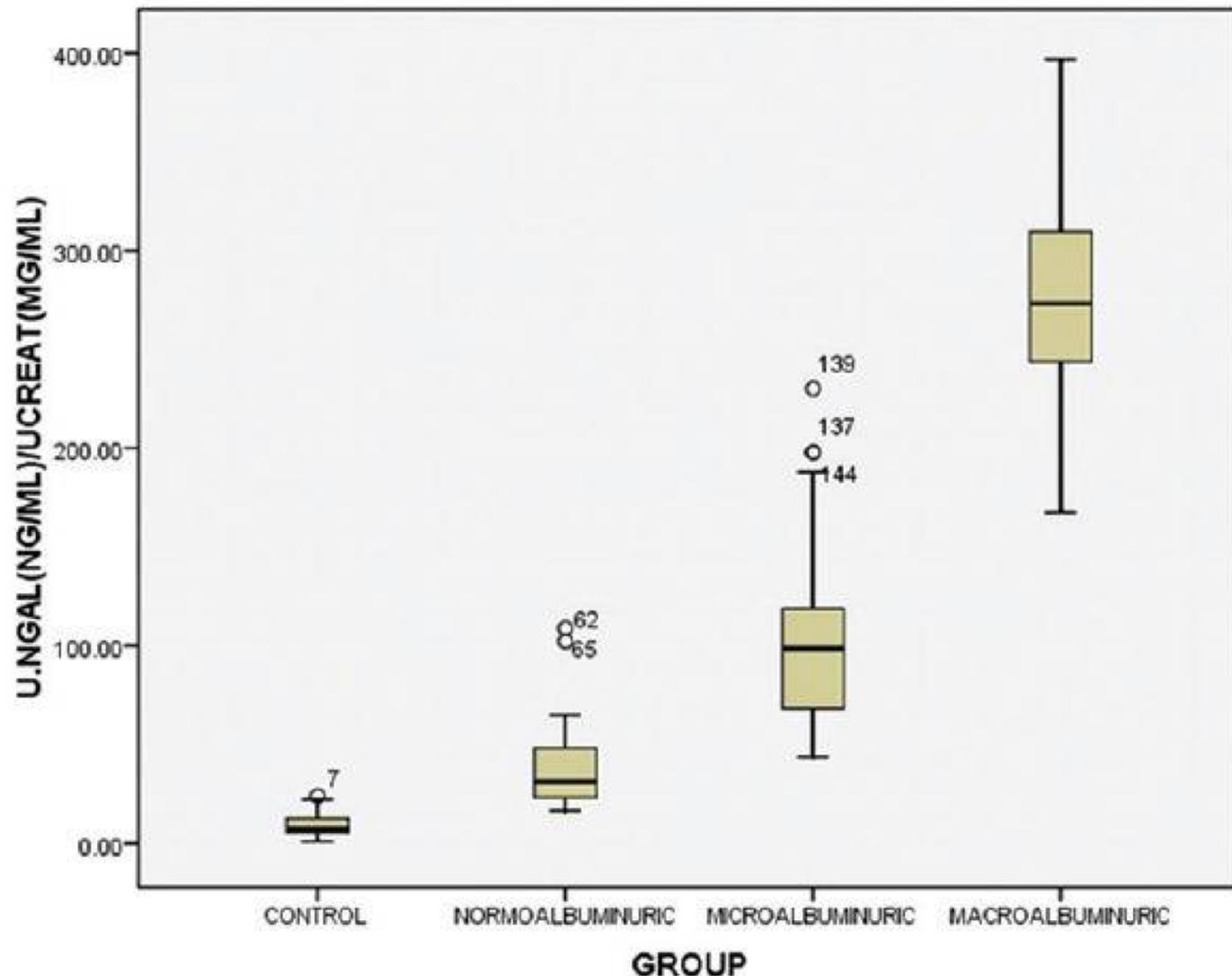
Urinary NGAL-Creatinine Ratio in

a) Control

b) Normo-albuminuria

c) Micro-albuminuria

d) Macro-albuminuria

Kaul, A et al. "Neutrophil Gelatinase-associated Lipocalin: As a Predictor of Early Diabetic Nephropathy in Type 2 Diabetes Mellitus" *Indian journal of nephrology* vol. 28,1 (2018): 53-60.

Research question:

Impact of intensive medical therapy on urinary NGAL excretion as a surrogate of renal tubular injury in animal model of diabetic nephropathy.

Hypothesis:

Establishment of good glycaemic control and weight loss will lead to reduction in urinary NGAL excretion.

Objectives:

1. To describe the association of urinary NGAL levels with degree of hyperglycaemia.

2. To evaluate changes in urinary NGAL excretion following intensive medical therapy.

METHODS

Age (week):   23   29   33   37

Baseline profile:

Disease Control (DC, n=9)

Post-intervention profile:

Zucker Diabetic Sprague-Dawley rats
(ZDSD, n=44)

Intensive Medical Therapy (IMT, n=8)
- 20% diet-induced weight loss
- Metformin
- Liraglutide
- Ramipril
- Rosuvastatin
- Fenofibrate

- Glycaemia
- Urinary excretion rates of NGAL and albumin

Sprague-Dawley rats (n=7)

- Glycaemia
- Urinary excretion rates of NGAL and albumin

Sprague-Dawley (SD, n=7)

- Glycaemia
- Urinary excretion rates of NGAL and albumin
- NGAL mRNA expression in kidney and liver tissue

Correlation between Hyperglycaemia and Urinary Biomarkers in ZDSD

Urinary Albumin Excretion
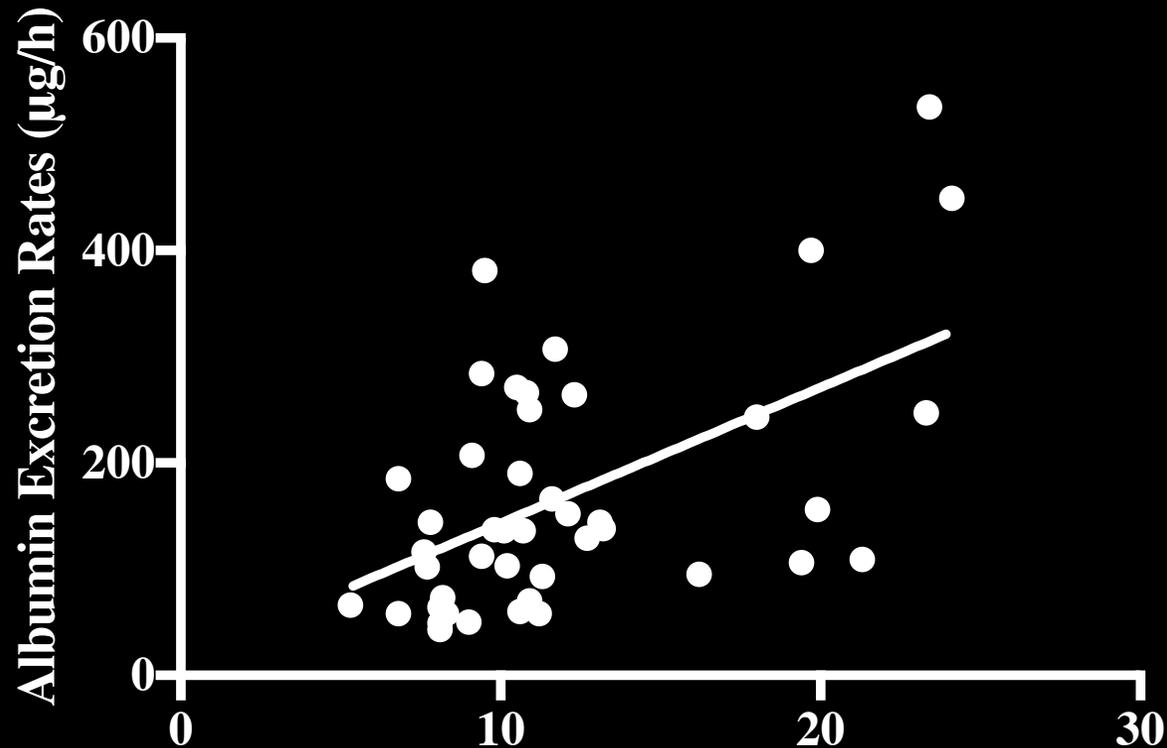
Urinary NGAL Excretion

Albumin: ρ=0.47, p=0.001
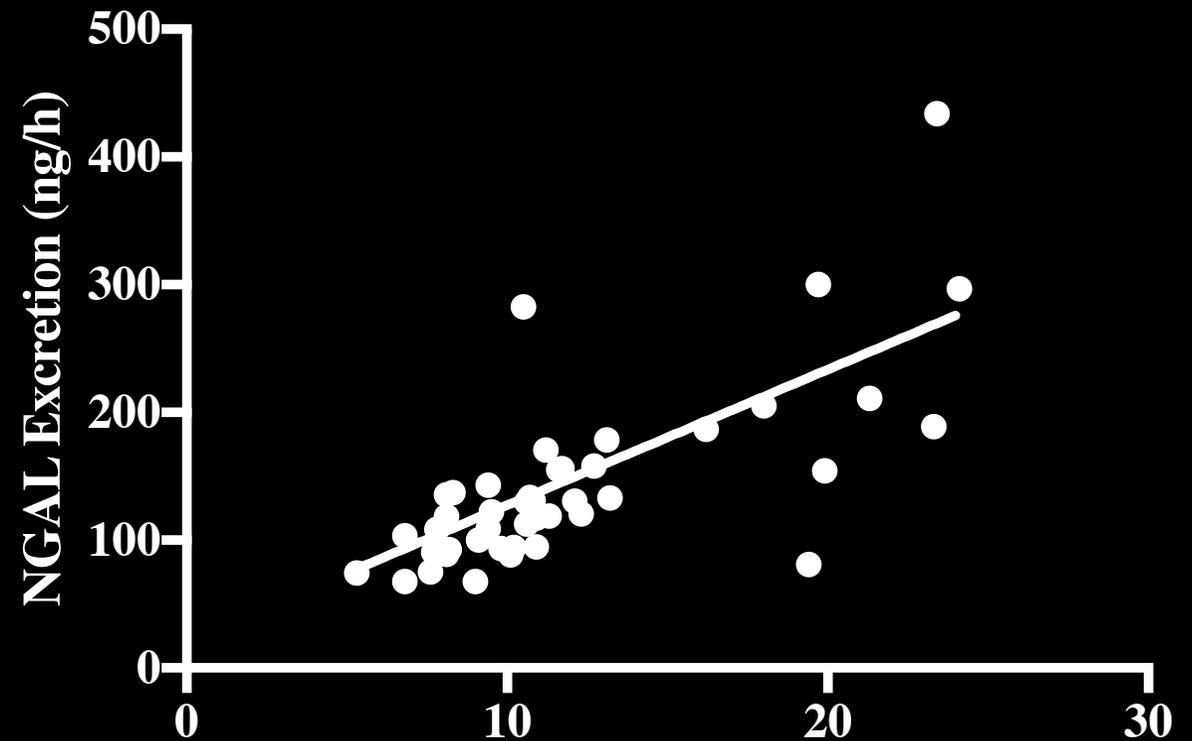
NGAL: ρ=0.71, p<0.001

Changes in Glycaemia at 4-week post-intervention

Plasma Glucose Levels

▲ Sprague-Dawley (SD)

● Disease Control (DC)

■ Intensive Medical Therapy (IMT)
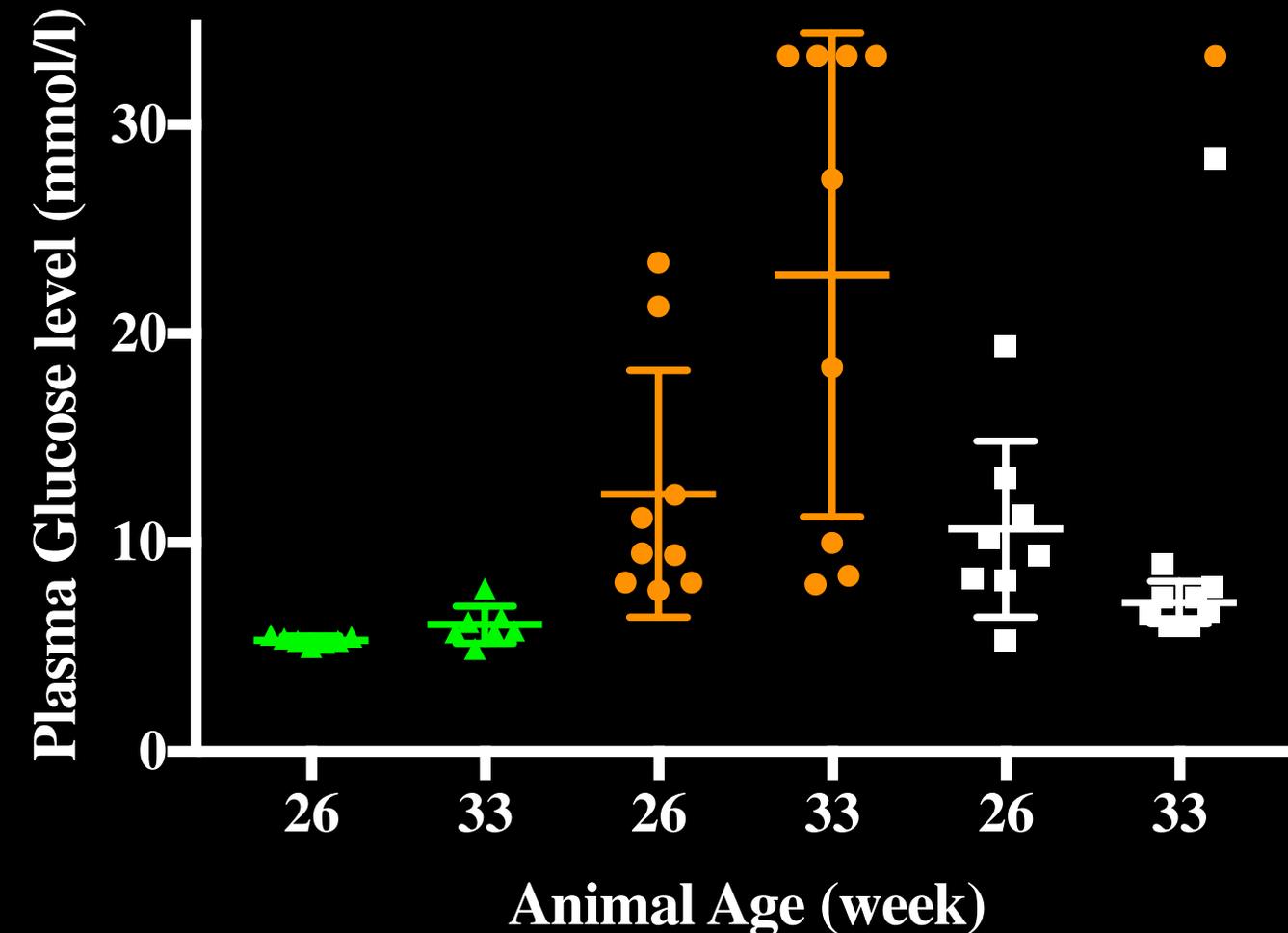
Group	Mean ± SD of Plasma Glucose Levels (mmol/l)		
	26-week	33-week	p-value
SD	5.3 ± 0.2	6.1 ± 0.9	0.031
DC	12.3 ± 5.9	22.8 ± 11.6	0.020
IMT	10.7 ± 4.2	7.1 ± 1.0	0.023

Changes in Urinary Albumin at 4-week post-intervention

Urinary Excretion of Albumin

Legend:
- Sprague-Dawley (SD)
- Disease Control (DC)
- Intensive Medical Therapy (IMT)

Group	Median of Urinary Albumin Excretion (µg/h, IQR)		p-value
	26-week	**33-week**	
SD	28.4 (21.0)	22.9 (13.7)	0.297
DC	109.1 (261.3)	849.4 (5727.0)	0.020
IMT	97.9 (67.4)	47.5 (28.6)	0.008
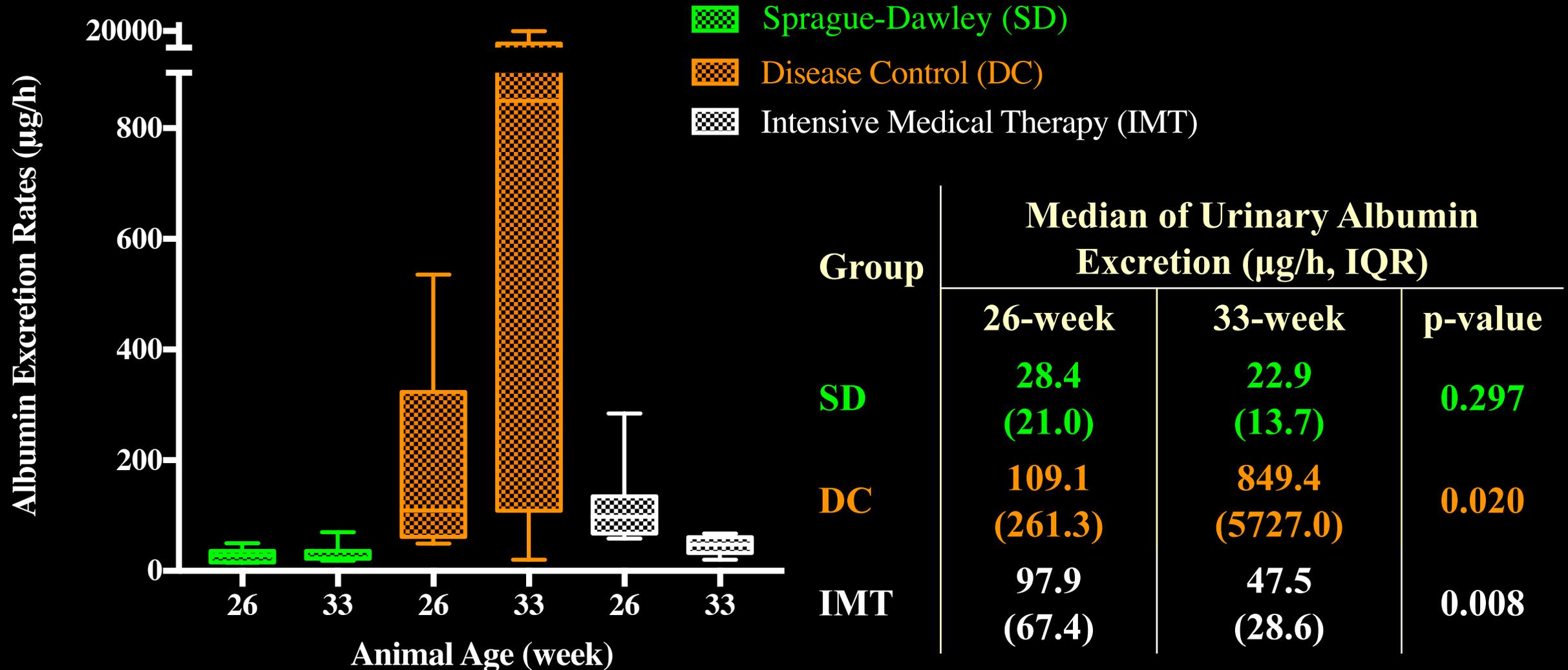
Changes in Urinary NGAL at 4-week post-intervention

Urinary Excretion of NGAL

Legend:
- Sprague-Dawley (SD)
- Disease Control (DC)
- Intensive Medical Therapy (IMT)
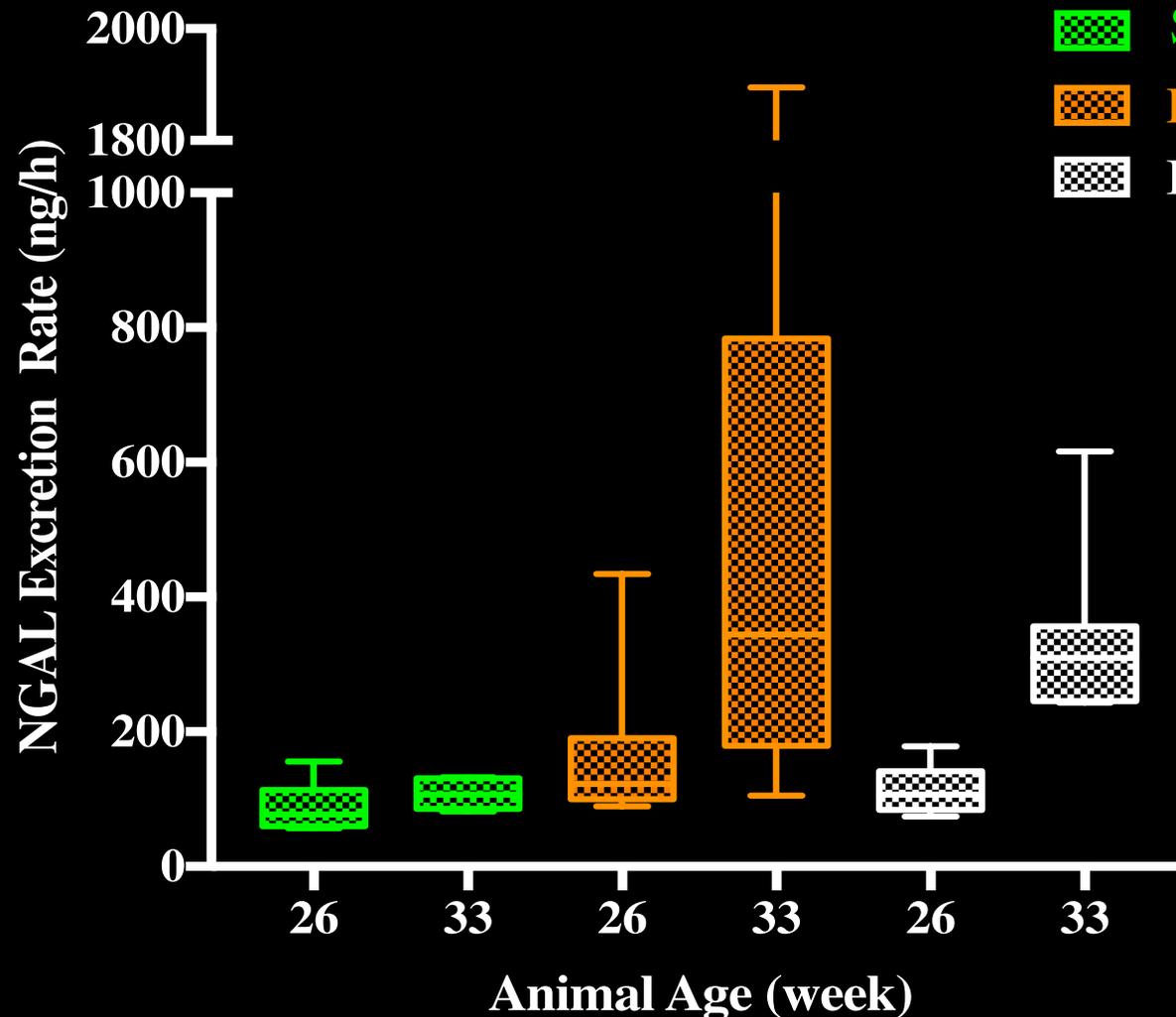
Group	Median of Urinary NGAL Excretion (ng/h, IQR)		p-value
	26-week	**33-week**	
SD	77.1 (53.2)	106.6 (45.1)	0.219
DC	122.4 (91.0)	344.6 (604.5)	0.012
IMT	106.6 (57.9)	310.2 (110.3)	0.008

Changes in Urinary Excretion of Albumin vs NGAL

Urinary Excretion of Albumin
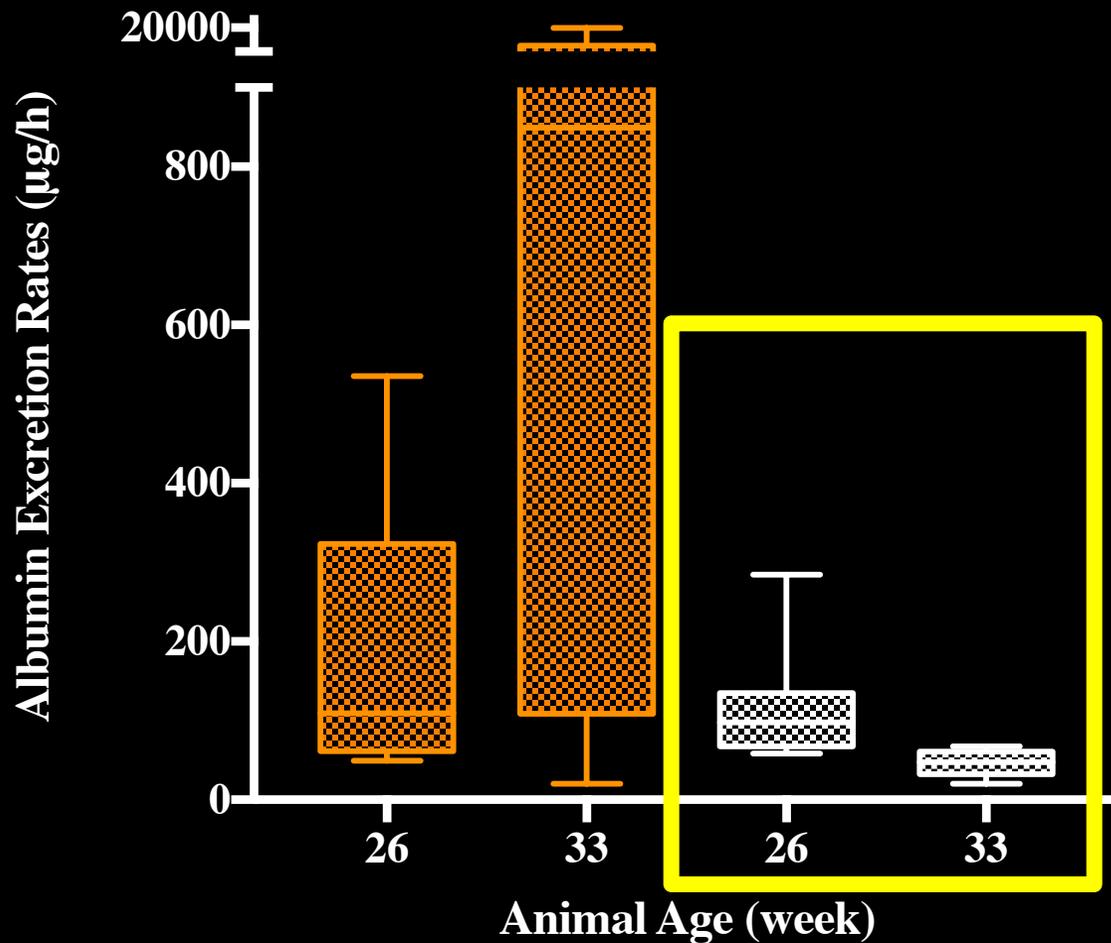
Urinary Excretion of NGAL
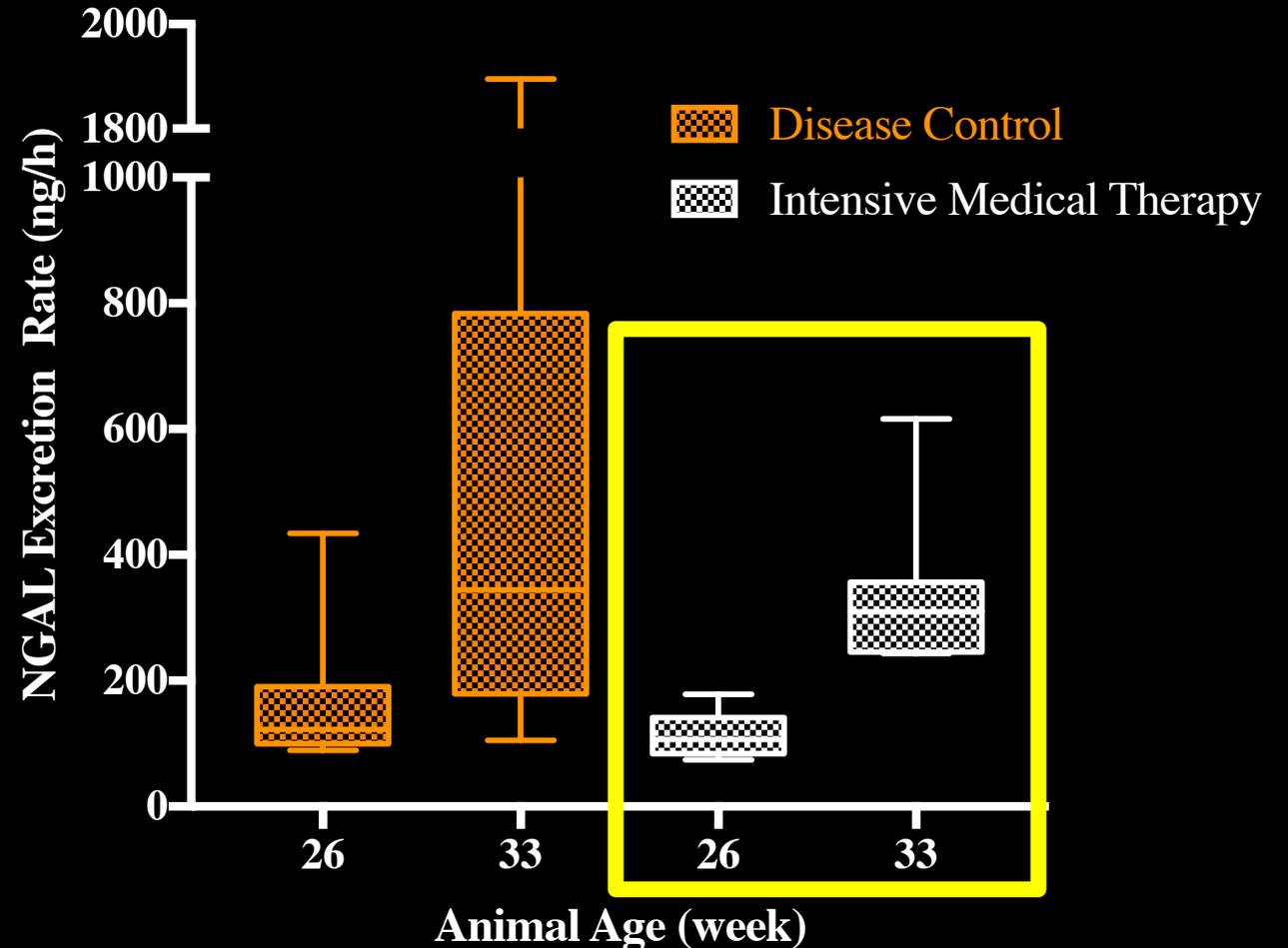
NGAL mRNA Expression in Liver and Kidney

Liver (pre-renal) NGAL mRNA Expression Level
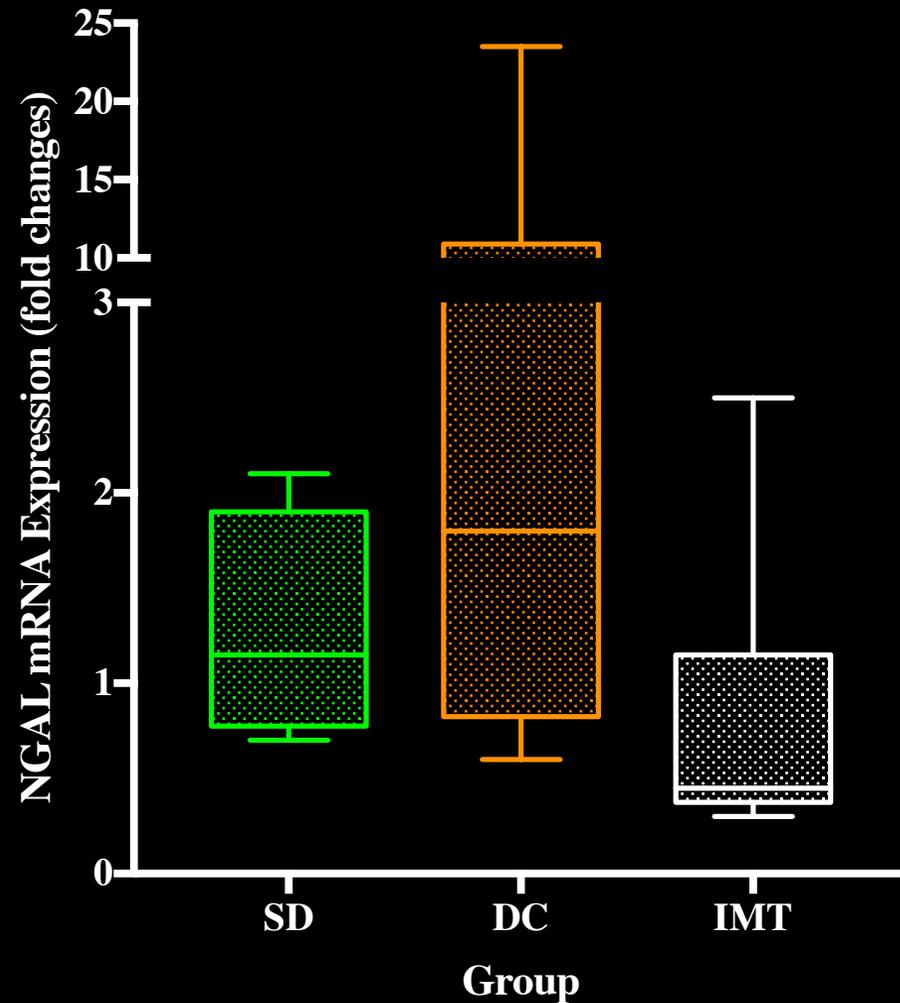
Kidney NGAL mRNA Expression Level
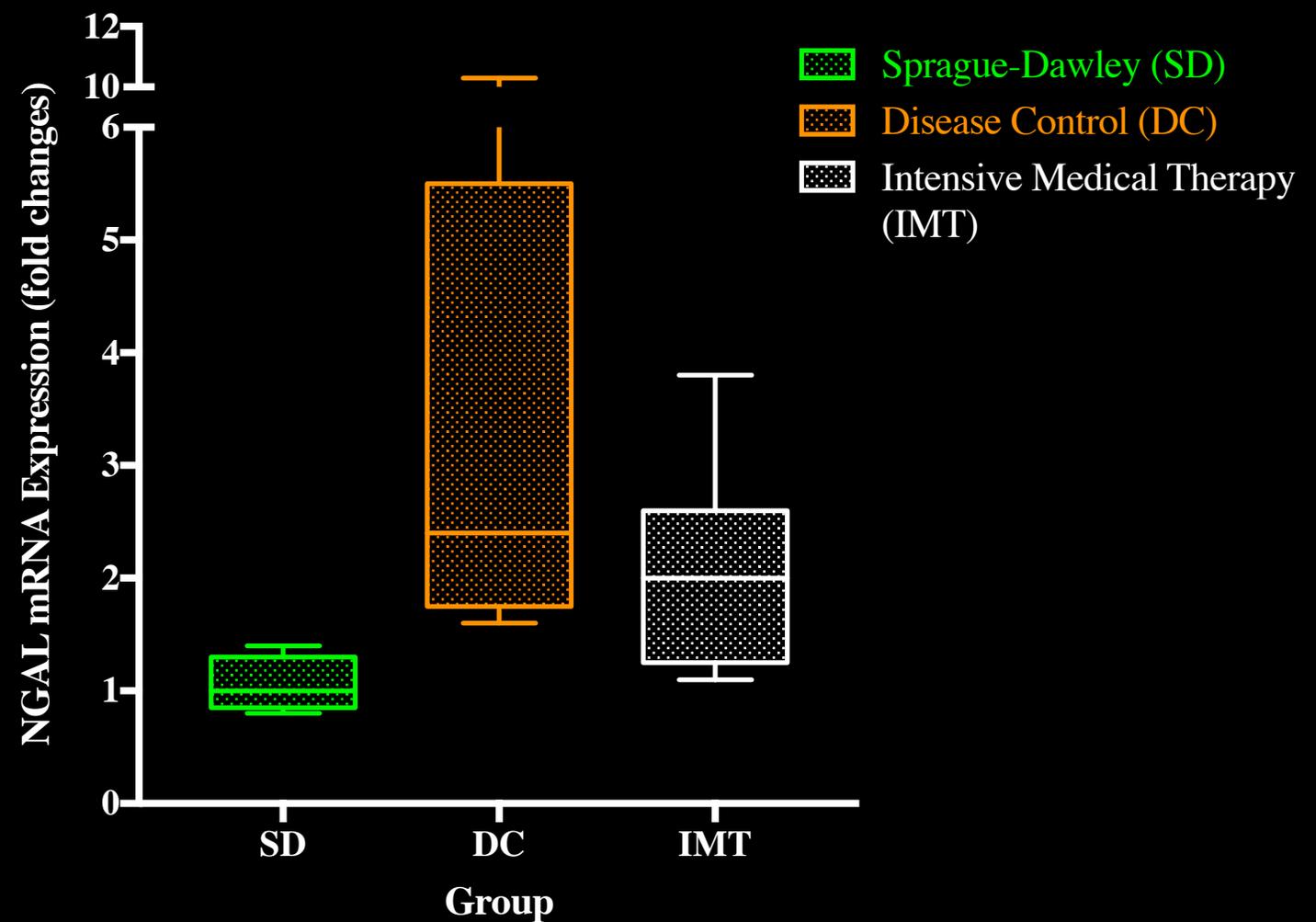
CONCLUSIONS

- A strong correlation was observed between plasma glucose levels and urinary NGAL.

- Intensive medical therapy paradoxically increased urinary excretion and renal expression of NGAL despite remission of hyperglycaemia and reduction in albuminuria.

- This may indicate **ongoing tubular stress in response to elements of intensified therapeutic regimens.**

Thank you

Supported by:

UCD School of Medicine
Excellence in Teaching & Research

UCD DCRC
Diabetes Complications
Research Centre

ASSIUT
UNIVERSITY

Pathological Society
Understanding Disease — Guiding Therapy