New insights on the pathogenesis of early stages of obesity-related glomerulopathy

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INTRODUCTION

•Kidney disease is an important cause of obesity-related comorbidity. A study carried out by our group first showed the presence of early histological lesions (mostly podocyte alterations) in obese patients lacking overt clinical renal symptoms.
•Several factors seem to be related to obesity-related glomerulopathy (ORG), although the pathogenic mechanisms are still unknown.

Renal injury in the extremely obese patients with normal renal function

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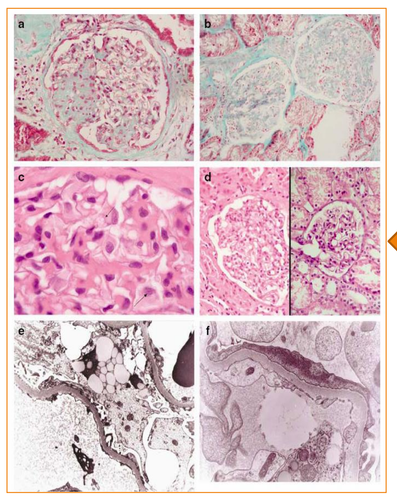
Kidney Int 2008



Clinical Study

Effect of Drastic Weight Loss after Bariatric Surgery on Renal Parameters in Extremely Obese Patients: Long-Term Follow-Up

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J Am Soc Nephrol 2006

Long-Term Normal Renal Function after Drastic Weight Reduction in Patients with Obesity-Related Glomerulopathy

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Obesity Facts 2015

Histological study

Etiopathogenic mechanism → ?

Inflammatory markers

Obesity, inflammation, and kidney disease

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Kidney Int 2008

Genes related to inflammatory cytokines and lipid metabolism have been found to be expressed in patients with ORG. Additionally, it is unknown whether these genes are expressed in the early stages of ORG.

Obesity-Related Glomerulopathy: Insights from Gene Expression Profiles of the Glomeruli Derived from Renal Biopsy Samples

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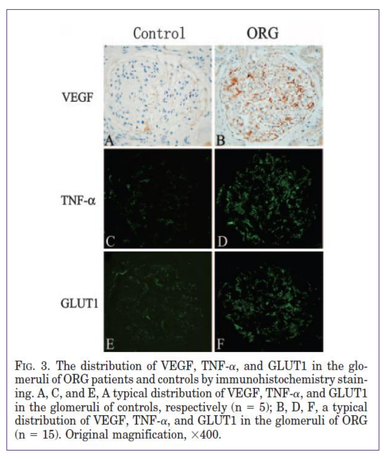


FIG. 3. The distribution of VEGF, TNF-α, and GLUT1 in the glomeruli of ORG patients and controls by immunohistochemistry staining. A, C, and E, A typical distribution of VEGF, TNF-α, and GLUT1 in the glomeruli of controls, respectively (n = 5); B, D, F, a typical distribution of VEGF, TNF-α, and GLUT1 in the glomeruli of ORG (n = 15). Original magnification, ×400.

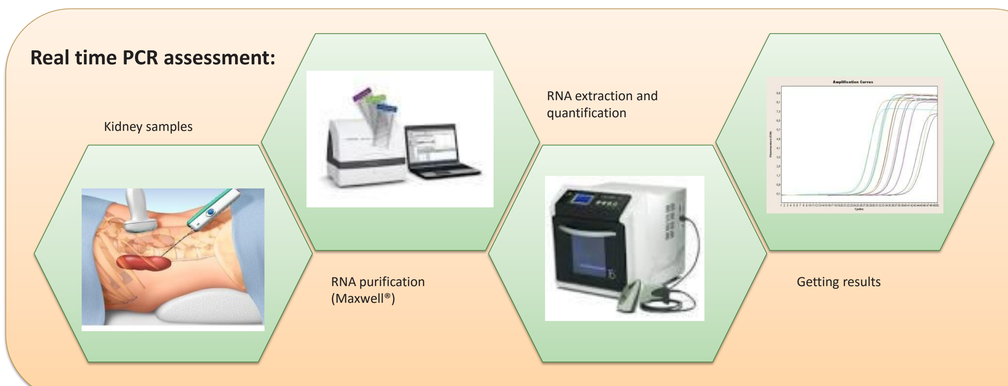
AIM

✓To investigate glomerular injury mechanisms in ORG by real time PCR assessment of the expression of several genes (interleukine-6, vascular endothelial growth factor, insulin-like growth factor-1, TNF-alpha, leptine receptor, glucose transporter-1, heart-type fatty acid binding protein, CD44 and spleen-derived interleukine-10) in renal biopsies of patients with early stages of ORG and renal biopsies of healthy non-obese patients.
✓The comparison of the gene expression profiles found in the two renal biopsy groups will detect differences allowing the establishment of a cause-effect relationship in ORG.

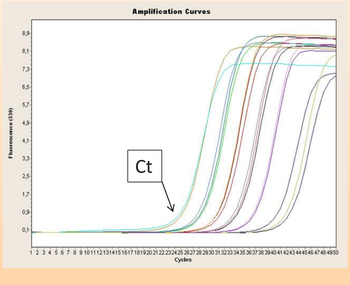
PATIENTS AND METHODS

Fifty morbidly obese patients (BMI≥ 40 Kg/m^2) without history of diabetes, without proteinuria and with normal renal function were selected and underwent a renal biopsy during bariatric surgery. Hystologic study showed early stages of ORG (matrix mesangial increase, mesangial cell proliferation, podocyte hypertrophy, glomerulomegaly and focal and segmental glomerulosclerosis). Control group were patients with normal weight and renal function. They were non-diabetic, non-hypertensive, and they were undergoing nephrectomy or donating a kidney.After real time PCR assessment, we have used the Livak Method to calculate the expression ratio or fold difference of our target genes. We have used Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as the housekeeping gene.

Real time PCR assessment:



The Livak Method:

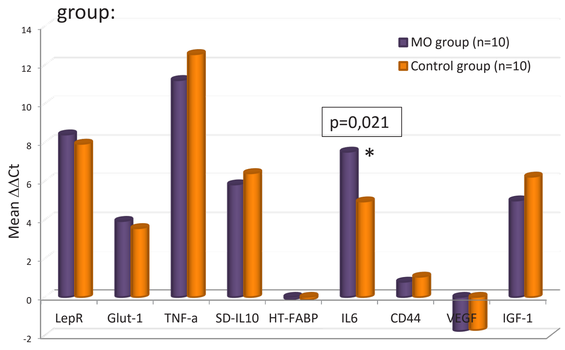


The livak (or $2^{-\Delta\Delta Ct}$) method requires that the target and reference genes:
•Both amplify at efficiencies near 100%
•Have efficiencies within 5% of each other

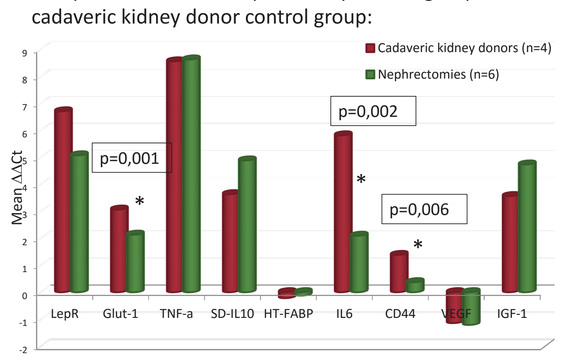
Three steps to the Livak method:
1. Normalize Ct (target gene to Ct (reference gene)
2. Normalize ΔCt of the test sample to ΔCt of calibrator
3. Calculate expressions ratio or fold difference ($2^{-\Delta\Delta Ct}$)

PRELIMINARY RESULTS

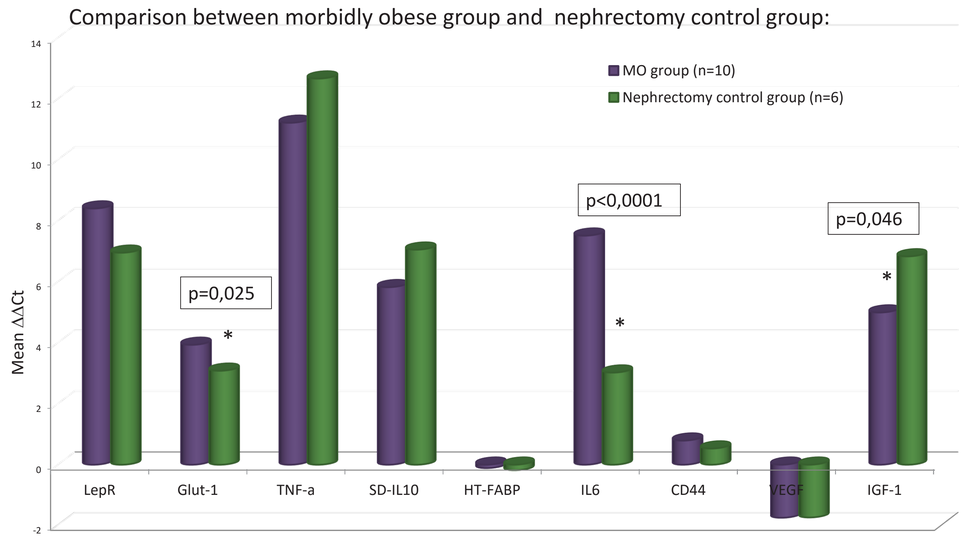
Comparison between morbidly obese group and control group:



Comparison between nephrectomy control group and cadaveric kidney donor control group:



Comparison between morbidly obese group and nephrectomy control group:



Fold difference between morbidly obese patients and nephrectomy control group:

Target genes	$2^{-\Delta\Delta Ct}$	p value
LepR	2,7302	NS
Glut-1	**1,809054**	**0,025**
TNF-α	0,3669409	NS
SD-IL10	0,427528	NS
HT-FABP	1,05262	NS
IL6	**22,367**	**<0,0001**
CD44	1,195817	NS
VEGF	0,992409	NS
IGF-1	**0,27977195**	**0,046**

The Livak Method

CONCLUSIONS

1. Although these are preliminary results, this study shows that inflammatory cytokines and insulin resistance (dysmetabolism caused by obesity) are involved in the development of ORG.
2. The expression levels of IL-6 gene (inflammatory cytokine) are increased 22,36-fold in kidney biopsies of morbidly obese patients when comparing with nephrectomy control group
3. The expression levels of Glucose transporter-1 gene (insulin resistance) are increased 1,8 fold in kidney biopsies of morbidly obese patients when comparing with nephrectomy control group
4. The expression leves of IGF-1 gene (insulin function) are decreased in kidney biopsies of morbidly obese patient when comparing with nephrectomy control group

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