

UROMODULIN, URINARY TRACT INFECTIONS AND RENAL SCARS

Ciro Corrado*, Rosa Cusumano*, Silvio Maringhini°

*Pediatric Nephrology, G. DI Cristina Hospital, Palermo

°Pediatric Unit, ISMETT, Palermo

INTRODUCTION

Urinary Tract Infections (UTI) are among the most common bacterial infections in childhood. **Febrile UTI (FUTI)** have been proved to produce **renal scars (RS)** in patients with VUR, but in some cases could be documented RS in children without UTI. The renal damage is **correlated with the grade of reflux and the number of UTI**, but **other factors** may have a role.

Chemoprophylaxis has been widely used to reduce occurrence of UTI in children with recurrent UTI and or VUR with limited results.

The identification of **biomarkers** that could noninvasively **identify children at risk for FUTI** has been claimed as a research priority.

INTRODUCTION - II

Uromodulin (UMOD) represents the most common urinary protein and is produced in the thick ascending limb cells of Henle's loop. Recent studies have shown the role of UMOD in **protecting from UTI**, by a binding with type I-fimbriated Escherichia coli. A defect of UMOD production may increase the susceptibility of UTI.

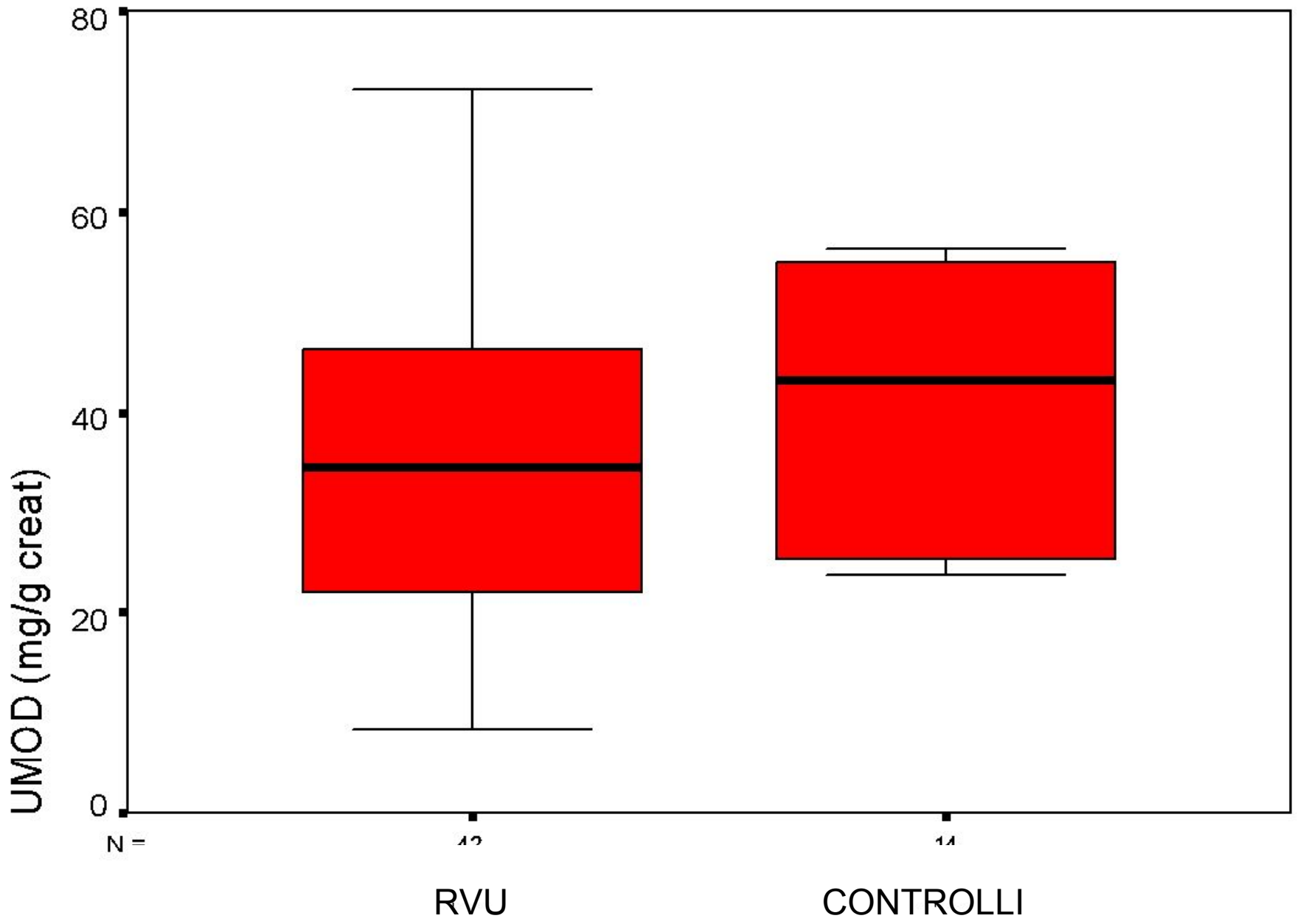
Measuring urine UMOD concentration and studying UMOD genotype in children with FUT1 may reveal if there is a group at increased risk of recurrent UTI and/or SCARS .

UMOD concentration and genotype could identify children predisposed to SCARS independently from UTI (Study A- B, personal data).

STUDY A

We studied 42 patients with VUR, A group of 17 controls (no VUR,UTI)

U was lower in pt with VUR ($24.9 \pm 12 \mu\text{g/ml}$) compared to controls ($40 \pm 21.5 \mu\text{g/ml}$).



STUDY A

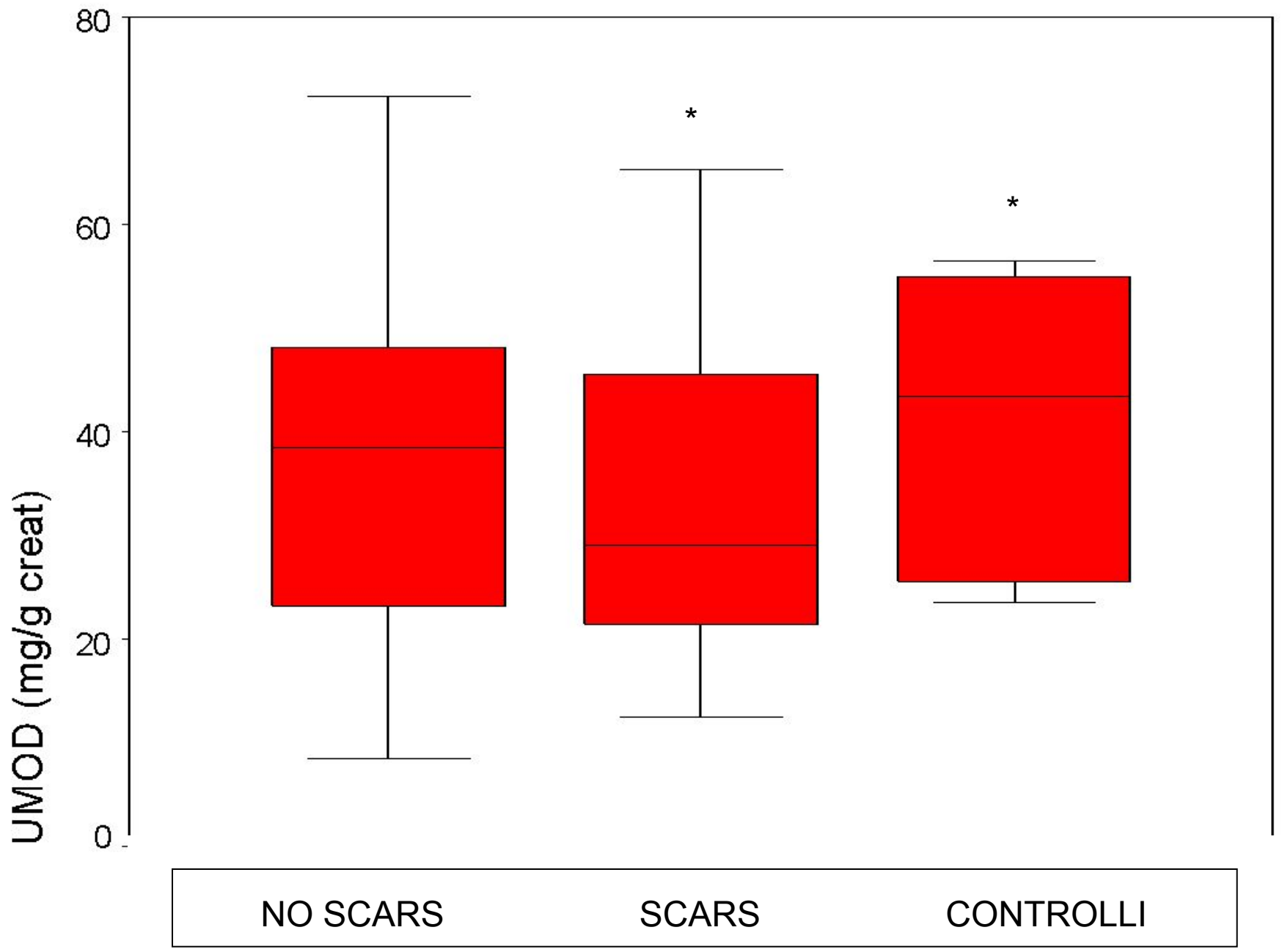
We studied 42 patients with VUR, A group of 17 controls (no VUR,UTI)

U was lower in pt with VUR ($24.9 \pm 12 \mu\text{g/ml}$) compared to controls ($40 \pm 21.5 \mu\text{g/ml}$).

Renal scars were detected in 22 pt (Group A)

No scar was detected in 20 patients (Group B)

U was lower in Group A ($21.7 \pm 12 \mu\text{g/ml}$) compared to Group B ($28.4 \pm 11.9 \mu\text{g/ml}$).



* p:NS

STUDY B

31 patients with VUR were enrolled.

Renal scars were detected in 16 children :

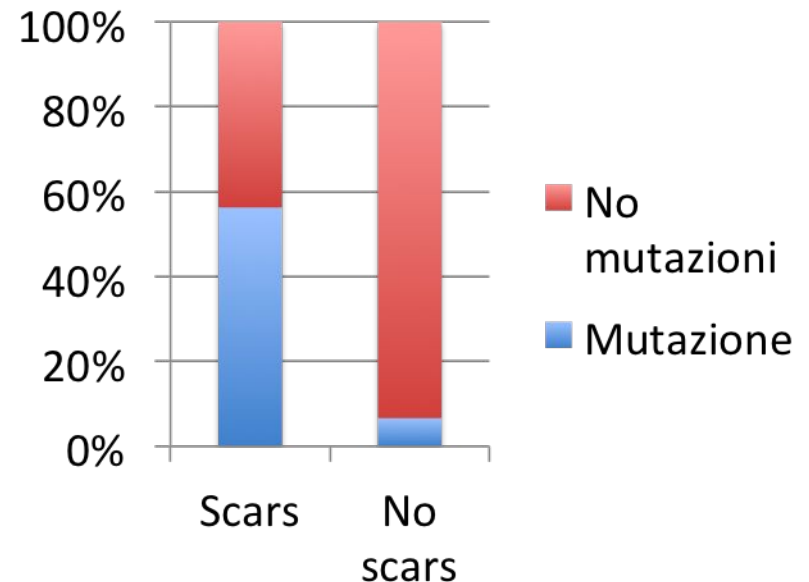
Genotype rs4293393

Genetic variant present in UMOD promoter
(single nucleotide polymorphism
Guanosine residue vs adenosine rs)

was present in 10 pts

1/15 pt (no scars) 6%

9/15 (scars) 60%



OBJECTIVES:

The **primary end point** of the study is the evaluation of **urine UMOD concentration in children with FUTI and in a control group comparable for age and sex with no history of UTI**. Aim of our study is to evaluate if low concentration of UMOD in the urine is associated with UTI and/or scars in children with VUR.

The secondary purpose of the study is the identification of a specific **mutation of the gene that encodes UROMOD, rs4293393 TC**, in the two groups of patients, which has been associated with a higher risk of nephropathy.

STUDY DESIGN

Multi-center, prospective study.

Children with a **new diagnosis of FUT1 *** will enter the study.

A **control group** of children of similar age and gender distribution, without any history of UTI or renal disease, will also be enrolled
UMOD concentration (U) measured ($\mu\text{g/ml}$) in first morning urine using an ELISA method.

A cystography will detect the presence and grade of VUR*.

A DMSA scan will detect the presence of a renal scar*.

•**(according to the Italian guidelines)**

For the analysis of the **primary endpoint**, the test group will be compared to the control group, for **secondary outcomes** we are planning to divide our patients in **four groups**:

VUR

VUR +
RS

NO VUR
NO RS

NO VUR
RS

STUDY POPULATION

Children with FUT1 will be recruited by all participating Centers.

All patients will fill in a **questionnaire** in order to obtain information regarding: family history of urinary tract malformations, urinary disorders, previous episodes of UTI and assumption of antibiotic tx.

Age, weight, height, SBP and DBP with oscillometric method.

Blood samples: serum sodium, creatinine and DNA for UMOD genotyping.

Urine samples for uromodulin (second morning urine samples) collected (mid-stream) in a sterile container and frozen within 2 h at -80°C. UMOD concentration (U) will be measured ($\mu\text{g/ml}$) along with creatinine and sodium > 1 month after resolution.

Imaging: Renal ultrasonography, cystography and DMSA renal scintigraphy (according to the Italian guidelines)

Control Group will be constituted by children of same age and sex

INCLUSION CRITERIA

Age between 0 and 18 years

Febrile ($>38^{\circ}$ C) UTI

Glomerular filtration rate (Schwartz f.) > 60 ml/min/1.73 m²

Agree statement

EXCLUSION CRITERIA

Age > 18 years

Glomerular filtration rate (Schwartz f.) ≤ 60 ml/min/1.73 m²

Patients with neurogenic bladder, myelomeningocele, uretero-pelvic junction and/or uretero-vescico junction obstruction, or other malformations leading to potential voiding disturbances, urethral valves

Patients with ongoing urinary tract infection.

PROCEDURE			Screening	Enrollment
Inclusion/exclusion criteria			X	
Informed Consent			X	
US			X	
DMSA scan			X	
Cystography			X	
Medical questionnaire				X
Vital signs				X
Blood Pressure				X
Urine analysis				X
Urine Culture				X
Renal function (BUN, serum creatinine)				X
Weight, height				X
Blood sample for DNA				X
Urinary sample for uromodulin (fozen at -80°C)				X

Data Management

Data will be recorded on excel.

Statistical Analysis

Data will be recorded and analyzed by SPSS Program.

Sample size

According to unpublished data in a limited number of pediatric patients, the mean value of UROMOD in urines is about 36 $\mu\text{g/g}$ of creatinine, and the standard deviation is about 16. We are interested to detect a **difference in UROMOD urinary concentration** between the test group and the control group of at least 9 $\mu\text{g/g}$ of creatinine **(25%)**. For a two sided test for inequality, with a power of 0.8 and an alpha level of 0.05, and assuming equal variance, **about 51 patients per group will be needed.**