Role of acyl-ghrelin, unacyl-ghrelin and obestatin in uremic cachexia in children and adolescents – Monzani Alice

Background and aim:

Cachexia, protein–energy wasting and growth retardation are common problems in pediatric patients with chronic kidney disease (CKD) and strongly predict morbidity and mortality [1]. Many potential factors are involved: low appetite and anorexia, decreased caloric intake, and increased resting metabolic rate. After renal transplantation (RTx) with normalization of renal function, improved appetite occurs, followed by catch-up growth, improved quality of life, and improved outcome.

The pathogenesis of CKD-associated cachexia is essentially unknown. Uremic toxins, chronic inflammation, and an altered plasma amino acid pattern have been proposed as causative factors, but a deregulation of orexigenic and anorexigenic hormones may also play a major role [2]. In healthy individuals, acyl-ghrelin (AG) leads to increased food intake with a subsequent increase in body weight and fat accumulation [3]. In contrast, unacyl-ghrelin (UAG) has opposite functions [3]. Obestatin is derived from the ghrelin precursor protein preproghrelin by alternative splicing and acts as an appetite inhibitor, similarly to UAG [4].

During uremia, plasma levels of orexigenic and anorexigenic hormones are altered. Previous studies in pediatric CKD patients reported increased total ghrelin levels, with AG levels similar to controls [1,5-7]. Following RTx, total ghrelin levels decrease to those of healthy controls [1]. Also obestatin has been reported to increase in CKD children, but few data are available on the regulation of obestatin under uremic conditions in children. To date, no data have been available on the AG/UAG balance in pediatric patients with renal insufficiency.

We analyzed the distribution of AG, UAG and obestatin in pediatric patients with different degrees of renal impairment, compared with healthy controls, investigating their potential contribution in the pathogenesis of uremic cachexia.

Subjects and methods:

We recruited uremic children and adolescents, i.e. subjects aged 1-20 years, with CKD stages II-V under conservative treatment (CKD-CT), or undergoing hemodialysis treatment (CKD-HD), or renal transplantation recipients (RTx). Exclusion criteria were the concomitant treatment with growth hormone and the presence of syndromic complexes. All the subjects were patients at the Pediatric Nephrology Division of IRCCS Ca' Granda - Ospedale Maggiore Policlinico – Milan, Italy. Data about age, primary renal disease, concomitant medications were collected from each subject. All the RTx patients received renal transplantation at least 6 months before the enrolment,

and all the CKD-HD patients had been on hemodialysis treatment for at least 3 months. The concomitant medication of uremic patients included bicarbonate, antihypertensive drugs, erythropoietin, and oral iron, calcitriol and phosphate binders as required.

The CKD stages were defined using the K/DOQI criteria of the US National Kidney Foundation: CKD stage I , GFR > 90 ml/min/1.73 m2; CKD stage II GFR 60–90 ml/min/1.73 m2; CKD stage III, GFR 30–60 ml/min/1.73 m2; CKD stage IV, GFR 15–30 ml/min/1.73 m2; CKD stage V, GFR <15 ml/min/1.73 m2; CKD stage V-D if replacement treatment by HD has been started [8].

Healthy children, outpatients of the Surgery Division of the IRCCS Ca' Granda - Ospedale Maggiore Policlinico – Milan, Italy, served as controls. They underwent a blood sample collection before a surgical intervention for the treatment of minor diseases that did not impair renal or endocrine function (i.e. phimosis, hydrocele, inguinal hernia, onychocryptosis, verrucae...).

The control subjects had no history of chronic disease and did not receive any regular medication. They were on unrestricted diet.

For all subjects, anthropometric measurements were performed (weight, height, waist circumference, biceps, triceps, subscapular, suprailiac skinfold thickness) and nutritional indexes were calculated (weight-SDS, height-SDS, BMI z-score, waist/height ratio, fat mass (FM)/Kg, fat-free mass (FFM)/Kg). Pubertal stage assessment was also performed.

Routine biochemical parameters [creatinine, urea, hemoglobin (Hb), C-reactive protein (CRP), glucose, insulin, total cholesterol (TOT-C), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglycerides (TG), albumin and IGF-I] were measured for all subjects, and other biochemical parameters [transferrin, prealbumin, bicarbonates (HCO3-), 25-OH Vitamin D (VitD), 1,25-(OH)2 VitD, apolipoprotein A and B (ApoA and ApoB), parathormone (PTH), omocystein, calcium, phosphorus] were measured only for the uremic patients at IRCCS Ca' Granda - Ospedale Maggiore Policlinico clinical laboratory. Glomerular filtration rate was estimated (eGFR) by the Schwartz formula [93], with k = 0.413, as appropriate for standardized creatinine. HOMA-IR was calculated by the formula: fasting plasma glucose (mg/dl) * fasting serum insulin (mU/l) / 405. Non-HDL cholesterol (n-HDL-C) was calculated by the formula: TOT-C – HDL-C. IGF-I SDS, Apolipoprotein B/apolipoprotein A (ApoB/ApoA) ratio and calcium by phosphorus product (Ca x P) were also calculated.

AG, UAG and obestatin levels determination was performed by the research laboratory of Pediatrics, Department of Health Sciences, Università del Piemonte Orientale, Novara – Italy.

Nutritional evaluation was performed only for the uremic patients. Daily Kcal and protein pro body kilo intake were estimated using a 3-day food diary. Hunger, satiety and food desire were evaluated by a visual analogue scale (VAS), and a 0-10 score was calculated for each parameter.

Mealtime behaviour problems were investigated by the Behavioral Pediatric Feeding Assessment

Scale (BPFAS) [98].

Resting energy expenditure (REE) was evaluated in 35 renal patients by indirect calorimetry (the other patients refused to undergo the measurement). REE% was calculated as follows: measured REE/predicted REE x100.

Bioimpedance was performed in renal patients by Tanita body composition analyser (Tanita corporation, Tokyo, Japan) to assess fluid overload.

Carotid Doppler ultrasonography was performed to measure the carotid intima-media thickness (cIMT).

Main results:

A total of 154 subjects were included in our cross-sectional study (M:F=100:54), 111 uremic patients and 43 control subjects. Out of 111 uremic patients, 43 were CKD-CT, 20 CKD-HD and 48 RTx. The 111 uremic patients (M:F=72:39) were aged 1.4 to 20 years, and their median age was 14.6 years (IQR 9.9-17.8). The 43 controls (M:F=28:15) were aged 1.4 to 17.6 years, and their median age was 8.1 years (IQR 5.7 – 12.7).

Study population characteristics are shown in Table 1.

The gender distribution was similar among the four groups, whereas control subjects were younger than uremic patients, even if a higher proportion of pubertal subjects was found in the control group (81.4% vs 51.4%, p=0.0013).

In uremic patients, the primary renal disease was congenital anomalies of the kidney and urinary tract (CAKUT) in 56 patients (36.4%), nephrotic syndrome in 15 patients (9.7%), ciliopathies in 12 patients (7.8%), atypical hemolytic uremic syndrome (aSEU) in 9 patients (5.8%), chronic glomerulonephritis in 5 patients (3.2%), renal insufficiency due to neonatal acute kidney injury in 2 patients (1.3%) and other renal disorders in 5 patients (3.2%). In 7 subjects (4.5%) the original cause of CKD was not known and a proper diagnosis was missing.

Table 1. Study population characteristics: clinical data with comparisons among the four groups

	CKD-CT (n=43)	**CKD-HD (n=20)**	**RTx (n=48)**	**CTR (n=43)**	**p value** (among the four groups)
Clinical data					
Gender, n (%) Males Females	 30 (69.8) 13 (30.2)	 9 (45) 11 (55)	 33 (68.7) 15 (31.3)	 28 (65.1) 15 (34.9)	NS
Age (years)	10.9 [*] [§] (6.5-16.4)	13.8 [#] [&] (9.4 – 16.7)	16.6 [£] (13.5 – 19.8)	8.1 (5.7 – 12.7)	**<0.0001** [*] <0.0001 *vs* RTx [§] 0.04 *vs* CTR [#] 0.01 *vs* RTx [&] 0.002 *vs* CTR [£] <0.0001 *vs* CTR

Pubertal stage, n (%) Pre-Pubertal Pubertal	 25 (58.1) * § 18 (41.9)	 13 (65) 7 (35)	 16 (33.3) 32 (66.7)	 8 (18.6) 35 (81.4)	**<0.0001** * 0.05 *vs*RTx § 0.001 *vs* CTR
CKD stage, n (%) Stage 0 Stage I Stage II Stage III Stage IV Stage V Stage VD	 0 0 6 (13.95) 18 (41.9) 13 (30.2) 6 (13.95) 0	 0 0 0 0 0 0 20 (100)	 0 6 (12.5) 18 (37.5) 21 (43.8) 3 (6.2) 0 0	 43 (100) 0 0 0 0 0 0	
Primary Renal Disease Ciliopathies Chronic GN Undiagnosed CKD CAKUT Nephrotic syndrome aSEU CKD post neo-AKI Others	 3 (7%) 1 (2.3%) 6 (14%) 28 (65.1%) 1 (2.3%) 2 (4.7%) 2 (4.7%) 0	 3 (15%) 1 (5%) 0 5 (25%) 6 (30%) 3 (15%) 0 2 (10%)	 6 (12.5%) 3 (6.3%) 1 (2.1%) 23 (47.9%) 8 (16.7%) 4 (8.3%) 0 3 (6.3%)		

GN: glomerulonephritis, CAKUT: congenital anomalies of the kidney and urinary tract, aSEU: atypical hemolytic uremic syndrome, neo-AKI: neonatal acute kidney injury.

Weight-SDS and height-SDS were significantly lower in uremic patients than in controls (-1.09 [1.81 – 0.09] vs. 0.21 [-0.61 – 0.94], p<0.0001, and -1.30 [-2.06 – -0.44] vs. 0.42 [-0.36 – 1.30], p<0.0001, respectively). However, BMI z-score was similar in uremic and control subjects (-0.44 [-1.24 – 0.41] vs. 0.04 [-0.85 – 0.91]). The prevalence of underweight subjects was similar in the four groups according to 2x4 contingency table and between uremic patients and controls (19.8% vs. 18.6%).

Anthropometric measurements are shown in table 2.

Table 2. Study population characteristics: anthropometric measures with comparisons among the four groups

	CKD-CT (n=43)	**CKD-HD (n=20)**	**RTx (n=48)**	**CTR (n=43)**	**p value** (among the four groups)
Anthropometric measures					
Weight-SDS	-0.39 (-1.81 – 0.26)	-1.73 (-2.65 – -0.70)	-0.76 (-1.31 – 0.19)	0.21 (-0.61 – 0.94)	**<0.0001**
Height-SDS	-0.97 (-1.68 – -0.14)	-1.54 (-2.67 – -0.64)	-1.17 (-2.11 – -0.66)	0.42 (-0.36 – 1.30)	**<0.0001**
BMI z-score	0.01 (-0.99 – 0.69)	-1.26 (-1.66 – -0.23)	-0.14 (-0.66 – 0.57)	0.04 (-0.85 – 0.91)	**0.006**
BMI category, n (%) Underweight Normalweight Overweight Obese Morbid obese	 9 (20.9) 23 (53.5) 10 (23.3) 1 (2.3) 0	 7 (35.0) 12 (60.0) 1 (5.0) 0 0	 6 (12.5) 31 (64.6) 10 (20.8) 1 (2.1) 0	 8 (18.6) 21 (48.8) 12 (27.9) 1 (2.35) 1 (2.35)	NS
Waist/height ratio	0.45 (0.42 – 0.49)	0.44 (0.42 – 0.49)	0.46 (0.42 – 0.50)	0.46 (0.42 – 0.52)	NS
FM%	22.3	23.1	25.6	-	**0.018**

	CKD-CT (n=43)	**CKD-HD (n=20)**	**RTx (n=48)**	**CTR (n=43)**	**p value** (among the four groups)
	(18.3 – 25.3)	(21.9 – 23.6)	(21.5 – 31.5)		
FM/Kg	7.7 (4.2 – 13.4)	9.3 (5.4 – 11.0)	13.8 (9.7 – 17.0)	-	**0.005**
FFM%	77.7 (74.7 – 81.7)	76.9 (76.4 – 78.1)	74.4 (68.5 – 78.5)	-	**0.018**
FFM/Kg	30.2 (19.9 – 42.7)	30.7 (18.6 – 34.4)	38.3 (27.2 – 42.2)	-	**0.039**
rx	616.0 (555.0 – 647.0)	678.5 (594.0 – 818.0)	603.5 (534.0 – 673.0)	-	**0.039**
xc	64.0 (57.0 – 68.0)	67.0 (58.0 – 76.0)	62.0 (58.5 – 68.0)	-	NS

AG levels were not different in the four groups (Figure 1) .

UAG was significantly higher in all uremic groups than in controls, and in particular the highest levels were found in CKD-HD patients, progressively reducing in CKD-CT, RTx and controls (Figure 2). Obestatin was significantly higher in CKD-HD patients than in CKD-CT, RTx and control subjects (Figure 3).

Figure 1. AG levels in CKD-CT, CKD-HD, RTx and CTR subjects.

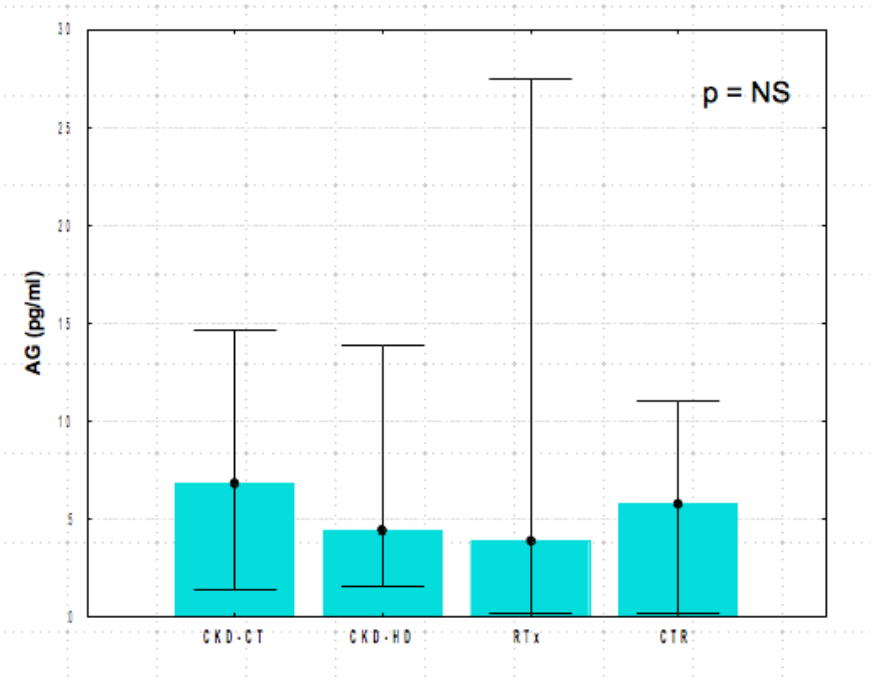


Figure 2. UAG levels in CKD-CT, CKD-HD, RTx and CTR subjects.

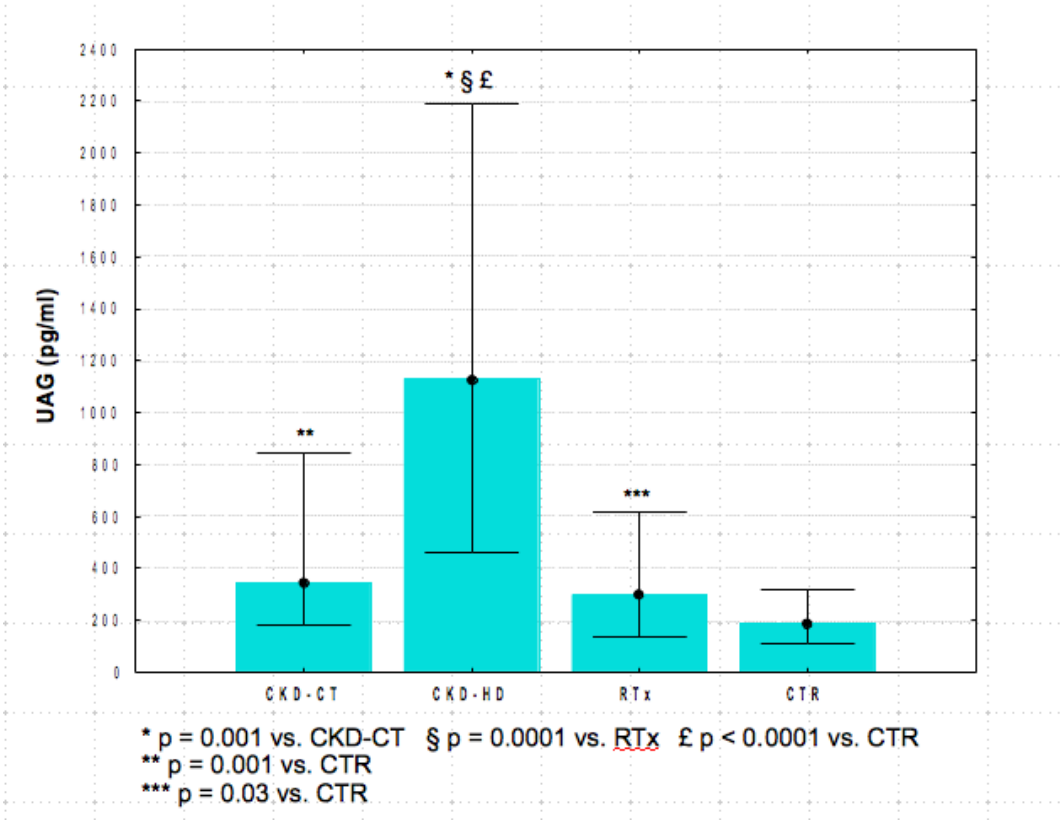
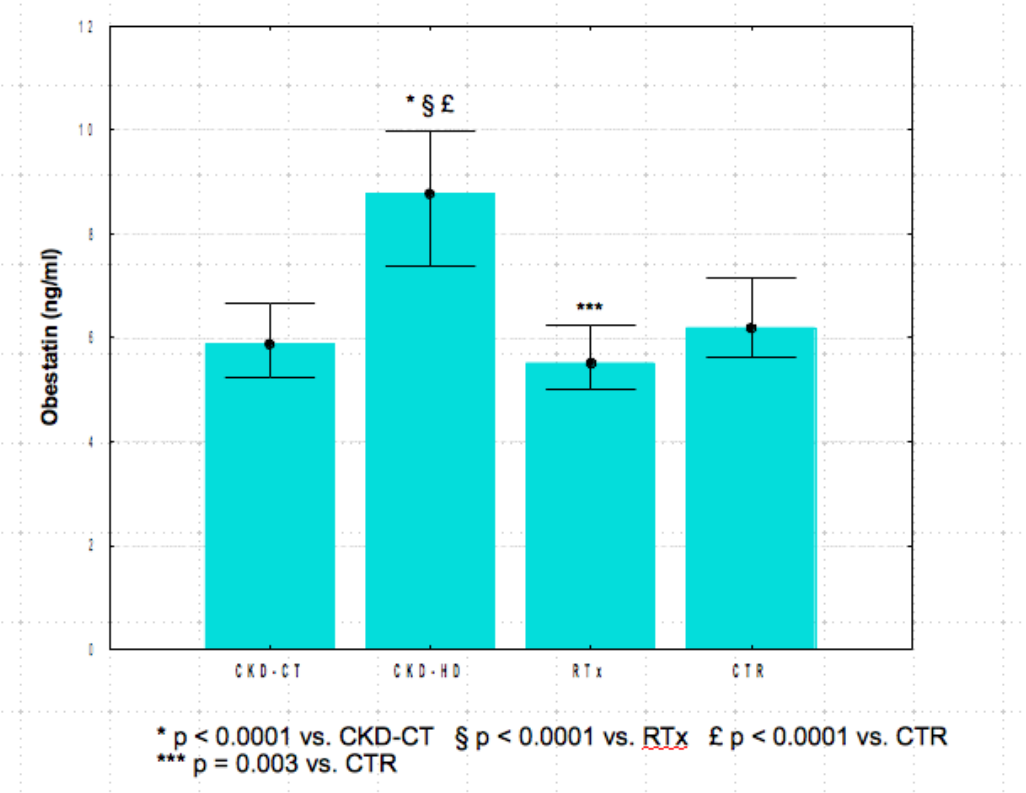


Figure 3. Obestatin levels in CKD-CT, CKD-HD, RTx and CTR subjects.



In particular, when orexigenic/anorexigenic hormones levels are compared according to CKD stage calculated by eGFR, no differences were found for AG, whereas median UAG and obestatin levels

were significantly different in different stages, with a trend to increase with the progression of renal impairment (Table 3).

Table 3. Median (IQR) levels of orexigenic/anorexigenic hormones according to CKD stages

	Stage I (n=6)	**Stage II** (n=24)	**Stage III** (n=39)	**Stage IV** (n=15)	**Stage V** (n=6)	**Stage VD** (n=20)	p (Kruskall-Wallis)
AG	6.50 (0.19-23.21)	6.75 (0.03-27.46)	4.56 (0.25-12.14)	8.94 (3.34-31.23)	2.91 (1.19-14.88)	4.41 (1.54-13.84)	0.76
UAG	275.2 (112.9 -92.8)	276.1 (169.7-666.2)	314.1 (195.7-617.4)	299.1 (131.2-672.9)	676.0 (130.1-1338.7)	1127.2 (463.3-2188)	**0.009**
Obestatin	5.68 (4.83-7.22)	5.41 (5.13-5.97)	5.81 (5.02-6.68)	5.74 (5.22-6.28)	6.35 (5.75-6.68)	8.76 (7.37-9.99)	**<0.0001**

UAG was positively correlated with creatinine and urea levels and inversely correlated with eGFR, also after adjustments for gender, age, pubertal status and BMI z-score. Similar positive and negative correlations were found for obestatin. AG did not correlate with renal parameters (Table 4).

Table 4. Correlations between orexigenic/anorexigenic hormones and renal parameters in all subjects (adjusted for gender, age, pubertal status and BMI z-score)

	AG	**UAG**	**Obestatin**
Renal parameters			
Creatinine	R = -0.054 NS	R = 0.434 p < **0.0001**	R = 0.473 p < **0.0001**
eGFR	R = 0.043 NS	R = -0.422 p **<0.0001**	R = -0.298 p **<0.0001**
Urea	R = -0.049 NS	R = 0.469 p **<0.0001**	R = 0.371 p **<0.0001**

Correlations between AG, UAG and obestatin and all the other continuous variables in all 154 subjects are shown in Table 5.

In the whole population, AG did not correlate with any of the anthropometric, laboratory, nutritional and cardiovascular parameter analyzed, with the exception of weak negative correlations with Hb and IGF-I SDS and positive correlation with UAG. Conversely, UAG was negatively correlated with all the anthropometric measures, except for waist/height ratio, and xc at bioimpedence. Similarly, obestatin was negatively correlated with weight-SDS, BMI z-score, FM/Kg, FFM/Kg and rx.

Table 5. Correlations between orexigenic/anorexigenic hormones and all the continuous variables (in all 154 subjects)

	AG	UAG	Obestatin
Clinical data			
Age	R = -0.15 NS	R = -0.248 p = **0.002**	R = -0.263 p = **0.001**
Anthropometric measures			
Weight-SDS	R = 0.024 NS	R = -0.471 p **<0.0001**	R = -0.223 p = **0.006**
Height-SDS	R = 0.022 NS	R = -0.296 p **<0.0001**	R = -0.130 NS
BMI z-score	R = 0 NS	R = -0.371 p **<0.0001**	R = -0.161 p = **0.05**
Waist/height ratio	R = 0.123 NS	R = -0.032 NS	R = 0.019 NS
FM/Kg	R = -0.101 NS	R = -0.518 p **<0.0001**	R = -0.269 p = **0.015**
FFM/Kg	R = -0.163 NS	R = -0.527 p **<0.0001**	R = -0.262 p = **0.018**
rx	R = 0.072 NS	R = 0.288 p = **0.004**	R = 0.301 p = **0.002**
xc	R = 0.04 NS	R = 0.068 NS	R = 0.078 NS
Laboratory data			
Creatinine	R = -0.020 NS	R = 0.273 p = **0.0007**	R = 0.147 NS
eGFR	R = -0.024 NS	R = -0.376 p **<0.0001**	R = -0.194 p = **0.016**
Urea	R = 0.056 NS	R = 0.405 p **<0.0001**	R = 0.167 p = **0.039**
Hb	R = -0.164 p = **0.047**	R = -0.271 p = **0.0007**	R = -0.115 p = 0.188
HCO3-	R = -0.049 NS	R = -0.295 p = **0.011**	R = -0.297 p = **0.010**
CRP	R = -0.048 NS	R = 0.013 NS	R = -0.082 NS
Glucose	R = 0.141 NS	R = -0.122 NS	R = -0.119 NS
Insulin	R = -0.028 NS	R = -0.170 NS	R = -0.065 NS
HOMA-IR	R = -0.003 NS	R = -0.180 p = **0.047**	R = -0.065 NS
TOT-C	R = -0.108 NS	R = -0.159 p = 0.050	R = -0.033 NS
HDL-C	R = -0.074 NS	R = 0.093 NS	R = -0.077 NS
LDL-C	R = -0.035 NS	R = -0.204 p = **0.012**	R = 0.029 NS
n-HDL-C	R = -0.049 NS	R = -0.143 NS	R = 0.081 NS

	AG	UAG	Obestatin
TG	R = -0.100 NS	R = 0.153 p = 0.066	R = 0.197 p = **0.016**
PNF-I	R = 0.126 NS	R = -0.076 NS	R = 0.130 NS
Albumin	R = -0.077 NS	R = -0.078 NS	R = -0.124 NS
IGF-1 SDS	R = 0.178 p = **0.037**	R = 0.078 NS	R = 0.179 p = **0.032**
Transferrin	R = 0.165 NS	R = -0.143 NS	R = -0.208 p = **0.032**
Prealbumin	R = -0.116 NS	R = -0.186 p = 0.066	R = 0.178 NS
25-OH VitD	R = -0.058 NS	R = -0.119 NS	R = -0.313 p = **0.002**
1,25-(OH)2 VitD	R = -0.003 NS	R = -0.301 p = **0.004**	R = -0.291 p = **0.004**
ApoA	R = 0.143 NS	R = 0.038 NS	R = -0.141 NS
ApoB	R = -0.045 NS	R = 0.328 p = **0.003**	R = -0.117 NS
ApoB/ApoA	R = -0.179 NS	R = -0.379 p = **0.001**	R = -0.104 NS
PTH	R = 0.074 NS	R = 0.257 p = **0.009**	R = 0.360 p **<0.0001**
Omocystein	R = -0.158 NS	R = -0.026 NS	R = -0.037 NS
Calcium	R = -0.078 NS	R = -0.020 NS	R = -0.052 NS
Phosphorus	R = 0.051 NS	R = 0.217 p = **0.026**	R = 0.326 p = **0.001**
Ca x P	R = 0.02 NS	R = 0.231 p = **0.017**	R = 0.327 p = **0.001**
AG	-	R = 0.215 p = **0.009**	R = 0.05 NS
UAG	R = 0.215 p = **0.009**	-	R = 0.310 p = **0.0001**
Obestatin	R = 0.05 NS	R = 0.310 p = **0.0001**	-
AG/UAG	-	-	R = -0.074 NS
UAG/AG	-	-	R = 0.203 p = **0.027**
Nutritional data			
Kcal/Kg/die	R = 0.059 NS	R = 0.427 p = **0.0004**	R = 0.162 NS
DPI/Kg/die	R = -0.023 NS	R = 0.311 p = **0.012**	R = 0.283 p = **0.022**
BPFAS	R = -0.032 NS	R = 0.246 p = **0.01**	R = 0.108 NS

	AG	UAG	Obestatin
Hunger VAS score	R = 0.097 NS	R = -0.217 p = 0.061	R = -0.105 NS
Satiety VAS score	R = 0.091 NS	R = -0.129 NS	R = -0.116 NS
Food desire VAS score	R = -0.069 NS	R = -0.236 p = **0.041**	R = -0.129 p = 0.271
REE%	R = 0.174 NS	R = 0.236 NS	R = 0.258 NS
Vascular parameters			
cIMT dx	R = 0.146 NS	R = -0.188 NS	R = -0.123 NS
cIMT sn	R = 0.045 NS	R = 0.127 NS	R = 0.148 NS

Conclusions and future perspectives:

One of the most relevant results of our study is the trend in UAG and obestatin levels, that were very high in CKD-HD and progressively reduced in CKD-CT, RTx and controls. Conversely, no difference was found in AG levels in the four groups. Our results are consistent with most of the previous reports about orexigenic/anorexigenic hormones in pediatric renal failure [1,5-7]. In previous reports, the elevation in total but not acyl-ghrelin suggested that the excess circulating ghrelin was UAG. This hypothesis has been confirmed in our series. Since UAG and obestatin are known to inhibit appetite, increased levels might contribute to cachexia in pediatric renal patients. The correlation analyses showed that both UAG and obestatin seem to behave as retentive molecules, being directly correlated with creatinine and urea and inversely correlated with eGFR, also after adjustment for known potential confounding factors such as gender, age, pubertal status and BMI z-score. Moreover, a trend to increase with the progression of renal failure was shown for both UAG and obestatin by comparisons among different CKD-stages.

The increase of anorexigenic hormones such as UAG and obestatin with the progression of renal impairment, known to be linked with a decline in nutritional status, suggest they could play a key role in uremic cachexia.

Secondly, UAG and obestatin showed a negative correlation with weight-SDS and BMI z-score. An inverse correlation between total ghrelin and BMI has been already demonstrated in healthy children [9] as well as in adults with end-stage renal disease [10].

We therefore showed that UAG, and at a minor extent obestatin too, is a good inverse biomarker of nutritional status in uremic children and adolescents, being negatively correlated with all the anthropometric measures.

Moreover, both UAG and obestatin were inversely correlated with fat mass and fat-free mass.

Therefore, with regard to their inverse correlation with fat-free mass, UAG and obestatin could be considered as promising biomarkers of muscle-wasting and sarcopenia, known to be linked to adverse long-term outcomes in uremic patients, even in conditions of normal BMI status [11].

In conclusion, UAG and obestatin seem to be promising inverse indicators of nutritional status in CKD children and adolescents, negatively related to renal function. Interesting perspectives of UAG and obestatin as biomarkers of uremic cachexia in pediatric age could be standing out. And therapeutic implications in terms of optimization of dialytic techniques to maximise their removal in CKD-HD patients could be as well hypothesized.

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Seminars (October 2014 – September 2015)

- 28.10.2014: “Natural compounds as modulators of epigenetic events” (Prof. Diederich)
- 21.11.2014: "Stem cell in the regeneration and repair of the tissues and organs" (Prof. Prat)
- 14.11.2014: "Tissue engineering: the state of the art" (Dott.Boccafoschi)
- 28.11.2014: "Humoral responses to HCV infection and clinical outcomes” (Prof. Patel)
-11.12.2014: "Meet the expert on Endocrinology and Metabolism" (organized by professors Aimaretti and Marzullo)
- 16.12.2014: "From the legend of Prometheus to regenerative medicine" (Prof. Musarò)
- 17.12.2015: "Microglia microvesicles: messengers from the diseased brain” (Prof. Furlan)
- 19.01.2015: “Anticancer strategy targeting cancer cell metabolism in ovarian cancer” (Prof. Dr Yong-Sang Song)
- 20.01.2015: “Different molecular mechanisms regulate hepatocyte differentiation during the transitions between epithelial and mesenchymal states” (Dr Alonzi)
- 21.01.2015: “Targeting the liver to cure myocarditis: a lesson from a model of STAT3-dependent auto-immune myocarditis” (Prof. Poli)
- 09.04.2015: "Signal control in iNKT cell development and function" (Prof Zhong)
- 21.04.2015: "Actin-based mechanisms in the control of gene expression and cell fate" (Prof. Percipalle)
- 07.05.2015: “An Integrated Approach to the Diagnosis and Treatment of Ovarian Cancer” (Prof. McDonald)
- 25.05.2015: "Ribosomopathies" (Prof. Ellis)
- 10.06.2015: "Basis of scientific research" (Prof. Filigheddu)

Congresses and courses:

- "Corso PBLS-D – esecutore sanitario" - Novara, 29.09.2014
- "Corso di rianimazione neonatale in sala parto" - Novara, 17.12.2014
- "4° Convegno sui Disturbi Specifici dell'Apprendimento"- Vigevano, 10.01.2015
- "Medical writing in endocrinology and metabolism" - Palermo, 16-18.04.2015
- "Corso PALS provider" - Novara, 28-29.04.2015
- "Master school: 3° corso avanzato sulla malattia di Fabry" - Monza, 6.05.2015
- "Corso propedeutico e pratico di ecografia dell'apparato urinario in età pediatrica" - Milano, 21.05.2015
- "Novità in Nefrologia Pediatrica" - Milano, 21.05.2015
- "XVII Workshop in endocrinologia e metabolismo dell'età evolutiva" - Milano, 22.05.2015

Abstracts and posters:

- "Ruolo di Ghrelina Desacilata nell'anoressia e malnutrizione uremica", selected as best oral communication and winner of "Premio Rizzoni" in 31° Congresso Nazionale SINePe, 1-3.10.2015 in Vieste (FG)
- "Ruolo di ghrelin non acilata (unacyl-ghrelin, UAG) nella cachessia uremica in pazienti pediatrici con insufficienza renale cronica", submitted to SIPPS, 15-18.10.2015, in Stresa (VB)
- "Unacyl-Ghrelin: A Key Molecule in Uraemic Cachexia in Children and Adolescents", selected for poster presentation at the ASN Kidney Week 2015 Annual Meeting, 5-8.11.2015 in San Diego, CA.

Scientific publications (October 2014 – September 2015):

- Monzani A, Genoni G, Cassone R, Binotti M, Ferrero F, Bona G. Hyperexcitability as the main sign of neonatal hypoxia. Minerva Pediatr. 2015;67:276-7.
- Cadario F, Prodam F, Savastio S, Monzani A, Balafrej A, Bellomo G, Bona G. Vitamin D status and type 1 diabetes in children: evaluation according to latitude and skin color. Minerva Pediatr. 2015;67:263-7.
- Bona G, De Luca F, Monzani A (Eds.) Thyroid Diseases in Childhood: Recent Advances from Basic Science to Clinical Practice. Springer 2015 (author and co-editor).
- Bona, Gianni, De Luca, Filippo, Monzani, Alice (Eds.)
- Miniero R, Talarico V, Aloe M, Monzani A, Bona G. Hemolytic uremic syndrome in children. Accepted for publication in Minerva Pediatrica.
- Ardissino G, Tel F, Possenti I, Testa S, Consonni D, Paglialonga F, Salardi S, Borsa-Ghiringhelli N, Salice P, Tedeschi S, Castorina P, Colombo R, Arghittu M, Daprai L, Monzani A, Tozzoli R, Brigotti M, Torresani E. Early Volume Expansion and Outcomes of Hemolytic Uremic Syndrome. Accepted for publication in Pediatrics.