



Evaluation of a novel osmotically volumetric urine index as a rapid and inexpensive marker for certain renal conditions

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Abstract. An open question remains the assessment of the patient's condition in various kidney diseases using inexpensive laboratory methods. The aim of this study was to evaluate the diagnostic tool, the osmolal-volume index of urine, calculated based on urine density and hourly diuresis. A retrospective study of medical records of 86 intensive care unit patients was carried out (34 – with diabetes insipidus, 30 – with acute renal failure, 22 – with chronic renal failure), as well as a prospective study involving 22 healthy individuals without renal pathology. Urine samples were collected three times over a three-hour period; the index and volume of each fraction were measured and averaged. One-way Analysis of Variance was used to evaluate the influence of study groups on osmotically volumetric urine index; means were separated using Fisher's Least Significant Difference procedure ($p < 0.01$). There was a significant difference between study groups regarding the proposed index ($p < 0.01$), and in healthy individuals it ranged from 8.0 to 12.0. In diabetes insipidus, the proposed index sharply decreased, acquiring values below 1.0. At the initial stage of acute renal failure, its value increased (22.0 ± 5.5), while at the stage of polyuria decreased to 2.0. Chronic renal failure was manifested by the index decrease (4.2 ± 2.1). The osmotically volumetric urine index is a dynamic indicator of the efficiency of excretory and concentration renal function applicable for the field hospitals where necessary lab equipment and reagents are unavailable and history of patient's water consumption, retention, and loss, is known. In case of impaired renal function, this index can vary significantly from 0.02 to 30. The simplicity of the method, its non-invasiveness, plus as the communicativeness, deserve the introduction of this marker into clinical practice

Keywords: renal failure; diabetes insipidus; urine density; diuresis rate; osmotically volumetric urine index

Introduction

A wide variety of reasons, namely, trauma, surgery, acute and chronic inflammatory diseases, etc., can lead to body homeostasis disorders in patients which require intensive

care. The kidneys are one of the main organs for homeostasis regulation due to the processes of filtration, reabsorption, secretion, with final urine release [1]. Kidneys

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regulate blood volume, osmotic blood pressure (osmoregulation), and concentration of blood organic substances and low-molecular weight electrolytes (ion regulation) [1]. Therefore, early and timely diagnosis of impaired renal function often plays a crucial role in understanding the mechanism of pathophysiological processes occurring in the body, evaluating the effectiveness of intensive care, and preventing possible further disorders of homeostasis.

O. Hnativ & M. Korda [2] studied and thoughtfully reviewed the modelling of hyperosmolar hypohydration in rats, manifested by diabetes insipidus (DI), and its influence on overall water-salt balance, homeostasis, and functional disorders. Patients with kidney pathology in intensive care units frequently require lab tests to check kidney functionality, which may be impossible in the case of field hospitals, where numerous patients must be attended simultaneously due to natural or man-made disasters, civil unrest, or wars. Under normal conditions, standard lab chemical tests include blood analysis (serum creatinine, blood urea nitrogen, cystatin C levels), as well as urinalysis (urine protein, albumin, creatinine levels, blood cells, glucose, microbiological analysis, among others) [3, 4]. Scientists R. Jin *et al.* [5] and R. Hojs *et al.* [6] suggested several derived indices, such as kidney estimated glomerular filtration rate (eGFR) as a function of serum creatinine, age, gender, race, body surface area, serum cystatin C; albumin to creatinine ratio (ACR) [7], which provides more in-depth evaluation of renal status. Structural changes in kidney tissue can be observed with either a computed tomography (CT) scan or ultrasound. In case of the absence of sophisticated equipment and chemical reagents, rapid and fairly useful information can be obtained with physical methods of examination, such as urine appearance, its hourly and daily volume, gravity measured with either manual/digital refractometer, hydrometer, or by test strips, as well as urine osmolality measured by urine freezing point depression [8-10].

In the case of limited financial, human, and other resources, when numerous patients are admitted simultaneously to low-equipped hospitals in urgent situations, the following criteria may become the most important in the diagnosis of the impaired renal function: non-invasiveness, simplicity, speed, and informativeness of the results. The aim of the current study was to evaluate a rapid aggregative diagnostic indicator based on hourly urine volume and its gravity, using a retrospective approach with the data from the groups of patients with certain pathologies and a control group, which included healthy individuals.

Materials and Methods

A retrospective study of medical records was carried out, which included total 86 intensive care unit (ICU) patients (34 – with DI group; 30 – with acute renal failure (ARF) group; 22 – with chronic renal failure (CRF) group) and 22 healthy individuals without renal pathology, control (C) group. The study was conducted on the premises of Ternopil University Hospital and clinical hospital “Feofania” of the State Affairs Department using records dated from

2016 till 2021. 22 healthy individuals without renal pathology (C group) were randomly selected from resident doctors of Ternopil University Hospital to match gender ratio of ICU patients as an ongoing part of the experiment.

Exclusion criteria for the study included age over 60 years, history of recent diuretics use, benign prostatic hyperplasia, type I and type II diabetes mellitus. Average age \pm standard deviation and male/female ratio for the DI group, ARF group, CRF group, and C group, were 43 ± 5 years old and 1.2, 40 ± 5 years old and 1.1, 39 ± 6 years old and 1.2, 27 ± 3 years old and 1.2, respectively. Individuals aged over two sigmas below or above the average age value were excluded from the study. Diabetes insipidus was diagnosed according to Robertson [11], with criteria including hypotonic ($<300 \text{ mOsm} \cdot \text{kg}^{-1}$) urine output above $50 \text{ mL} \cdot \text{day}^{-1} \cdot \text{kg}^{-1}$ body weight and polydipsia ($>3.0 \text{ L} \cdot \text{day}^{-1}$). Acute renal failure and chronic renal failure were diagnosed according to KDIGO guidelines [3, 4]. Using standard clinical and biochemical examinations at the Department of Anaesthesiology and Intensive Care, ICU patients were catheterised with urinary catheters and were subjected to the targeted study of renal excretory and concentrating ability.

The diuresis rate was measured as a urine volume excreted through the kidneys per one hour. Continuous checking of the diuresis rate in ICU patients which have urinary catheters is a routine procedure performed by medical personnel but supervised by an anaesthesiologist on duty. Three consecutive urine volumes over three one-hour periods were collected hourly and analysed after presumptive onset of kidney malfunctioning symptoms before diuretics use with standard physiological water and nutrient supplementation. Healthy individuals (C group) were advised to consume daily-recommended drinking water volume (2.0 litres per day) and to avoid using any type of diuretic drugs and caffeine. The urine samples from healthy individuals were collected after noon over three consecutive hours, and hourly urine volume was recorded. Each portion of the urine excreted per hour was analysed for its gravity ($\text{g} \cdot \text{L}^{-1}$) using a refractometer (Fisherbrand™ Handheld Analogue Clinical Refractometer, Thermo Fisher Scientific, Waltham, MA, US). The results from each experimental subject (three values) were averaged and used for further data analysis and interpretation.

A method for assessing renal function based on the simultaneous measurement of urine density and diuresis rate was previously suggested and named “osmotically volumetric urine index” (OVUI, $\text{g} \cdot \text{h} \cdot \text{mL}^{-1} \cdot \text{L}^{-1}$) by previous research [12]. The OVUI calculation formula is as follows:

$$OVUI = (UG - 1000) \cdot 100 / (3 \cdot V_{hour}), \quad (1)$$

where *OVUI* is osmotically volumetric urine index, *UG* – urine gravity, measured by refractometer, $\text{g} \cdot \text{L}^{-1}$, *V_{hour}* – diuresis rate per hour (urine volume in mL, excreted per hour).

The above-mentioned index, OVUI, was evaluated, and a range of its values were established for healthy

individuals and patients with renal pathology, as well as with diabetes insipidus. It is important to note that refractometric examination of the patient's urine can be performed directly near the patient's bedside, with minimal time and biological fluid used. This allows monitoring of renal function every hour, assessing the dynamics of the pathological process and intensive care efficiency.

Assuming a normal distribution of the calculated OVUI value, one-way ANOVA was used to analyse the influence of the study group (group C, group DI, group CRF, group ARF) on the OVUI value. If the influence of the study groups was significant ($p < 0.01$), means were separated using the Fisher LSD method. Statistical analysis was performed using commercially available software Statistica ver. 10.0 (StatSoft Inc, Tulsa, OK, US).

Standard written consent on use and processing of personal data was obtained from each individual involved in the study. The study was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects [13] and approved by the local Institutional Research Ethics Committee of I. Horbachevsky Ternopil National Medical University Ministry of Health of Ukraine.

Results and Discussion

It has been established that the osmotically volumetric urine index may be considered as an effective marker of impaired renal function. The results of analysis of groups DI, ARF, CRF, together with the data from group C, are shown in Table 1.

Table 1. OVUI of the investigated groups

Group	Ave OVUI \pm st. dev., $g \cdot h \cdot mL^{-1} \cdot L^{-1}$	
C	10.0 ± 1.2	*b
DI	0.40 ± 0.13	d
ARF, early phase	22.0 ± 5.5	a
CRF	4.2 ± 2.1	c

Notes: * – means with the same letters are not significantly different ($p < 0.01$)

Source: compiled by the authors

Healthy individuals without renal pathology. There was a significant influence of study groups on the calculated OVUI value ($p < 0.01$). Healthy individuals (group C) who received food and water consumption in the amount of physiological needs, had an average OVUI \pm standard deviation of 10 ± 1.2 , ranging from 8.0 to 12.0.

The OVUI decreased below 8.0 with an excessive water consumption in healthy individuals, while it increased above 12.0 when water intake into the body was limited (data not

shown). Similarly, when conducting intensive care in patients with preserved renal function, the growth of OVUI above 12.0 indicated insufficient volemic support or unresolved water deficiency in the body, while excessive hemodilution, as well as the use of forced diuresis, was manifested by a decrease in OVUI below 8.0 (data not shown). The correlation between the diuresis rate and the urine gravity in healthy individuals in normal physiological conditions and at different options of the body hydration are shown in Figure 1.

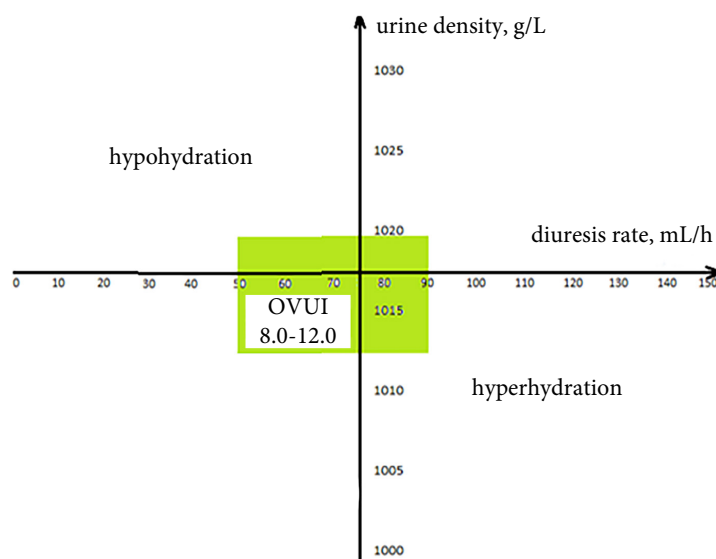


Figure 1. Osmotically volumetric urine index

in healthy individuals under physiological fluid supplementation, retention, and loss (green box)

Source: compiled by the authors

In diabetes insipidus (central and nephrogenic), OVUI ranged from 0.2 to 0.6, and correlated with severity of the pathology, with lower values detected in more severe cases (Fig. 2). Based on previous experience with corrective actions, the efficiency of homeostasis correction in diabetes insipidus is evidenced by the dynamics of the constant growth of the

OVUI above 1.0 with it eventually reaching normal physiological values. In the case presented here, diabetes insipidus was manifested by the OVUI shift to the right and down (Fig. 2).

Acute renal failure. At a shock stage of acute renal failure, OVUI increased above 15.0 up to 30.0 $g \cdot h \cdot mL^{-1} \cdot L^{-1}$ (Fig. 3).

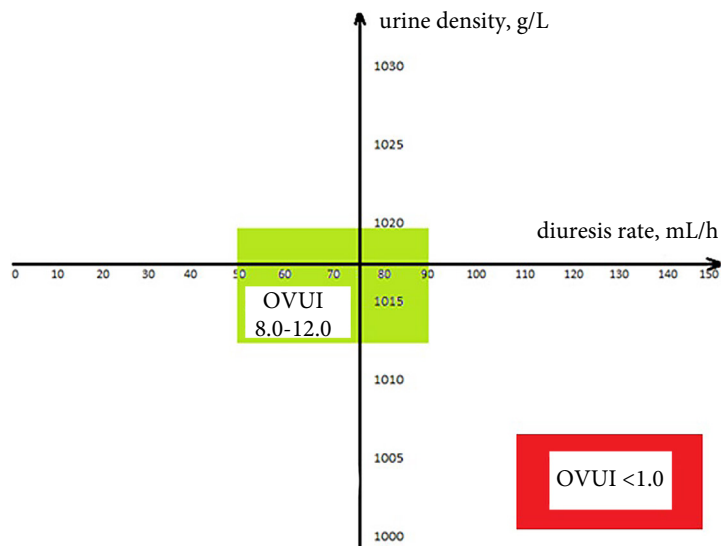


Figure 2. Osmotically volumetric urine index in diabetes insipidus (red box).
OVUI shifts to the right and down compared to the norm

Source: compiled by the authors

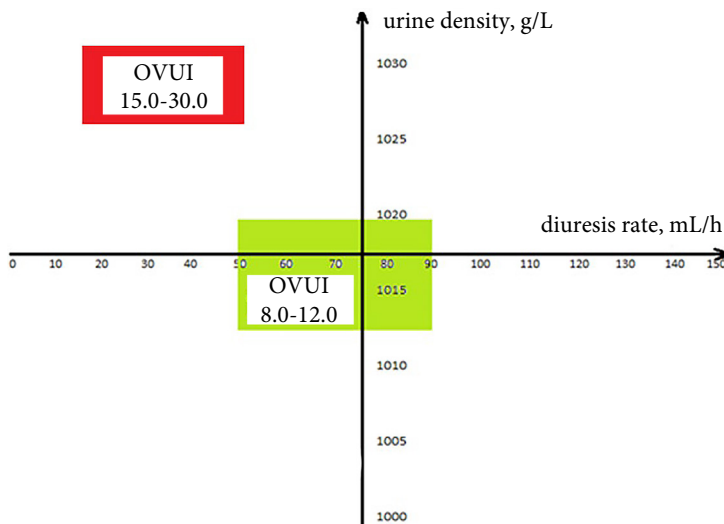


Figure 3. Osmotically volumetric urine index in acute renal failure, early phase (red box).
OVUI shifts to the left and up compared to the norm

Source: compiled by the authors

In acute renal failure in the polyuria phase, the OVUI falls below normal, approaching 1.0. With the administration of particular drugs (X-ray contrast agents, mannitol, dextrans, nephrotoxic antibiotics) OVUI increases above 12.0 due to the increase in the urine density. OVUI normalization indicates the restoration of kidneys excretory

and concentrating capacity and the patient's recovery. On the diagram, it is manifested by the OVUI shift back to the right and down.

Chronic renal failure was manifested by a decrease in osmotically volumetric urine index below 8.0 and to 2.0-3.0. There is a direct correlation between the OVUI and the

disease severity: the lower OVUI values indicate that tubular function is largely impaired, and glomerular function is still sufficient (Fig. 4). To summarise, the shown data suggested

that OVUI in its presented form may be a valuable tool for evaluation of such conditions as diabetes insipidus, acute and chronic renal failure as compared to healthy individuals.

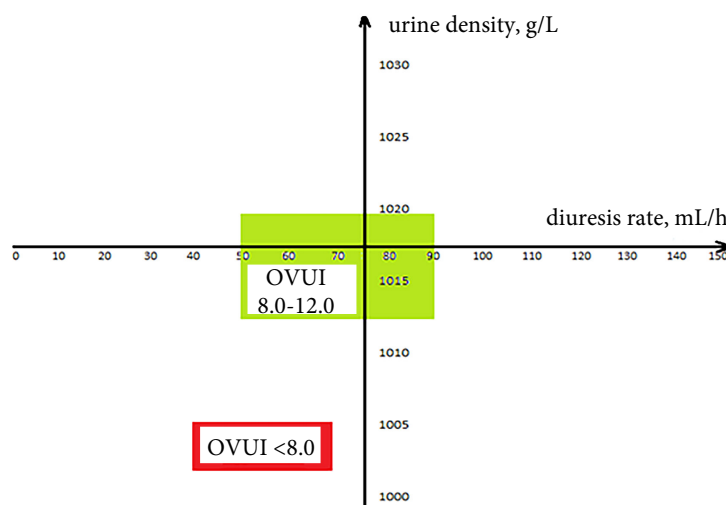


Figure 4. Osmotically volumetric urine index in chronic renal failure (red box).
OVUI shifts to the left and bottom compared to the norm

Source: compiled by the authors

A healthy person under normal physiological conditions excretes urine at a rate of $0.8-1.0 \text{ mL}\cdot\text{kg}^{-1}$ body weight within one hour, with urine gravity ranging from $1,012$ to $1,025 \text{ g}\cdot\text{L}^{-1}$, which indicates the ability of the kidneys to filter and concentrate biological fluid [1]. Moreover, in acute kidney injury, one of the sufficient signs is urine volume of below $0.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for consecutive 6 hours [3]. Although urine flow rate alone is a poor measurement of kidney function, oliguria generally reflects a decreased GFR. However, according to KDIGO [3, 4], acute kidney disease or chronic kidney disease may take progress even without any substantial decrease in urine flow rate. According to M. Pradella *et al.* [8], Similarly, urine gravity can physiologically fall below $1,012$ in the case of high fluid intake or rise above $1,025$ after taking no fluids for 12 hours overnight.

Hypersthenuria, or increased concentration of solutes in urine, causes an increase in urine gravity and may be associated with dehydration, emesis, diarrhoea, excessive sweating, urinary tract infection, glycosuria, hepatorenal syndrome, renal artery stenosis, decreased kidney blood flow as a result of heart failure. Urine gravity greater than $1,035 \text{ g}\cdot\text{L}^{-1}$ is consistent with obvious dehydration [14]. The decreased concentration of solutes in urine, or hyposthenuria, may be associated with pyelonephritis, renal failure, diabetes insipidus, interstitial nephritis, acute tubular necrosis, and excessive fluid intake.

The solute concentration in urine can be measured either by specific gravity (hydrometer, refractometer, test strips), which depends on the number and weight of the solute particles in urine, or by osmolality (urine freezing point depression method), which depends only on the number of solute particles [8, 15]. As hydrometer use requires larger

urine volumes, which is inconvenient and impossible in the case of oliguria, refractometers and test strips become a viable option. Though studies, S.J. Barton & S.S. Holmes [16] showed promising results for urine specific gravity (USG) stick test strips, later studies questioned their usefulness, mentioning high urine pH (above 7.0), urine glucose and urine protein as interfering factors, as well as overall lack of correlation [15, 17, 18], which leaves refractometers as the most viable option for USG and UG measurements.

The OVUI value (Fig. 1) for healthy individuals should be taken with certain caution, as D.J. Casa *et al.* [19] classified well-hydrated individuals with UG at below $1,010$, minimally dehydrated – with UG between $1,010$ and $1,020$, and significantly dehydrated – with UG between $1,021$ and $1,030$, which do not fall within OVUI $8.0-12.0$ box.

During diabetes insipidus (central and nephrogenic), previous study also showed that OVUI was one of the earliest, most informative and efficient diagnostic criteria, especially starting from the first hours of pathology development [12]. Similar to the presented here results, this index also decreased sharply, gaining values even below 0.5 ($p < 0.001$) [12]. It was also noticed that typically such OVUI shifts in diabetes insipidus occurred long before the development of clinical signs of impaired hydration of the body, hypernatraemia and hyperosmolarity of blood plasma inherent in patients with such condition [12, 20].

Continuous OVUI measurements and analysis make it possible to determine at what level (glomerular or tubular) renal failure occurred. Usually, diuresis decrease to $0.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ascertains oligoanuria and is a serious sign of acute renal failure [3, 4]. As expected, an increase in the index was also characteristic of parenchymal acute renal

injury, such as the initial stage of acute diffuse glomerulonephritis and hepatorenal syndrome. As diuresis is restored, this indicator decreases, approaching the norm. However, a decrease in OVUI against the background of a low rate of diuresis, indicates the exaltation of the kidneys concentrating capacity – i.e., the involvement of the renal tubules in the pathological process. In the polyuria stage acute renal failure, the OVUI fell below normal, approaching 1.0.

During chronic renal failure, low OVUI values (<5.0), which do not change during the day when examining sequential portions of urine, indicate a pronounced renal concentration failure, when the density of glomerular filtrate equals to the density of final excreted urine and serve as a marker of an unfavourable course of diffuse chronic glomerulonephritis and pyelonephritis. In the terminal stage of nephrosclerosis due to the progression of oliguria against the background of low urine density, the osmotically volumetric urine index may again acquire values close to normal ones.

There are some drawbacks in using refractometers for urine solute concentration measurements. For example, osmolality measurement as an alternative to refractometry is considered a golden standard and is normally used for more detailed analysis in ARF and CRF, but is less convenient [17, 21]. However, some researchers even proposed simple equations to derive osmolality values from refractometer-read UG [22, 23]. Contrary, C.E. Costa *et al.* [17] stated that refractometry-obtained UG could not substitute more precise and informative osmolality value. The authors wrote that the correlation coefficient between osmolality and refractometer-read UG in many cases was weak even after adjustments with urine glucose and protein presence, and only osmolality had a significant non-linear correlation with serum creatinine [15].

To summarise, though both investigated urine parameters (urine hourly volume and refractometer-read UG) may vary significantly even in healthy individuals, their composite-derived index can be useful in clinical settings, especially if history of patient's fluid replacement or loss, as well as previous medicine administration and general anamnesis, are well-known. However, for final diagnosis

and treatment options, serum/urine creatinine levels, urine albumin levels, serum cystatin C levels, urine output, and composite eGFR and ACR values should be used instead.

Conclusions

As the main goal of the current research was evaluation of a novel osmotically volumetric urine index as a rapid and inexpensive marker for certain renal conditions, the targeted aims were achieved. Osmotically volumetric urine index may be used as a dynamic indicator of the efficiency of excretory and concentration functions of the kidneys in case of emergency, lack of appropriate equipment, and known anamnesis and history of drug administration, fluid replacement and loss. It was shown that under normal physiological conditions, OVUI ranged between of 8.0-12.0, but could vary widely even in healthy individuals. However, in the cases of impaired renal function, this index varied significantly from 0.02 to 30. Based on continuous OVUI monitoring, it may be possible to predict renal pathology, as well as track its progress and the adequacy of intensive care. The simplicity of the method, its communicativeness and non-invasiveness, make OVUI measurements a useful tool at the point of introduction of the marker into the clinical settings. Further research is warranted to explore OVUI's utility in diagnosing specific kidney diseases, its correlation with established markers, and its role in predicting patient outcomes. Additionally, comparing OVUI with existing methods and investigating its applications in various clinical settings will be crucial. Ultimately, OVUI holds promise for improving early detection and management of kidney dysfunction, leading to better patient care and potentially reducing healthcare costs.

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Conflict of Interest

The authors declare no conflict of interest.

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Оцінка нового осмотично-об'ємного індексу сечі як швидкого та недорогого маркера для певних захворювань нирок

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Анотація. Відкритим питанням залишається оцінка стану пацієнта при різноманітних захворюваннях нирок, використовуючи недорогі лабораторні методи. Метою цього дослідження була оцінка діагностичного інструменту, осмотично-об'ємного індексу сечі, що розраховується на основі щільності сечі і щогодинного діурезу. Проведено ретроспективне дослідження медичної документації 86 пацієнтів відділення інтенсивної терапії (34 – з нецукровим діабетом, 30 – з гострою нирковою недостатністю, 22 – з хронічною нирковою недостатністю), а також проспективне дослідження за участю 22 здорових осіб без патології нирок. Зразки сечі відбирали тричі протягом трьох послідовних годин; значення запропонованого індексу та об'єм кожної фракції вимірювали та усереднювали. Однофакторний дисперсійний аналіз використовувався для оцінки впливу досліджуваних груп пацієнтів на показник запропонованого індексу, статистична значимість різниці між величинами була оцінена критерієм Фішера ($p < 0,01$). Між досліджуваними групами спостерігалась статистично достовірна різниця щодо запропонованого індексу ($p < 0,01$), в той час як у здорових осіб вона коливалася від 8,0 до 12,0. При нецукровому діабеті індекс різко знижувався, набуваючи значень нижче 1,0. На початковій стадії гострої ниркової недостатності індекс зростав ($22,0 \pm 5,5$), а на стадії поліурії знижувався до 2,0. Хронічна ниркова недостатність характеризувалася зниженням запропонованого показника ($4,2 \pm 2,1$). Отже, осмотично-об'ємний індекс сечі – це динамічний індикатор ефективності виділення та концентрації ниркової функції, який може застосовуватися у польових госпіталах, де немає необхідного лабораторного обладнання та реагентів та відома історія споживання, затримки та втрати води пацієнтом. При порушенні функції нирок цей показник може істотно коливатися від 0,02 до 30. Простота методу, його неінвазивність, а також інформативність заслуговують на впровадження цього маркера в клінічну практику

Ключові слова: ниркова недостатність; нецукровий діабет; щільність сечі; швидкість діурезу; осмотично-об'ємний індекс сечі