ORIGINAL ARTICLE

The effect of a multidisciplinary weight loss program on renal circadian rhythm in obese adolescents

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Abstract

Adolescent obesity is a serious health problem associated with many comorbidities. Obesity-related alterations in circadian rhythm have been described for nocturnal blood pressure and for metabolic functions. We believe renal circadian rhythm is also disrupted in obesity, though this has not yet been investigated. This study aimed to examine renal circadian rhythm in obese adolescents before and after weight loss.

In 34 obese adolescents (median age 15.7 years) participating in a residential weight loss program, renal function profiles and blood samples were collected at baseline, after 7 months, and again after 12 months of therapy. The program consisted of dietary restriction, increased physical activity, and psychological support. The program led to a median weight loss of 24 kg and a reduction in blood pressure. Initially, lower diurnal free water clearance (-1.08 (-1.40–-0.79) mL/min) was noticed compared with nocturnal values (0.75 (-0.89–-0.64) mL/min). After weight loss, normalization of this inverse rhythm was observed (day -1.24 (-1.44–1.05) mL/min and night -0.98 (-1.09–-0.83) mL/min). A clear circadian rhythm in diuresis rate and in renal clearance of creatinine, solutes, sodium, and potassium was seen at all time points. Furthermore, we observed a significant increase in sodium clearance. Before weight loss, daytime sodium clearance was 0.72 mL/min (0.59–0.77) and nighttime clearance was 0.46 mL/min (0.41–0.51). After weight loss, daytime clearance increased to 0.99 mL/min (0.85–1.17) and nighttime clearance increased to 0.78 mL/min (0.64–0.93).

Conclusion: In obese adolescents, lower diurnal free water clearance was observed compared with nocturnal values. Weight loss led to a normalization of this inverse rhythm, suggesting a recovery of the anti-diuretic hormone activity. Both before and after weight loss, clear circadian rhythm of diuresis rate and renal clearance of creatinine, solutes, sodium, and potassium was observed.

What is Known:
• *Obesity-related alterations in circadian rhythm have been described for nocturnal blood pressure and for metabolic functions. We believe renal circadian rhythm is disrupted in obesity, though this has not been investigated yet.*

What is New:
• *In obese adolescents, an inverse circadian rhythm of free water clearance was observed, with higher nighttime free water clearance compared with daytime values. Weight loss led to a normalization of this inverse rhythm, suggesting a recovery of the anti-diuretic hormone activity.*
• *Circadian rhythm in diuresis rate and in the renal clearance of creatinine, solutes, sodium, and potassium was preserved in obese adolescents and did not change after weight loss.*

Kim Pauwaert and Sarah Dejonckheere contributed equally to this work.

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Abbreviations

ACE	Angiotensin-converting enzyme
ADH	Anti-diuretic hormone
AGT	Angiotensinogen
AngII	Angiotensin II
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
FWC	Free water clearance
GFR	Glomerular filtration rate
RAAS	Renin-angiotensin-aldosterone system
RFP	Renal function profile
RPF	Renal plasma flow

Introduction

Adolescent obesity is a serious public health problem worldwide. During the last few decades, the prevalence of childhood and adolescent obesity has increased at an alarming rate, not only in the Western world but also in low- and middle-income countries (WHO) [35]. Up to 11–15% of Belgian children and adolescents are overweight and 3–5% are reportedly obese. Children with obesity have an increased risk of becoming obese adults [4, 11, 18, 20, 31] and, developing chronic conditions, such as cardiovascular disease, diabetes mellitus (DM), hypertension, and kidney disease [19, 28].

We hypothesized that adolescent obesity is associated with a disruption of renal circadian rhythm. Like many other biological processes, renal functions exhibit clear circadian variations. Urine production and voiding tend to predominate during the awakening phase, whereas increased urine storage and reduced micturition frequency predominate during the sleeping phase [25]. This circadian rhythm is believed to be driven by a self-sustained central system, located in the suprachiasmatic nucleus of the hypothalamus, communicating with peripheral systems in nearly every cell type [10, 25]. This system influences renal blood flow and circulating hormones affecting urine production and storage, sympathetic/parasympathetic tone, blood pressure (BP), and thus, glomerular filtration rate (GFR), and water and solute handling [9].

Disturbances in proper voiding rhythms are typically present in children with nocturnal enuresis and elderly individuals with nocturia [10]. Renal circadian rhythm in obesity has not yet been investigated. Previous studies, however, have observed obesity-related alterations in the circadian rhythm of other biological functions. Macumber et al. [21] demonstrated that obesity is associated with a relative decrease in nocturnal BP dipping in children. Pagano et al. [26] discussed the deranged circadian rhythm of metabolic functions and glucose homeostasis in obese adults.
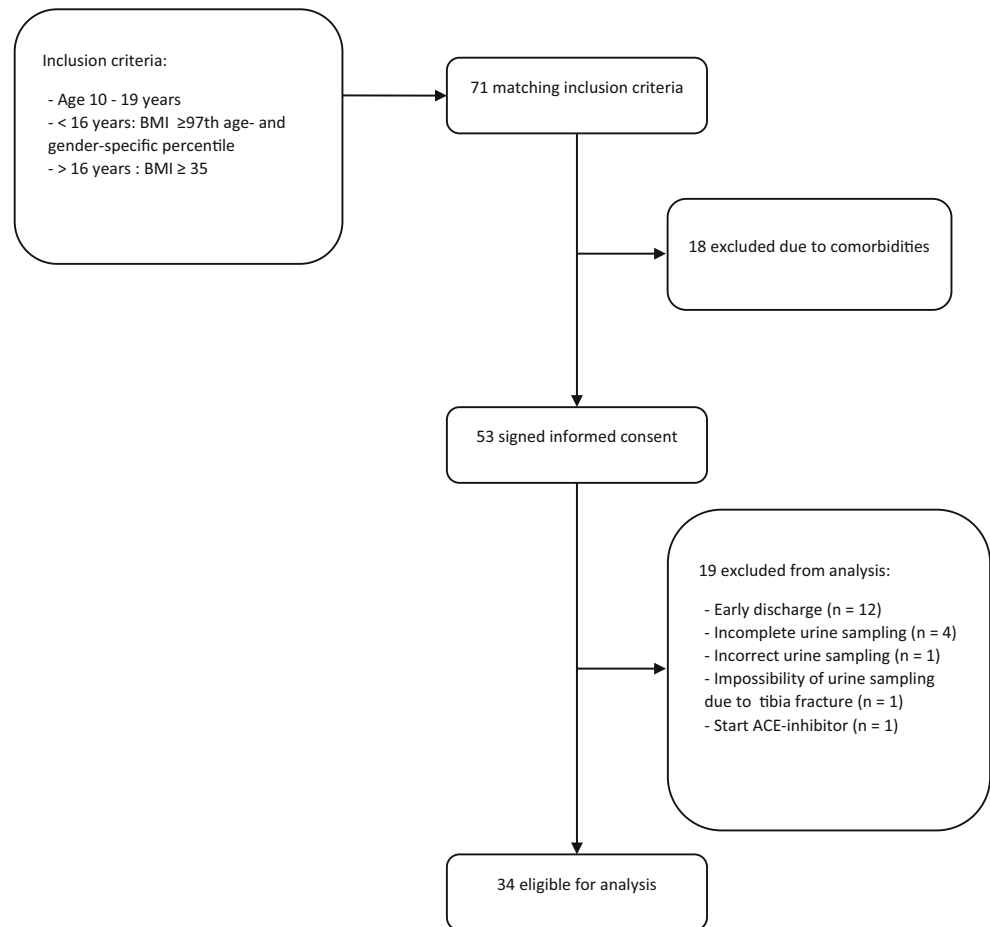
Subsequently, obesity-related kidney dysfunction has been examined in adults. This dysfunction is believed to be indirectly mediated by comorbid conditions, such as DM and hypertension, and directly mediated by physical compression of the kidneys by visceral adiposity, inflammation, endothelial dysfunction [33], hyperinsulinemia [27], and a deranged endocrine activity of the visceral adipose tissue. Hyperinsulinemia leads to increased sodium and potassium reabsorption, independently of GFR and plasma aldosterone [22, 26]. Deranged endocrine activity may affect kidney function through three mechanisms: an overactive renin-angiotensin-aldosterone system (RAAS) [3, 6, 28, 30], a dysregulated natriuretic peptides system [29], or an overactive sympathetic nervous system [7]. These direct and indirect mechanisms contribute to impaired pressure natriuresis, increased renal tubular sodium reabsorption, and blood volume expansion [14, 19]. As a result, a compensatory increase in renal plasma flow (RPF), glomerular pressure, and hyperfiltration sets in to maintain sodium balance. This compensation spurs the development of glomerular hypertension, increased glomerular permeability, and proteinuria, and ultimately leads to glomerulomegaly and focal segmental glomerulosclerosis [5, 16, 29, 32]. Several studies showed that weight loss in obese patients can improve glomerular hemodynamics and, thus, counteract the development of obesity-related renal insufficiency [2, 5]. We propose that these aforementioned mechanisms of kidney disease contribute to a derangement of the renal circadian rhythm as well.

The objective of this prospective study was to examine renal circadian rhythm in obese adolescents before and after weight loss.

Materials and methods

Patient selection

This prospective interventional study was performed at the medical pediatric rehabilitation center "Zeepreventorium", De Haan, between July 2016 and June 2017. Obese adolescents aged 10 to 19-year-olds were recruited at the beginning of a 12-month residential obesity treatment program. Exclusion criteria were comorbidities (kidney failure, heart failure, liver failure, DM, and diabetes insipidus), pregnancy, and intake of medication with a potential effect on urine output (diuretics, desmopressin, ACE-inhibitors, AngII receptor antagonists, non-steroidal anti-inflammatory drugs, corticosteroids, lithium, and selective serotonin reuptake inhibitors). After data collection, 19 patients were excluded from analysis due to early discharge, incomplete urine sampling, incorrect urine sampling, impossibility of urine sampling due to a tibial fracture, or start of an ACE-inhibitor (Fig. 1).

Fig. 1 Flowchart overviewing patient selection for analysis

Inclusion criteria:

- Age 10 - 19 years
- < 16 years: BMI ≥97th age- and gender-specific percentile
- > 16 years : BMI ≥ 35

71 matching inclusion criteria

18 excluded due to comorbidities

53 signed informed consent

19 excluded from analysis:

- Early discharge (n = 12)
- Incomplete urine sampling (n = 4)
- Incorrect urine sampling (n = 1)
- Impossibility of urine sampling due to tibia fracture (n = 1)
- Start ACE-inhibitor (n = 1)

34 eligible for analysis

Participants followed a multidisciplinary program, which consisted of moderate dietary restriction, psychological support, and regular physical activity. The diet consisted of 1600–1900 kcal/day, 200–250 g of carbohydrates, 25–35 g of fats, 75–90 g of proteins, and a sodium and potassium content of 2.5–4 g daily. Adolescents were encouraged to drinking at least 2 glasses of water (or milk during breakfast) with their meals and carry a water bottle at all times. This water replaced the soda or juice that the adolescents were used to drink before enrollment. Physical activity consisted of 2 h of supervised play and lifestyle activities daily, 100 min of physical education courses per week at school, and 150 min of supervised training sessions every week. Qualified physiotherapists supervised the participants during all training sessions [1].

Data collection

Data was collected at the following 3 time points: at the onset of the residential program in July 2016, mid-term after 7 months of treatment and at its completion after 12 months in June 2017. All patients completed a renal function profile (RFP) and a morning blood sample. BP, body weight, and height were measured. Standardized measurements were obtained at all time points: identical daily routines with standardized meals and fluid intake, similar sports activities, and comparable day-night rhythm.

Anthropometry and comorbidities

Anthropometric measurements were performed after breakfast, with the subjects wearing light school uniform clothing, without footwear. Bodyweight was measured on a digital scale with a precision of 0.1 kg and height was measured to the nearest 0.01 m using a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight/heigth^2 (kg/m^2). BMI z-score was calculated as BMI adjusted to weight, height, and age. Overweight and obesity were defined as a BMI equal to or above the age- and gender-specific 85th and 97th percentile respectively according to regional charts in adolescents younger than 16 years. In adolescents older than 16 years, overweight and obesity were defined as BMI ≥ 30 and ≥ 35 respectively.

BP was measured three times in the seated position by an automated electronic sphygmomanometer (GE Healthcare, Carescape V100). Hypertension was defined as a mean systolic and/or diastolic BP equal to or above the age-, gender-, and height-specific 95th percentile [23]. Presence of insulin

resistance was extracted from the medical files of the participants.

RFP and blood sampling

A RFP is a 24 h-urine collection in which urine samples are collected at fixed time points every 3 h, starting 3 h after the first-morning void. Daytime samples were taken at 9 am (1), 12 am (2), 15 pm (3), 18 pm (4), and 21 pm (5). The nighttime samples were taken at 0 am (6), 3 am (7), and 6 am (8). The volume of each sample, and of each micturition in between, was noted to calculate the 24 h, daytime and nighttime urine volume and diuresis rate. After an overnight fast, a sober serum sample was taken.

Biochemical analyses

Sodium, potassium, osmolality, and creatinine were measured in the blood sample and for each of the 8 urine samples. The renal clearance of creatinine, solutes, sodium, and potassium (Usubst × Uflow/Psubst), free water clearance (FWC) (urine flow-solute clearance), fractional excretion of sodium, and potassium (Usubst × Pcreat/Ucreat × Psubst) were calculated. eGFR was calculated and corrected for the body surface area (BSA) (creatinine clearance × 1.73/BSA).

Statistical analysis

Statistical analysis was performed using SPSS®, version 25. The median, interquartile range (IQR), and frequency were recorded as descriptive parameters. The Shapiro-Wilk test was used to identify the normal distribution of the variables. The McNemar test was used to compare two paired categorical variables. The continuous variables were analyzed using the non-parametric Wilcoxon matched-pairs signed-ranks test. Statistical significance was assessed using two-tailed tests and determined by $p < 0.05$. To identify independent predictors for altered circadian rhythm, a multivariate Cox regression analysis with calculation of the hazard ratio was performed.

The study was approved by the Ghent University Hospital review board (EC 2015/1438). The Declaration of Helsinki was followed and conducted in accordance with the legal regulations in Belgium. Written informed consent was obtained from both the parents and all individual participants included in the study.

Results

Patient characteristics and comorbidities

A total of 34 patients were eligible for analysis. Median age at baseline was 15.7 (14.1–16.7) years, and 73.5% of participants

were female. One year of treatment led to a median weight loss of 24.0 (17.9–33.5) kg or 21.9 (18.7–28.3) %. The median BMI z-score at baseline was calculated at 2.42 (2.23–2.73) and decreased significantly ($p < 0.001$) after treatment (1.56 (1.28–1.92)). Each adolescent participating in the study showed a weight loss (minimum weight loss of 11.9 kg). Weight loss was more pronounced in the male group, leading to a median male weight loss of 41.9 kg compared with females (21.4 kg). After treatment, 6 adolescents had a normal BMI, 12 were overweight, and 16 remained obese. A significant decrease in BP was observed after both 7 and 12 months of weight loss. At the end of the treatment program, the systolic BP decreased significantly ($p < 0.001$) to a median of 114.5 (106.5–120.55) mmHg and the diastolic BP decreased ($p = 0.043$) to a median of 67.5 (62–72.25) mmHg. Initially, 27 (79.4%) patients were assessed as hypertensive. After 12 months of weight loss, only 4 (11.8%) patients were classified as hypertensive. Before weight loss, 28 (82.4%) patients had insulin resistance, which diminished significantly ($p < 0.001$) to 6 (17.6%) patients at the end of the program (Table 1 and Fig. 2).

Renal function profile

Diuresis rate

Before and after 12 months of weight loss, the diuresis rate was significantly lower during the nighttime compared with daytime measurements ($p = 0.013$ and $p = 0.002$, respectively). Nevertheless, this circadian rhythm appeared more pronounced after weight loss. A significant increase in diuresis rate was reported after 7 and 12 months of treatment ($p < 0.001$ and $p < 0.001$, respectively) (Table 2 and Fig. 3).

Creatinine clearance

A significant decrease in nighttime creatinine clearance compared with daytime clearance was demonstrated before ($p < 0.001$) and after ($p = 0.043$) weight loss. Creatinine clearance was not statistically different between baseline measurement and follow-up time points ($p = 0.4$ and $p = 0.071$, respectively) (Table 2 and Fig. 3). We calculated the eGFR as creatinine clearance per 1.73 m^2 and noted a significant increase ($p = 0.007$) to a median eGFR after weight loss of 137.57 (123.50–155.73) mL/min.

Free water clearance

Before and after 7 months of treatment, nocturnal FWC was significantly higher than daytime values ($p < 0.001$ and $p < 0.001$, respectively). After 12 months of weight loss, nighttime FWC did not differ from daytime levels ($p = 0.091$). After 7 and 12 months of treatment, no significant change in FWC was observed ($p = 0.082$ and $p = 0.321$,

Table 1 Patient characteristics

	Baseline	After 7 months	p value*[1]	After 12 months	p value*[2]
Height (m)	1.69 (1.62–1.77)	1.70 (1.63–1.78)	/	1.70 (1.64–1. 79)	/
Weight (kg)	108.4 (93.5–130.4)	85.4 (77.3–108.4)	< 0.001	78.3 (72.8–100.9)	< 0.001
BMI (kg/m^2)	37.2 (33.4–43.8)	29.6 (27.4–34.3)	< 0.001	28.04 (25.51–31.23)	< 0.001
BMI z-score	2.42 (2.23–2.73)	1.81 (1.43–2.19)	< 0.001	1.56 (1.28–1.92)	< 0.001
Systolic BP (mmHg)	134 (127.75–143)	120 (112.75–125.25)	< 0.001	114.5 (106.5–120.25)	< 0.001
Diastolic BP (mmHg)	72 (64.75–79)	61.5 (58–68.25)	0.002	67.5 (62–72.25)	0.043
Hypertension	27 (79.4%)	9 (26.5%)	< 0.001	4 (11.8%)	< 0.001
Insulin resistance	28 (82.4%)	/	/	6 (17.4%)	< 0.001

*Differences between the groups before and after treatment were calculated with the Wilcoxon matched-pairs signed-ranks test and McNemar test. Data are reported as median (interquartile range); P values < 0.05 were considered statistically significant and are in italics

[1] Comparing measurements at baseline and after 7 months

[2] Comparing measurements at baseline and after 12 months

respectively). However, we noted a trend toward lower FWC after weight loss (Table 2 and Fig. 4). When calculating the FWC per 1.73 m^2, we noted no significant change ($p = 0.062$) from baseline (-0.73 (-1.05–-0.61) to after 12 months of treatment (-1.04 (-1.30–-0.70). A multivariate logistic regression analysis was done to evaluate gender, obesity, and hypertension after treatment as potential risk factors for a disrupted circadian rhythm of FWC. However, none of these factors was determined to be potential risk factors (gender ($p = 0.41$), hypertension ($p = 0.95$), obesity after treatment ($p = 0.84$)).
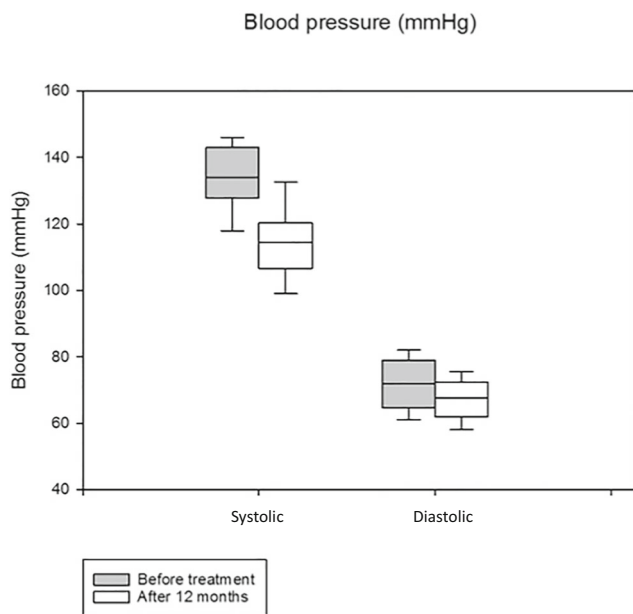
Solute clearance

Compared with daytime values, a significant decrease in solute clearance during the night was reported at all time points ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). A significant increase in solute clearance was seen after 7 ($p < 0.001$) and 12 months of weight loss ($p < 0.001$) (Table 2 and Fig. 4).

Sodium clearance A significant circadian rhythm with lower nighttime sodium clearance values than daytime measurements was observed at all time points ($p < 0.001$, $p = 0.013$, $p = 0.029$, respectively). U4 shows a clear dip in sodium clearance before and after treatment. For sodium clearance, a significant increase was noted after 7 and 12 months of weight loss ($p = 0.03$ and $p < 0.001$, respectively) (Table 2 and Fig. 4). Fractional excretion of sodium exhibited a similar pattern with a significant increase from 0.44 (0.34–0.51) % to 0.62 (0.48–0.73) % ($p < 0.001$) after treatment.

Potassium clearance Nocturnal potassium clearance was significantly lower than daytime measurement at all points ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). A significant increase in potassium clearance was reported after 7 ($p < 0.001$) and 12 months ($p < 0.001$) (Table 2 and Fig. 4). A significant increase in baseline fractional excretion of potassium (5.79 (4.96–6.55) %) was observed after 12 months (7.69 (6.43–9.82) %) ($p < 0.001$).

Discussion

The objective of this prospective study was to examine renal circadian rhythm in obese adolescents before and after weight loss.

Blood pressure (mmHg)

Fig. 2 Differences in systolic and diastolic blood pressure before and after 12 months of weight loss-therapy

Table 2 Interpretation of RFP

		Baseline	After 7 months	p value*[1]	After 12 months	p value*[2]
Diuresis rate (mL/min)	Day	0.78 (0.67–1.00)	0.87 (0.70–1.15)	0.009	1.38 (0.94–1.70)	< 0.001
	Night	0.57 (0.46–0.81)	0.74 (0.65–0.97)	< 0.001	0.87 (0.75–1.05)	< 0.001
	24 h	0.78 (0.69–0.86)	0.80 (0.71–1.28)	< 0.001	1.21 (0.89–1.49)	< 0.001
Creatinine clearance (mL/min)	Day	165.15 (132.27–191.75)	167.85 (147.80–181.47)	0.3	158.03 (144.49–179.01)	0.993
	Night	133.61 (118.76–158.95)	135.15 (121.76–146.80)	0.5	147.67 (132.40–163.58)	0.071
	24 h	149.84 (135.12–182.12)	156.78 (141.24–170.67)	0.4	160.86 (142.15–173.67)	0.437
FWC (mL/min)	Day	− 1.08 (− 1.40–− 0.79)	− 1.33 (− 1.59–− 1.02)	0.2	− 1.24 (− 1.44–− 1.05)	0.561
	Night	− 0.75 (− 0.89–− 0.64)	− 0.90 (− 1.10–− 0.72)	0.059	− 0.98 (− 1.09–− 0.83)	0.055
	24 h	− 0.95 (− 1.14–− 0.78)	− 1.09 (− 1.45–− 0.92)	0.082	− 1.09 (− 1.42–− 0.96)	0.321
Solute clearance (mL/min)	Day	1.97 (1.65–2.30)	2.48 (2.18–2.69)	0.004	2.64 (2.19–2.97)	0.001
	Night	1.36 (1.24–1.60)	1.79 (1.59–1.94)	< 0.001	1.87 (1.73–2.13)	< 0.001
	24 h	1.79 (1.60–1.97)	2.27 (2.09–2.46)	< 0.001	2.39 (2.12–2.58)	< 0.001
Sodium clearance (mL/min)	Day	0.72 (0.59–0.77)	0.75 (0.68–0.98)	0.1	0.99 (0.85–1.17)	< 0.001
	Night	0.46 (0.41–0.51)	0.62 (0.46–0.79)	0.003	0.78 (0.64–0.93)	< 0.001
	24 h	0.65 (0.55–0.70)	0.79 (0.65–0.87)	0.03	0.91 (0.85–1.10)	< 0.001
Potassium clearance (mL/min)	Day	11.83 (10.63–13.31)	15.42 (13.46–19.24)	< 0.001	16.80 (13.93–19.11)	< 0.001
	Night	3.51 (2.98–4.06)	4.41 (3.49–5.89)	< 0.001	4.79 (4.37–5.71)	0.002
	24 h	9.05 (7.62–9.82)	12.28 (10.15–113.53)	< 0.001	12.89 (10.33–15.19)	< 0.001

*Data are reported as median (95% confidence interval). Day sample includes the first 5 urine collections, whereas the night sample includes the last 3 urine samples; p values < 0.05 were considered statistically significant and are in italics

[1] Comparing measurements at baseline and after 7 months

[2] Comparing measurements at baseline and after 12 months

In the present study, an inverse circadian rhythm of FWC was observed, both before and after 7 months of treatment, with lower daytime compared with nighttime values. This finding is inconsistent with the theory that in healthy children
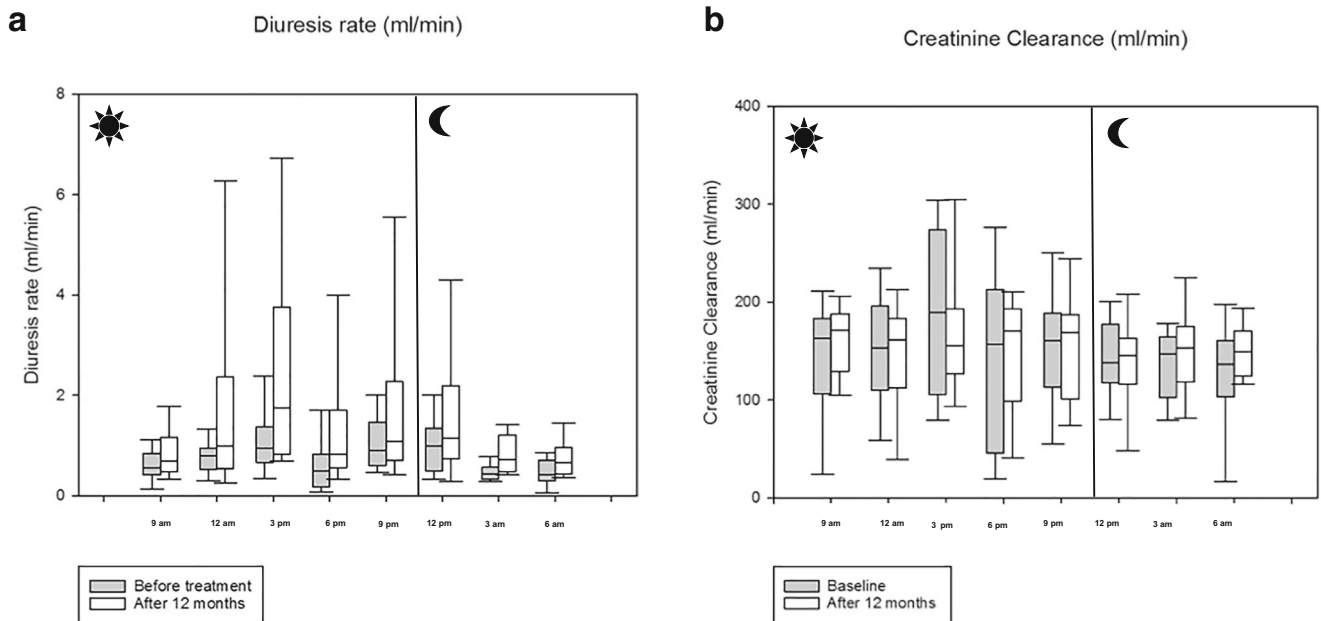
a Diuresis rate (ml/min)

b Creatinine Clearance (ml/min)

Fig. 3 Change in different parameters at 3 h fixed time points before and after 12 months of weight loss therapy. **a** Change in diuresis rate (mL/min), **b** change in creatinine clearance (mL/min). Differences between baseline and after treatment measurement of every time point were calculated with the Wilcoxon matched-pairs signed-ranks test. p values < 0.05 were considered statistically significant and are mentioned with an asterisk (*). The end of the whiskers represents the 5th and 95th percentile of the measurements
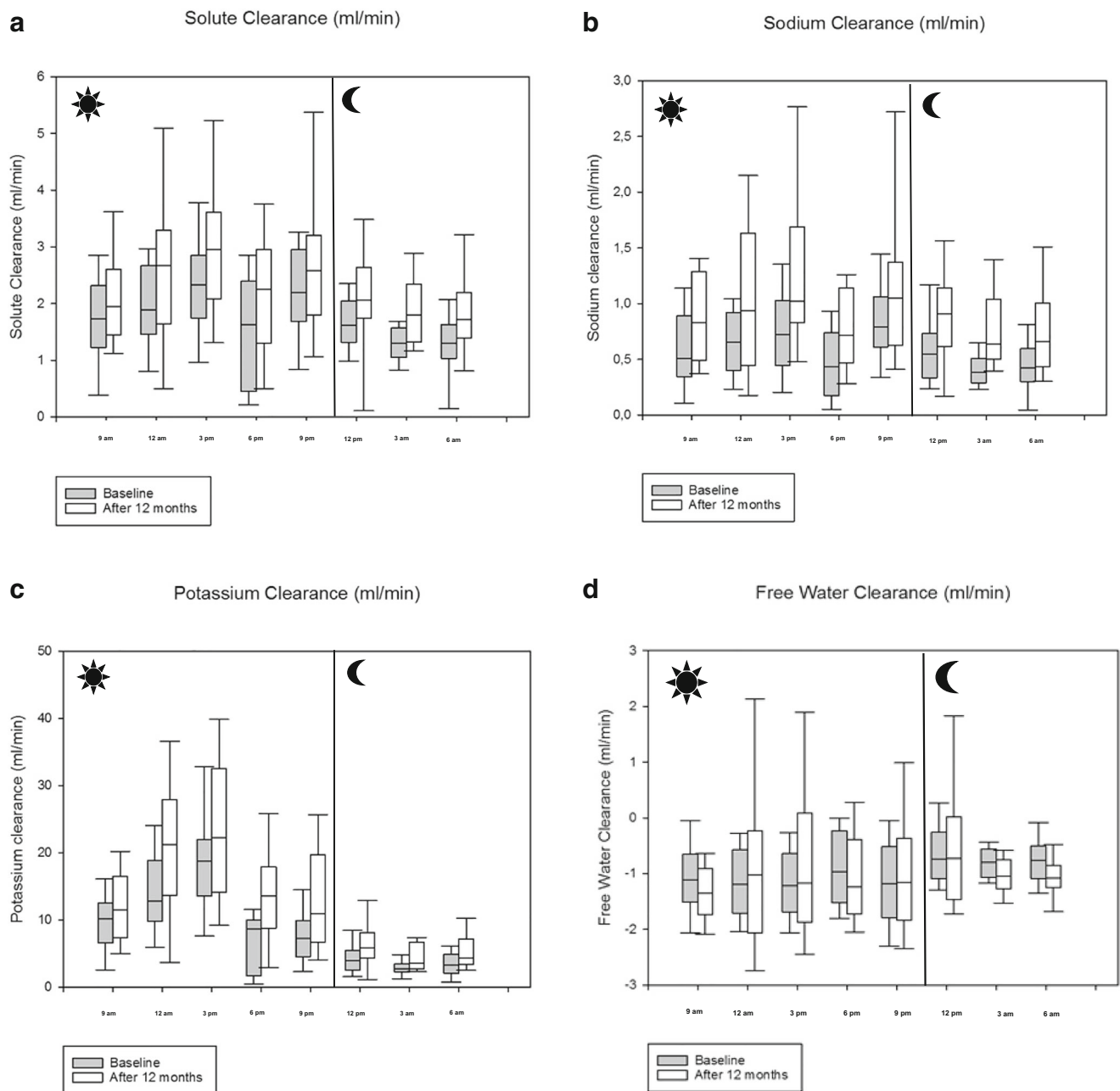
Fig. 4 Change in water handling and solutes clearance at 3 h fixed time points before and after 12 months of weight loss therapy. **a** Solute clearance (mL/min); **b** sodium clearance (mL/min); **c** potassium clearance (mL/min); **d** change in free water clearance (mL/min). Differences between baseline and after treatment measurement of every time point were calculated with the Wilcoxon matched-pairs signed-ranks test. *p* values < 0.05 were considered statistically significant and are mentioned with an asterisk (*). The end of the whiskers represents the 5th and 95th percentile of the measurements

and adults, increased secretion of ADH is expected during the night. The elevated excretion of ADH comes along with a reduction in FWC during nighttime compared with daytime. This mechanism is essential, as it leads to the production of more concentrated urine during the night and thus, a reduction in micturition frequency [17]. The disrupted day-night rhythm of FWC in our population may be provoked by a reversed ADH activity with lower ADH levels during the night, leading to a higher nocturnal FWC during the night. Another possible explanation is the nocturnal mobilization of obesity-related peripheral edema as obesity may be a cause of lower extremity lymphedema and venous insufficiency. As a result, interstitial fluid accumulates in the lower extremities while standing during daytime and is reabsorbed into the circulation when laying down during sleep. This shift represents a surplus of free water that the kidneys need to remove trough a stimulated natriuretic peptides system and suppressed ADH [8, 12, 13]. After 12 months of weight loss, no significant difference in day

and nighttime FWC was reported, suggesting a normalization of the circadian rhythm.

Clear circadian rhythms of diuresis rate and of the renal clearance of creatinine, solutes, sodium, and potassium were observed at baseline and after completion of the weight loss program. The dip of sodium clearance in sample U4 can be explained by the daily 2 h of play and lifestyle activities before U4 sampling. Blunted renal circadian rhythms in accordance with disrupted daily rhythms of BP and other metabolic functions in obese patients were expected, as described in previous studies [21, 26]. This largely preserved renal circadian rhythm may be explained by the short duration of obesity in our adolescent study population, perhaps being too short to affect the rhythm of renal function. Another possibility is that our study sample is a variant of the obese population with preserved renal circadian rhythm. Further research to investigate these circadian rhythms in the obese population is necessary.

An overall median weight loss of 24 kg did not affect creatinine clearance and even led to a significant increase in eGFR. A decrease was expected since Chagnac et al. [5] and Navarro-Díaz et al. [24] reported a substantial decrease in renal hyperfiltration after bariatric surgery in obese adults. The eGFR was calculated as milliliter per minute per 1.73 m^2 and showed a significant increase after 12 months of weight loss. This discrepancy is likely an artifact attributable to the decrease in BSA and not due to a change in renal size or function. Several possible explanations for the lack of change in creatinine clearance in this study are plausible. Firstly, the follow-up period of this study was short and, 47% of adolescents were still obese after 12 months of treatment. As a result, weight loss may not have been sufficient or prolonged enough to affect changes in renal filtration. Second, it is possible that the hyperfiltration theory is not correct or not applicable for obese adolescents.

A decrease in the obesity-related hyperactive RAAS established by weight loss has been described in previous studies [6, 15, 34] and was confirmed by our findings. A significant increase in sodium clearance was observed after 12 months of weight loss, which can be explained by lower aldosterone concentrations. This increase in sodium clearance only becomes evident at the end of the treatment program, suggesting that adequate weight loss is necessary. The observed elevation in potassium clearance after weight loss cannot necessarily be attributed to diminished activity of the RAAS. This elevation may be explained by an increased intake of potassium since meals were not identical at each test moment. The significant decrease in both systolic and diastolic BP after weight loss can be explained by a normalization of the RAAS, as well.

Limitations of this study include the small number of participants, the short follow-up period and the fact that plasma renin and aldosterone measurements were not included in the study protocol. Moreover, this study is only generalizable to adolescents without obesity-related comorbidities, as these patients were excluded from the analysis. Another limitation is the inability to isolate weight loss from a multidisciplinary program including many lifestyle modifications. Furthermore, it was not possible to use values that corrected for BSA, because of its large variability within and between the obese patients. In addition, the exact water intake by the adolescents was not measured. This could be a confounder, as increased water consumption after initiation of the program can influence the renal function profiles. The GFR was calculated and not measured through inulin clearance in the 24-h urine sample. In addition, 24-h blood pressure measurement was not performed. Lastly, due to practical and ethical limitations of the study, we could not include a control group of healthy non-obese adolescents.

Conclusion

In the present study, 34 obese adolescents were monitored during a 12-month weight loss program. This program led to a median weight loss of 24 kg, a reduction in both systolic and diastolic BP, and improvement of insulin resistance.

Initially, an inverse circadian rhythm of FWC was observed, with lower daytime compared with nighttime values. This may be provoked by a deranged ADH activity and the nocturnal mobilization of obesity-related peripheral edema. After 12 months of weight loss, normalization of this inverse rhythm was noticed.

Furthermore, this study showed clear circadian rhythms in diuresis rate and the renal clearance of creatinine, solutes, sodium, and potassium at the beginning and end of the weight loss program. Possible explanations for this largely preserved renal circadian rhythm include a short duration of obesity in our adolescent study population.

A decrease in the obesity-related hyperactive RAAS was suggested as a result of the significant increase in sodium clearance that was observed. Future studies with a larger study population, healthy controls, and a longer follow-up period must be performed to confirm our findings.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Ghent University Hospital review board (EC 2015/1438). The Declaration of Helsinki was followed and conducted in accordance with the legal regulations in Belgium.

Informed consent Informed consent was obtained from all individual participants and their parents included in the study.

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