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SERUM POTASSIUM, SODIUM AND CALCIUM LEVELS IN HEALTHY INDIVIDUALS — LITERATURE REVIEW AND DATA ANALYSIS

Abstract: Purpose: The human body is known to be composed of 24 elements, among which potassium, sodium and calcium are considered to be essential. These necessary components play a significant physiological role which includes regulation of the electrical and mechanical action of the heart. Abnormal concentration of the above-mentioned ions, i.e. water-electrolyte imbalance, may result in cardiac arrhythmias, muscle contraction disorders, disturbances of neuronal activity and influences the drugs activity.
Methods: The study aimed at gathering and analyzing results of publicly available research which reported serum concentration of these ions. This information, together with an additional collection of data (gender, age, height, weight, measurement method), is presented in table form attached as supplementary material.
Results: The serum ions concentrations means weighted by the study-specific sample sizes indicated statistically significant differences between males and females for all ions — K^+ 4.21 and 4.09, Na^+ 140.1 and 138.17, Ca^{2+} 2.42 and 2.31 respectively).
Conclusions: Obtained results correspond with the current laboratory reference values. As potassium, sodium and calcium follow the circadian rhythm, publications reporting serum concentration values were also collected and presented. Further studies are planned to describe such phenomenon in a form of the statistical model.

Key words: serum, potassium, calcium, sodium, healthy volunteers.

INTRODUCTION

The human body is made up of 24 elements, among them mineral elements, which include major and trace elements and constitute ca. 0.7% of total atoms [1]. The most common mineral elements include calcium (Ca^{2+}), sodium (Na^+) and potassium (K^+). The aim of the study was to collect and analyze data describing total serum concentration of these ions in healthy individuals.

POTASSIUM, SODIUM, CALCIUM — BODY CONCENTRATION, HOMEOSTASIS AND PHYSIOLOGICAL ROLE

The key organ involved in the regulation of potassium and sodium levels is the kidney (up to 90% of potassium and 95% of sodium daily excretion) with renin-

angiotensin-aldosterone (RAA) as the most important regulatory hormone system [2, 3]. Sodium is also excreted with sweat and potassium with feaces [4]. Natriuresis is promoted by atrial natriuretic peptide, hipercalcemia or hipokaliemia and inhibited by RAA, while kaliuresis is supported by aldosterone and decreased by RAA blockade [5]. Both cations excretion is dependent on many hormonal and humoral factors, including the activity of the sympathetic nervous system. Mechanisms responsible for the balance between potassium intra- and extracellular concentration play a crucial role in maintaining its serum level. There are many ionic pumps and ion channels regulated by the above-mentioned hormones and involved in Na^+ and K^+ homeostasis. Among them the most important one and responsible for formation of transmembrane potential and maintaining the resting potential in all living cells is Na^+/K^+-ATPase, which actively transport potassium into and sodium out of the cells [3, 6].

Calcium homeostasis is regulated mainly by hormones and vitamins: parathyroid hormone, calcitonin and 1α, 25-dihydroxyvitamin D. Extracellular calcium is regulated through exchanges with bones, excretion through the kidney, and oral intake. As calcium serum level need fast and accurate control, renal excretion guarantees relatively rapid regulation with approximately 250 mmol of calcium filtered by the glomeruli per day [7], and only a small fraction (1–10 mmol/day) of the filtered load is excreted [8]. Approximately 100 mmol from the 25–30 moles of total skeletal calcium is considered to be available for immediate exchange with serum resources [9].

POTASSIUM

The physiological serum concentration of this ion is in the range of 3.5 to 5.0 milimole per liter (mM). It is one of the most important ionic components of the intracellular fluid. Potassium is a necessary element playing a physiological role in multiple processes such as the electrical impulse conduction and the contraction of smooth and skeletal muscles, including the heart. It is the increased efflux of K^+ ions from cardiomyocytes that determines their return to the resting state. It also facilitates cell membrane function and proper enzyme activity. Its role is especially significant in the excitable cells, such as neurons. The resting potential of these cells depends mainly on potassium, since their membrane is the most permeable to this ion [1].

SODIUM

The human body contains ca. 105 grams of sodium located mainly in the bones, extracellular fluids (i.e. serum) and tissues. Bone crystals play a reservoir role and release sodium in case of serum level deficiency [9]. Its presence in the nerves and muscle tissues, also those of the heart, is of the greatest importance. The

physiological level in the serum ranges from 135 mM to 145 mM. The sodium ion is the major extracellular cation, responsible for the osmotic pressure of body fluids. In excitable cells, rapidly increasing membrane permeability to sodium ions is responsible for formation of action potential [1].

CALCIUM

The physiological concentration of total calcium in serum is assumed to lie between 2.2 and 2.6 mM [10]. About half of this is free in solution, with the remainder bound to serum albumin and other serum components, such as citrate and thus clear differentiation between plasma and serum concentration needs to be undertaken during the data analysis. The total amount of calcium in the extracellular fluid is about 1 gram [11]. Nearly all of the body's calcium is stored in bones (ca. 99%). Calcium is involved in many physiological processes in the human body. Apart from being the second messenger, enzyme cofactor and component of bone tissue, it also plays a role in muscle contraction. Increased membrane permeability of cardiomyocytes to calcium ions results in a characteristic plateau (phase two of the action potential) [1, 12].

CIRCADIAN RHYTHMS

It is a well-known phenomenon that some physiological parameters follow a rhythmical pattern during the 24-hour diurnal cycle, which is regulated by an internal time-keeping system consisting of the endogenous biological master clock located in the hypothalamic suprachiasmatic nuclei and structures present in the peripheral tissues [13]. They are also influenced by external parameters, including lifestyle, feeding behaviours, etc. [14]. Among the ions analyzed in this study, potassium and sodium clearly follow the circadian variation, which has been shown in numerous investigations and described using the cosinor model [15–18]. The rhythmicity of the serum calcium concentration is less clear, although some studies have testified to its existence (see the Results section) [17, 19].

PHYSIOLOGICAL CONSEQUENCES OF DISRUPTING ION LEVELS

Due to the fact that potassium, sodium and calcium are involved in a number of physiological processes, proper ionic concentration is crucial to ensure correct functioning of the entire body. Abnormal ionic levels may be graded according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0) presented in Table 1. Depending on the grade, the patient may remain asymptomatic (usually Grade 1), require hospitalization (Grade 3), experience life threatening consequences (Grade 4) or even die (always classified as Grade 5, regardless of ionic concentration levels) [20].

Table 1

Grades of abnormal ionic concentration according to CTCAE v 4.0 [20].

Grade	Ion					
	K^+		Na^+		Ca^{2+}	
	Hypokalemia	Hyperkalemia	Hyponatremia	Hypernartemia	Hypocalcemia*	Hypercalcemia*
1	<LLN — 3.0 mM	>ULN — 5.5 mM	<LLN — 130 mM	>ULN — 150 mM	<LLN — 8.0 mg/dL; <LLN — 2.0 mM	>ULN — 11.5 mg/dL; >ULN — 2.9 mM
2	<LLN — 3.0 mM but symptomatic	>5.5 — 6.0 mM	—	>150 — 155 mM	<8.0 — 7.0 mg/dL; <2.0 — 1.75 mM	>11.5 — 12.5 mg/dL; >2.9 — 3.1 mM
3	<3.0 — 2.5 mM	>6.0 — 7.0 mM	<130 — 120 mM	>155 — 160 mM	<7.0 — 6.0 mg/dL; <1.75 — 1.5 mM	>12.5 — 13.5 mg/dL; >3.1 — 3.4 mM
4	<2.5 mM	>7.0 mM	<120 mM	>160 mM	<6.0 mg/dL; <1.5 mM	>13.5 mg/dL; >3.4 mM
5	Death					

LLN — lower limit of normal;
ULN — upper limit of normal;
*Separate values given for ionized calcium level.

POTASSIUM

A reduction of potassium level (hypokalemia) is associated with muscle weakness due to rhabdomyolysis, which may subsequently lead to paralysis, hypoventilation and respiratory failure. Other symptoms include: hypotension, cramping, fasciculation, urinary retention and paralytic ileus. Persistent hypokalemia results in an impairment of the renal concentrating ability. The effect of mild hypokalemia on the electrocardiogram (ECG) may be minimal. Grade ≥2 hypokalemia results in the sagging of the ST segment, increases the length of the PQ interval, the T wave becomes depressed while the U wave is elevated. In profound hypokalemia, the T wave is gradually getting bigger, while the U wave is getting larger. The T wave may sometimes merge with the U wave, which may be mistaken for the long QT syndrome. Abnormally low potassium levels are also the reason for premature ventricular and atrial contractions, tachyarrhythmias and atrioventricular blocks. Severe hypokalemia may result in ventricular fibrillation and torsade de pointes [4].

Mild hyperkalemia rarely causes any symptoms. High potassium levels may, however, cause flaccid paralysis and confusion. In grade 2, ECG changes may be observed, such as PR interval prolongation and QT interval shortening. A further increase in the level of potassium (grade 3) may result in a greater widening of the QRS complex, loss of P wave and ventricular arrhythmias. In the end, the QRS complex degenerates into a sine-wave pattern, and asystole or ventricular fibrillation occurs [4].

SODIUM

Hyponatremia is associated with such symptoms as: confusion, lethargy, fatigue, headache, nausea, vomiting, loss of appetite, spasms, cramps, seizures, depressed neural reflexes and ST elevation on ECG. If the serum sodium concentration falls to grade 4, stupor, neuromuscular hyperexcitability, hyperreflexia, seizures and coma appear, which may lead to death [4, 13, 20].

The major symptoms of hypernatremia are connected with brain cell shrinkage. Depending on the duration of the ion abnormal level and on actual blood volume the signs of hypernatremia may include: thirst, neuromuscular excitability, confusion, seizures, coma and cardiopulmonary arrest [4, 20].

CALCIUM

In the case of profound hypocalcemia, hypersensitivity in the neuromuscular system, known as tetany, is followed by tremors, uncontrolled muscle contraction and finally, convulsions, which lead to larynx and/or diaphragm contractions and subsequent death. Arrhythmias or heart blocks are also possible. Mild hy-

pocalcemia is related to bone abnormalities and dehydration, while severe hypocalcemia may cause ECG abnormalities, such as QT intervals and ST segments prolongation, T-wave elevation or its inversion [5, 20].

Chronic form of hypercalcemia is connected with neurological and neuromuscular disturbances as adynamia, vomiting, gastric ulcers, pancreatitis, renal failure, and cardiac arrhythmia or hypertension. Severe hypercalcemia (grade 4) may also result in cardiac arrest. A strong increase in the level of calcium is accompanied by QTc interval shortening, PQ interval elongation (similarly to hypokaliemia) and possible arrhythmias [5, 20].

MATERIALS AND METHODS

STUDY ASSUMPTIONS

Publicly available scientific literature was chosen as the only source of data, reported either directly in the text or in the form of graphs and figures, which were digitized using specialized software [21]. Mean serum concentration expressed in mM was chosen as the analyzed endpoint. Dispersion was described using the standard deviation (SD). If different units were reported, the gathered values were recalculated to mM and SD, respectively. There was no publication date restriction and it was assumed that all measurement methods used in the analyzed studies were equally precise and sensitive. However, information about the measurement method was collected whenever possible and is reported below. Additional reported data include: the sex ratio, mean age in years (presented either as a mean value with the dispersion measure [SD] or range, depending on the studied report), height (cm) and weight (kg), which were collected whenever possible. Ethnicity was not considered and analyzed as an independent factor, therefore reported data are not racially stratified.

LITERATURE ANALYSIS AND COLLECTED DATA PROCESSING

Main Scopus, Medline and Google Scholar searches were performed. The key phrases used during the searches were: “potassium serum concentration”, “calcium serum concentration”, “sodium serum concentration”, AND “healthy volunteers” or “control” either in the article title, keywords or abstract. To find articles describing circadian variation, the following terms were used: “circadian”, “diurnal” and “rhythm”. Every available English-language paper was carefully evaluated and the results were noted down in two Excel spread sheets, separately for static (time of the measurement not reported) and dynamic values (circadian rhythm, with the time of measurement reported). Collected data describing ionic concentration were further analysed for the differences between genders. For

this analysis, records containing information about the mean age of the studied cohort, separately for males and females, were chosen. As there is no standard method for the bivariate and multivariate analysis of aggregated data age — concentration interdependence was visually analysed as presented on the attached as the supplementary materials scatterplots which indicate no correlation for potassium and sodium (Supplement 2). There might be a weak interdependence between age and calcium ion concentration although individual data would be needed to falsify such hypothesis. For each ion, an overall mean of the serum concentration was calculated as a mean of study-specific means weighted by study-specific sample sizes. We also calculated an overall standard deviation, describing dispersion of individual concentration values around the overall mean. Calculations were performed separately for men and women.

RESULTS

STATIC DATA

The full set of collected data is presented in the supplementary results section as a separate file (Supplement 1). Table 2 presented below contains data records chosen for further analysis for potassium, sodium and calcium, respectively. Demographic and physiological parameters include gender and age. The mean serum ionic concentration is a dependent parameter. The number of individuals in all studies was also reported. Table 2 presents also the serum ions concentration means weighted by the study-specific sample sizes and overall standard deviations around the overall mean. The two sample t-test indicated statistically significant differences between males and females for all ions. All p-values were below 0.001.

CIRCADIAN DATA

The full set of collected data describing circadian rhythm of the serum concentration of the three studied ions is presented in Table 3.

DISCUSSION

The aim of the study was to collect and analyze reports providing data on the serum concentration of three necessary elements — potassium, sodium and calcium. Collected data were further analysed to provide average values and their dispersion separately for males and females. There is a noticeable general trend toward higher ionic concentration in men than in women. The statistical signifi-

cance of this phenomenon was further tested using two sample t-tests ($p < 0.001$). It could be speculated that differences in the ions levels may be partially responsible for the differences between genders in the incidence of the drugs triggered arrhythmias or the incidence of death resulting from cardiovascular events, especially in various age subgroups [22, 23]. The problem is obviously much more complex. Other factors including e.g. hormones turnover affect simultaneously both: cations levels and death rate due to cardiovascular diseases or the risk of arrhythmias. It has been shown that not only do men and women vary in term of steroid hormonal system, but also they have different expression of genes encoding heart ions channels [24]. There are separate studies needed to falsify such hypothesis. Then, ions levels could serve as one of the available surrogates: cheap, accessible and often studied in the population also for other indications.

Different normal range values of metabolic panel components for men and women are already used for some parameters such as liver function tests, uric acid, creatinine, creatine kinase, hormone levels and others. However, for potassium, sodium and calcium, no differences between sexes in normal ranges have been used so far in daily clinical practice [5, 10].

The calculated values could be compared with the reference values. The most commonly used standard concentrations for the three analysed ions are presented in Table 1. Data gathered from the literature correspond with the presented range.

It is worth noticing that the concentration of ions just below or above the normal range are not always considered pathological or require treatment (see Table 1). There may be numerous plausible explanations for this, one of them being the fact that normal value ranges may vary slightly among different laboratories. Moreover, the existence of biological variation has been widely described, such as the above-mentioned biological cycles or rhythms which may also play significant role. All individuals, regardless of the study type, experience these inter- and intra-subject variations, which should never be ignored.

Ion serum concentration can be also affected by the demographic, sociological and physiological factors, including age, ethnicity, geographic location as well as diet, which was also reported [25–27]. Data obtained in different laboratories may be influenced by pre-analytical and analytical factors. As for the former, patient preparation, proper sample collection, transport and testing time and conditions must be ensured as these elements may change ionic concentration. For example, prolonged transport time may indicate higher potassium levels due to the lysis of cellular components and prolonged venous stasis during blood collection may result in calcium level abnormalities.

Our study collected records gathered throughout three decades. Comparing the older with more recent data we have to bear in mind the difficulties and possible errors resulting from that as it is undeniable that the laboratory standards have undergone great variation in that time in terms of calibration regulations, performing population-based reference values and the type of reagents or methods

used. Most of the studies are performed using automatic analyzers [25, 28]. Other laboratories use flame photometry [26, 29] or ion-sensitive electrodes [24] and in the case of some results, the method used remains unknown [2]. Depending on the type of method (direct or indirect), some difficulties in testing have been described, such as erroneous sodium results in individuals with disrupted protein concentration when using indirect ion-selective electrode method [28]. Such parameters were not analysed in our study due to the lack of data, which is probably the greatest source of uncertainty. On the other hand, currently, the same automated analyzers and techniques are widely used around the world, so we are not afraid to compare data from different laboratories, because possible biases or errors described above may affect all of them to a similar extent.

The collected data are intended to be used as the source of information about physiological variability during the modelling and simulation of the drug-triggered left ventricular wall electrophysiology disruption [30].

Table 2

Serum potassium, sodium and calcium concentration derived from the healthy volunteers studies. Weighted means of the serum ions concentration.

Author [Ref.]	Year	Gender	n	Age [years]		K^+ [mM]				
				Mean	SD	Concentration	SD	Total n	Mean weighted concentration	SD
Chun [13]	2008	Female	59	23.8	4.6	4.06	0.31	328	4.09	0.45
			49	23.5	4.2	4.02	0.35			
Luft [31]	1979		115	32.7	15.0	4.25	0.32			
			35	28.5	10.0	4.14	0.35			
Hallen [32]	1994		6	21.0	0.5	4.25	0.29			
Martinerie [33]	2009		47	31.9	4.2	3.70	0.7			
Heenan [34]	2003		17	27.1	5.8	4.20	0.41			
Federenko [35]	2011	Male	10	24.0	7.5	4.14	0.02	496	4.21	0.35
			10	24.0	7.5	4.15	0.02			
McKenna [36]	1997		6	21.2	1.5	4.40	0.25			
Miller [37]	2009		9	25.0	2.0	4.40	0.30			
Karakoc [38]	2005		10	18.4	1.3	4.10	0.30			
Krapf [25]	1991		4	28.1	3.6	4.50	0.40			
			5	28.1	3.6	4.60	0.45			
Pearson [39]	2011		11	21.0	2.0	4.00	0.33			

Table 2 cont.

Author [Ref.]	Year	Gender	n	Age [years]		K^+ [mM]				
				Mean	SD	Concentration	SD	Total n	Mean weighted concentration	SD
Chun [13]	2008	Male	52	22.9	4.3	4.13	0.36	496	4.21	0.35
			39	22.1	3.7	4.04	0.31			
Luft [31]	1979		145	28.9	13.3	4.30	0.36			
			42	30.7	11.7	4.24	0.32			
Bonfils [9]	2010		27	68.0	3.1	4.00	0.20			
Jartti [18]	1998		6	24.0	0.0	4.00	0.24			
			6	24.0	0.0	4.20	0.24			
Afshar [40]	2009		18	18.9	0.9	4.20	0.30			
Zorbas [41]	2001		10	25.0	7.7	4.16	0.12			
			10	24.5	8.0	4.12	0.14			
			10	23.9	6.7	4.12	0.11			
Zorbas [42]	2001		10	24.7	6.8	4.20	0.30			
			10	23.9	7.0	4.00	0.50			
			10	25.4	5.6	4.10	0.20			
Zorbas [43]	1998		10	23.8	4.2	4.70	0.11			
			10	25.4	3.0	4.50	0.13			
			10	24.9	3.0	4.60	0.13			
Laso [44]	1991		6	21.6	0.5	3.80	0.12			
Chun [13]	2008	Female	59	23.8	4.6	137.8	2.30	322	138.17	4.40
			49	23.5	4.2	137.8	2.10			
Luft [31]	1979		115	32.7	15.0	140.3	4.29			
			35	28.5	10.0	139.3	2.37			
Martinerie [33]	2009		47	31.9	4.2	132.3	4.80			
Heenan [34]	2003		17	27.1	5.8	140.0	1.65			
McKenna [36]	1997	Male	6	21.2	1.5	139.7	1.00	553	140.10	3.02
Miller [37]	2009		9	25.0	2.0	141.0	1.00			
Karakoc [38]	2005		10	18.4	1.3	142.0	3.80			
Krapf [25]	1991		4	28.1	3.6	141.5	1.00			
			5	28.1	3.6	139.3	1.60			
Pearson [39]	2011		11	21.0	2.0	139.0	3.32			
Chun [13]	2008		52	22.9	4.3	137.9	2.16			
			39	22.1	3.7	137.9	1.87			

Table 2 cont.

Author [Ref.]	Year	Gender	n	Age [years]		K^+ [mM]				
				Mean	SD	Concentration	SD	Total n	Mean weighted concentration	SD
Luft [31]	1979	Male	145	28.9	13.3	141.3	3.61	553	140.10	3.02
			42	30.7	11.7	139.9	2.59			
Bonfils [9]	2010		27	68.0	3.1	139.0	1.90			
Afshar [40]	2009		18	18.9	0.9	136.7	3.10			
Zorbas [41]	2001		10	25.0	7.7	139.1	0.60			
			10	24.5	8.0	140.3	1.00			
			10	23.9	6.7	142.3	0.40			
Zorbas [42]	2001		10	24.7	6.8	140.0	0.50			
			10	23.9	7.0	138.0	0.70			
			10	25.4	5.6	137.0	0.50			
Zorbas [43]	1998		10	23.8	4.2	143.0	0.80			
			10	25.4	3.0	142.0	1.10			
			10	24.9	3.0	141.0	1.50			
Sothern [18]	1996		21	51.3	8.7	140.3	0.96			
			14	41,0	7.2	140.3	0.20			
Miller [37]	2010		10	25.4	0.7	138.6	2.21			
			10	25.4	0.7	139.3	1.90			
Zorbas [45]	1994		10	25.5	7.6	143.0	0.10			
			10	24.9	9.7	140.0	0.13			
Goldberg [46]	1973	Female	271	48.0	12.8	2.375	0.13	1783	2.31	0.14
Horwitz [61]	2010		15	58.0	8.1	2.325	0.10			
			10	57.0	7.0	2.325	0.08			
			10	55.0	5.1	2.375	0.08			
			6	60.0	7.3	2.45	0.06			
Lorentzon [29	2001		69	17.0	1.2	2.14	0.08			
Schlemmer [47]	1999		11	24.0	5.0	2.31	0.03			
			11	24.0	5.0	2.33	0.07			
Yan [48]	2002		48	30.9	3.2	2.46	0.30			
			48	66.9	2.7	2.63	0.14			
Engel [50]	2010		1272	56.9	6.4	2.29	0.10			
Brandi [7]	2002		6	40.5	13.5	2.33	0.05			
			6	28.0	16.2	2.32	0.03			

Table 2 cont.

Author [Ref.]	Year	Gender	n	Age [years]		K^+ [mM]				
				Mean	SD	Concentration	SD	Total n	Mean weighted concentration	SD
Blanchard [49]	2001	Male	5	35.0	17.9	2.25	0.06	475	2.42	0.20
			4	33.0	4.0	2.26	0.08			
			48	31.1	3.4	2.66	0.14			
			50	68.9	2.9	2.44	0.16			
Goldberg [46]	1973		248	48.7	12.8	2.425	0.18			
Zorbas [41]	2001		10	25.0	7.7	2.27	0.06			
			10	24.5	8.0	2.25	0.06			
			10	23.9	6.7	2.27	0.08			
Zorbas [42]	2001		10	24.7	6.8	2.14	0.01			
			10	23.9	7.0	2.15	0.02			
			10	25.4	5.6	2.15	0.03			
Zorbas [45]	1994		10	25.5	7.6	2.29	0.30			
			10	24.9	9.7	2.29	0.15			
			10	25.2	8.5	2.31	0.25			
Zorbas [43]	1998		10	23.8	4.2	2.5	0.07			
			10	25.4	3.0	2.55	0.06			
			10	24.9	3.0	2.55	0.10			

Table 3

Circadian rhythm of the serum concentration derived from the available literature sources.

Author	Year	Ref.	Age	SD	Sex M/F	Time of day	Ion					
							K^+	SD	Na^+	SD	Ca^{2+}	SD
Williams	1972	[51]	22,5	3.0	4/2	10:00	4.50	0.13	141.00	2.45		
						14:00	4.47	0.19	141.00	4.90		
						17:00	4.48	0.23	140.00	4.90		
						23:00	4.10	0.28	139.00	1.23		
Jubiz	1972	[52]	22-32		8/2	08:00					2.60	0.05
						10:00					2.63	0.08
						12:00					2.63	0.05
						14:00					2.60	0.05
						16:00					2.60	0.05
						18:00					2.63	0.08
						20:00					2.70	0.08
						22:00					2.63	0.05

Table 3 cont.

Author	Year	Ref.	Age	SD	Sex M/F	Time of day	Ion					
							K^+	SD	Na^+	SD	Ca^{2+}	SD
Jubiz	1972	[52]	22-32		8/2	00:00					2.58	0.05
						02:00					2.55	0.08
						04:00					2.53	0.05
						06:00					2.55	0.03
						08:00					2.60	0.05
Morrison	1979	[53]	19-30		9/11	08:30	4.10	0.26	140.70	1.64	2.37	0.08
						12:30	4.07	0.23	140.20	1.65	2.40	0.08
						16:30	3.95	0.26	140.80	1.72	2.39	0.08
Pocock	1989	[54]	40-59		603/0	9:00-10:00	4.39	0.35				
					1041/0	10:00-11:00	4.42	0.25				
					947/0	11:00-12:00	4.41	0.27				
					847/0	12:00-13:00	4.38	0.28				
					426/0	13:00-14:00	4.26	0.33				
					317/0	14:00-15:00	4.26	0.45				
					735/0	15:00-16:00	4.26	0.29				
					918/0	16:00-17:00	4.25	0.25				
					912/0	17:00-18:00	4.26	0.25				
					863/0	18:00-19:00	4.26	0.29				
Rittig	2006	[55]	13.2	0.8	6/4	08:00	4.12		142.20			
						14:00	4.12		141.90			
						20:00	4.16		141.40			
						23:00	3.95		142.60			
						02.00	3.92		141.60			
						05:00	4.15		141.60			
						08.00	4.29		142.10			
Solomon	1991	[56]	37	7	2/6	12:00	4.10	0.20				
						16:00	4.14	0.28				
						20:00	4.00	0.28				
						00:00	3.98	0.20				
						04:00	4.12	0.25				

Table 3 cont.

Author	Year	Ref.	Age	SD	Sex M/F	Time of day	Ion					
							K^+	SD	Na^+	SD	Ca^{2+}	SD
Solomon	1991	[56]	37	7	2/6	08:00	4.13	0.17				
						12:00	4.07	0.28				
						16:00	4.10	0.25				
Rejnmark	2002	[57]	58	50-71	0/12	10:00					2.43	0.07
						08:00					2.36	0.03
Sothern	1996	[18]	51	8.65	21/0	19:00			140.50	1.70		
						22:00			139.90	1.33		
						01:00			139.80	1.01		
						04:00			140.10	1.05		
						07:00			138.60	2.25		
						10:00			140.20	2.06		
						13:00			141.50	1.74		
						16:00			141.70	1.83		
Statland	1973	[58]			3?/0	08:00	5.35		140.50		2.58	
						11:00	4.74		141.90		2.57	
						14:00	4.34		140.00		2.60	
Schlemmer	1999	[47]	24	5	0/11	08:00					2.33	0.07
						11:00					2.32	0.07
						14:00					2.28	0.05
						17:00					2.30	0.03
						20:00					2.29	0.05
						23:00					2.31	0.08
						02:00					2.30	0.07
						05:00					2.32	0.07
						08:00					2.31	0.07
Markowitz	1985	[59]	17-35		13/0	09:30					2.32	
						10:30					2.32	
						11:30					2.32	
						12:30					2.31	
						13:30					2.30	
						14:30					2.29	
						15:30					2.28	
						16:30					2.28	
						17:30					2.27	
						18:30					2.26	
						19:30					2.26	
						20:30					2.26	

Table 3 cont.

Author	Year	Ref.	Age	SD	Sex M/F	Time of day	Ion					
							K^+	SD	Na^+	SD	Ca^{2+}	SD
						21:30					2.25	
						22:30					2.24	
						23:00					2.23	
						00:30					2.22	
						01:30					2.22	
						02:30					2.21	
						03:30					2.21	
						04:30					2.21	
						05:30					2.21	
						06:30					2.21	
						07:00					2.23	
						08:00					2.31	
						09:00					2.31	
Even	2007	[60]	12.6	1.8	5/3	20:00					2.25	0.12
						00:00					2.17	0.13
						02:00					2.18	0.08
						08:00					2.25	0.16

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

REFERENCES

1. *Vander A., Sherman J., Luciano D.*: Human physiology — The Mechanisms of Body Function. 8th edition, McGraw-Hill, Boston, 2001. **— 2.** *Ronco C., Bellomo R., Kellum J.A.*: Critical Care Nephrology: Expert Consult. Saunders/Elsevier, Philadelphia, 2009. **— 3.** *Singer G.G., Brenner B.M.*: Fluid and electrolyte disturbances. In Harrison's Principles of Internal Medicine Ed. Kasper D.L., Braunwald E., Fauci A.S., Hauser S.L., Longo D.L., Jameson J.L., 16th edition, McGraw Hill, New York, 2005; 258–226. **— 4.** *Copp D.H., McPherson G.D., McIntosh H.W.*: Renal excretion of calcium

in man: estimation of Tm-Ca. Metabolism. 1960; 9: 680–685. — **5.** *Ceriotti F., Henny J., Queraltó J., Ziyu S., Özarda Y., Chen B., Boyd J.C., Panteghini M.*: IFCC Committee on Reference Intervals and Decision Limits (C-RIDL), Committee on Reference Systems for Enzymes (C-RSE): Common reference intervals for aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) in serum: results from an IFCC multicenter study. Clin Chem Lab Med. 2010; 48: 1593–1601. — **6.** *Giebisch G.*: Renal potassium transport: mechanisms and regulation. Am J Physiol. 1998; 274: 817–833. — **7.** *Brandi L., Egfjord M., Olgaard K.*: Pharmacokinetics of 1,25(OH)(2) D(3) and 1alpha(OH)D(3) in normal and uraemic men. Nephrol Dial Transplant. 2002; 17: 829–842. — **8.** *Parfitt A.M.*: Calcium homeostasis. In Physiology and Pharmacology of Bone Ed. Mundy G.R., Martin T.J., Springer-Verlag, Berlin, 1993; 1–66. — **9.** *Bonfils P.K., Damgaard M., Taskiran M., Goetze J.P., Norsk P., Gadsbřll N.*: Impact of diuretic treatment and sodium intake on serum volume in patients with compensated systolic heart failure. Eur J Heart Fail. 2010; 12: 995–1001. — **10.** *Kratz A., Lewandrowski K.B.*: Normal reference laboratory values. N Engl J Med. 1998; 339: 1063.

11. *Ganong W.F.*: Review of Medical Physiology. 20th edition, McGraw-Hill, New York, 2003. — **12.** World Health Organization & Food and Agriculture Organization of the United Nations. Vitamin and mineral requirements in human nutrition. World Health Organization, Geneva, 2004. — **13.** *Chun T.Y., Bankir L., Eckert G.J., et al.*: Ethnic differences in renal responses to furosemide. Hypertension. 2008; 52: 241–248. — **14.** *Dibner C., Schibler U., Albrecht U.*: The mammalian circadian timing system: organization and coordination of central and peripheral clocks. Annu Rev Physiol. 2010; 72: 517–549. — **15.** *Bernardi M., DePalma R., Trevisani F., et al.*: Serum potassium circadian rhythm. Relationship with aldosterone. Horm Metab Res. 1985; 17: 695. — **16.** *Ekmekcioglu C., Touitou Y.*: Chronobiological aspects of food intake and metabolism and their relevance on energy balance and weight regulation. Obes Rev. 2011; 12: 14–25. — **17.** *Kanabrocki E.L., Scheving L.E., Halberg F., Brewer R.L., Bird T.J.*: Circadian variations in presumably healthy men under conditions of peace time army reserve unit training. Space Life Sci. 1973; 4: 258–270. — **18.** *Sothern R.B., Vesely D.L., Kanabrocki E.L., et al.*: Circadian relationships between circulating atrial natriuretic peptides and serum sodium and chloride in healthy humans. Am J Nephrol. 1996; 16: 462–470. — **19.** *Jartti T.T., Kuusela T.A., Kaila T.J., Tahvanainen K.U., Välimäki I.A.*: The dose-response effects of terbutaline on the variability, approximate entropy and fractal dimension of heart rate and blood pressure. Br J Clin Pharmacol. 1998; 45: 277–285. — **20.** U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events v 4.03, 2009.

21. Sourceforge. http://digitizer.sourceforge.net/ (accessed 02-05-2013). — **22.** *Ebert S.N., Liu X.K., Woosley R.L.*: Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. J Womens Health. 1998; 7: 547–557. — **23.** *Kawasaki R., Machado C., Reinoehl J.*: Increased propensity of women to develop torsades de pointes during complete heart block. J Cardiovasc Electrophysiol. 1995; 6: 1032–1038. — **24.** *Yang P.C., Clancy C.E.*: In silico Prediction of Sex-Based Differences in Human Susceptibility to Cardiac Ventricular Tachyarrhythmias. Front Physiol. 2012; 3: 360. — **25.** *Krapf R., Beeler I., Hertner D., Hulter H.N.*: Chronic respiratory alkalosis. The effect of sustained hyperventilation on renal regulation of acid-base equilibrium. N Engl J Med. 1991; 324: 1394–1401. — **26.** *Kratz A., Ferraro M., Sluss P.M., Lewandrowski K.B.*: Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Laboratory reference values. N Engl J Med. 2004; 351: 1548–1563. — **27.** *Reidenberg M.M., Gu Z.P., Lorenzo B., et al.*: Differences in serum potassium concentrations in normal men in different geographic locations. Clin Chem 1993; 39: 72–75. — **28.** *Lang T., Prinsloo P., Broughton A.F., Law-son N., Marenah C.B.*: Effect of low protein concentration on serum sodium measurement: pseudohypernatraemia and pseudonormonatraemia. Ann Clin Biochem. 2002; 9: 66–67. — **29.** *Lorentzon M., Lorentzon R., Lerner U.H., Nordström P.*: Calcium sensing receptor gene polymorphism, circulating calcium concentrations and bone mineral density in healthy adolescent girls. Eur J Endocrinol. 2001; 144: 257–261. — **30.** *Vesely D.L., Sothern R.B., Scheving L.E., et al.*: Circadian relationships between circulating atrial natriuretic peptides and serum calcium and phosphate in healthy humans. Metabolism. 1996; 45: 1021–1028.

31. *Luft F.C., Grim C.E., Fineberg N., Weinberger M.C.*: Effects of volume expansion and contraction in normotensive whites, blacks, and subjects of different ages. Circulation. 1979; 59: 643–650. **— 32.** *Hallén J., Gullestad L., Sejersted O.M.*: K+ shifts of skeletal muscle during stepwise bicycle exercise with and without beta-adrenoceptor blockade. J Physiol. 1994; 477: 149–159. **— 33.** *Martinerie L., Pussard E., Foix-L'Hélias L., et al.*: Physiological partial aldosterone resistance in human newborns. Pediatr Res. 2009; 66: 323–328. **— 34.** *Heenan A.P., Wolfe L.A., Davies G.A., McGrath M.J.*: Effects of human pregnancy on fluid regulation responses to short-term exercise. J Appl Physiol. 2003; 95: 2321–2327. **— 35.** *Federenko Y.F., Deogenov V.A., Kakuris K.K., Yerullis K.B.*: Muscle potassium and potassium losses during hypokinesia in healthy subjects. Biol Trace Elem Res. 2011; 143: 668–676. **— 36.** *McKenna M.J., Heigenhauser G.J., McKelvie R.S., MacDougall J.D., Jones N.L.*: Sprint training enhances ionic regulation during intense exercise in men. J Physiol. 1997; 501: 687–702. **— 37.** *Miller K.C., Mack G., Knight K.L.*: Electrolyte and serum changes after ingestion of pickle juice, water, and a common carbohydrate-electrolyte solution. J Athl Train. 2009; 44: 454–461. **— 38.** *Karakoc Y., Duzova H., Polat A., Emre M.H., Arabaci I.*: Effects of training period on haemorheological variables in regularly trained footballers. Br J Sports Med. 2005; 39: e4. **— 39.** *Pearson J., Low D.A., Stöhr E., et al.*: Hemodynamic responses to heat stress in the resting and exercising human leg: insight into the effect of temperature on skeletal muscle blood flow. Am J Physiol Regul Integr Comp Physiol. 2011; 300: 663–673. **— 40.** *Afshar R., Sanavi S., Jalali Nadooshan M.R.*: Urinary sodium and potassium excretion following karate competitions. Iran J Kidney Dis. 2009; 3: 86–88.

41. *Zorbas Y.G., Kakurin V.J., Afonin V.B., Kuznetsov N.A.*: Electrolyte changes in serum and urine of athletes during acute and rigorous bed rest and ambulatory conditions. Biol Trace Elem Res. 2001; 79: 49–65. **— 42.** *Zorbas Y.G., Kakurin V.J., Denogratov S.D., Yarullin V.L., Deogenov V.A.*: Urinary and serum electrolyte changes in athletes during periodic and continuous hypokinetic and ambulatory conditions. Biol Trace Elem Res. 2001; 80: 201–219. **— 43.** *Zorbas Y.G., Kakurin A.G., Kuznetsov N.K., Federov M.A., Yaroshenko Y.Y.*: Magnesium loading effect on magnesium deficiency in endurance-trained subjects during prolonged restriction of muscular activity. Biol Trace Elem Res. 1998; 63: 149–166. **— 44.** *Laso F.J., González-Buitrago J.M., Martín Ruiz C., de Castro S.*: Hormonal regulation of potassium shifts during graded exhausting exercise. Eur J Appl Physiol Occup Physiol. 1991; 62: 292–296. **— 45.** *Zorbas Y.G., Federenko Y.F., Naexu K.A.*: Calcium loading and renal function in trained subjects during restriction of muscular activity and chronic hyperhydration. Biol Trace Elem Res. 1994; 41: 137–156. **— 46.** *Goldberg D.M., Handyside A.J., Winfield D.A.*: Influence of demographic factors on serum concentrations of seven chemical constituents in healthy human subjects. Clin Chem. 1973; 19: 395–402. **— 47.** *Schlemmer A., Hassager C.*: Acute fasting diminishes the circadian rhythm of biochemical markers of bone resorption. Eur J Endocrinol. 1999; 140: 332–337. **— 48.** *Yan L., Prentice A., Zhou B., et al.*: Age- and gender-related differences in bone mineral status and biochemical markers of bone metabolism in Northern Chinese men and women. Bone. 2002; 30: 412–415. **— 49.** *Blanchard A., Jeunemaitre X., Coudol P., et al.*: Paracellin-1 is critical for magnesium and calcium reabsorption in the human thick ascending limb of Henle. Kidney Int. 2001; 59: 2206–2215. **— 50.** *Engel P., Fagherazzi G., Boutten A., et al.*: Serum 25(OH) vitamin D and risk of breast cancer: a nested case-control study from the French E3N cohort. Cancer Epidemiol Biomarkers Prev. 2010; 19: 2341–2350.

51. *Williams G.H., Tuck M.L., Rose L.I., Dluhy R.G.*: Underwood RH. Studies of the control of serum aldosterone concentration in normal man. 3. Response to sodium chloride infusion. J Clin Invest. 1972; 51: 2645–2652. **— 52.** *Jubiz W., Canterbury J.M., Reiss E., Tyler F.H.*: Circadian rhythm in serum parathyroid hormone concentration in human subjects: correlation with serum calcium, phosphate, albumin, and growth hormone levels. J Clin Invest. 1972; 51: 2040–2046. **— 53.** *Morrison B., Shenkin A., McLelland A., et al.*: Intra-individual variation in commonly analyzed serum constituents. Clin Chem. 1979; 25: 1799–1805. **— 54.** *Pocock S.J., Ashby D., Shaper A.G., Walker M., Broughton P.M.*: Diurnal variations in serum biochemical and haematological measurements. J Clin Pathol. 1989; 42: 172–179. **— 55.** *Rittig S., Matthiesen T.B., Pedersen E.B., Djurhuus J.C.*: Circadian variation of angiotensin II and aldosterone in nocturnal enuresis: relationship to arterial blood pressu-

re and urine output. J Urol. 2006; 176: 774–780. — **56.** *Solomon R., Weinberg M.S., Dubey A.*: The diurnal rhythm of serum potassium: relationship to diuretic therapy. J Cardiovasc Pharmacol. 1991; 17: 854–859. — **57.** *Rejnmark L., Lauridsen A.L., Vestergaard P., Heickendorff L., Andreasen F., Mosekilde L.*: Diurnal rhythm of serum 1,25-dihydroxyvitamin D and vitamin D-binding protein in postmenopausal women: relationship to serum parathyroid hormone and calcium and phosphate metabolism. Eur J Endocrinol. 2002; 146: 635–642. — **58.** *Statland B.E., Winkel P., Bokelund H.*: Factors contributing to intra-individual variation of serum constituents. 1. Within-day variation of serum constituents in healthy subjects. Clin Chem. 1973; 19: 1374–1379. — **59.** *Markowitz M.E., Rosen J.F., Mizruchi M.*: Circadian variations in serum zinc (Zn) concentrations: correlation with blood ionized calcium, serum total calcium and phosphate in humans. Am J Clin Nutr. 1985; 41: 689–696. — **60.** *Even L., Bader T., Hochberg Z.*: Nocturnal calcium, phosphorus and parathyroid hormone in the diagnosis of concealed and subclinical hypoparathyroidism. Eur J Endocrinol. 2007; 156: 113–116.

61. *Horwitz M.J., Tedesco M.B., Garcia-Ocańa A., et al.*: Parathyroid hormone-related protein for the treatment of postmenopausal osteoporosis: defining the maximal tolerable dose. J Clin Endocrinol Metab. 2010; 95: 1279–1287.

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