https://doi.org/10.46389/rjd-2024-1736
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2024; volume 31, issue 4, pages 411–419

Original Article

Peculiarities of transtubular transport of calcium and phosphates in the dynamics of the development of alloxan-induced experimental Diabetes Mellitus

Olha Olenovych [1] *, Anatoliy Gozhenko [2], Yelyzaveta Tkach [3]

[1] Department of Clinical Immunology, Allergology and Endocrinology, Bukovinian State Medical University, Chernivtsi, Ukraine

[2] State Enterprise Ukrainian Scientific Research Institute of Transport Medicine of Ministry of Health of Ukraine, Odesa, Ukraine

[3] Department of Internal Medicine, Clinical Pharmacology and Occupational Diseases, Bukovinian State Medical University, Chernivtsi, Ukraine

* Correspondence to: Department of Clinical Immunology, Allergology and Endocrinology, Bukovinian State Medical University, Teatralna Sq. 2, 58002, Chernivtsi, Ukraine. Phone:+380955288554; E-mail: olenovych.olga@bsmu.edu.ua

Received: 14 August 2024 / Accepted: 21 November 2024

Abstract

The objectives of the research were to study the peculiarities of the intrarenal mechanisms of calcium and phosphates homeostasis regulation under the condition of experimental diabetes. The experiments were carried out on 54 white non-linear mature male rats – 24 animals with 11-, 26- and 46-day long alloxan-induced experimental diabetes mellitus and 30 intact animals of the control. Creatinine, sodium, calcium and phosphates in the urine were determined. Electrolytes excretion, calcium-phosphorus, calcium- and phosphorus-creatinine, sodium-calcium and sodium-phosphorus ratios in urine were calculated. The study's results demonstrated the increase of sodium-dependent excretion of calcium and phosphates, mainly hyperfusional in nature, on the 11th day of the experiment provided by the distal tubules with underlying functional overstrain of the tubulo-tubular feedback. The predominance of sodium-dependent distal counter-transport of calcium was preserved on the 26th day of the experiment, while phosphate reabsorption was related mainly to the proximal tubules. Reabsorptive defect of phosphates in the proximal and distal tubules was a probable reason for the increase of their urine content and maximal strain of phosphate homeostasis mechanisms on the 46th day of the experiment, preserved concerning calcium. These results evidence the preserved compensatory and functional autoregulatory renal mechanisms for calcium and phosphate exchange.

Keywords: alloxan, experimental diabetes mellitus, renal function, calcium, phosphates.

Introduction

Diabetes mellitus (DM) is characterized by the development of acute and chronic complications that differ in the rate of progression and severity and usually negatively affect the patient's quality of life and lead to early disability and death. Recently, pathological changes in the bone tissue are increasingly included in the group of chronic complications of DM [1–4]. Convincing data indicate a tendency to decrease bone mass and change the bone tissue microarchitecture, observed in the case of DM [5–7]. Despite the achievements in researching the mechanisms and manifestations of pathological changes in the bone tissue caused by DM, there is no consensus on the character, frequency and causes of skeletal changes in conditions of controlled hyperglycemia [5, 8].

At the same time, the state of human mineral metabolism and bone remodeling is largely determined by the activity of the kidneys as the main efferent link to

the regulation of water-salt metabolism [9]. Without diminishing the value of such important links of the physiological regulation of the mineral composition of the bodily biological fluids as the condition of the musculoskeletal system metabolism and the processes of mineral substances reabsorption in the gastrointestinal tract, it should be admitted that the state of renal failure significantly stipulates the negative dynamics of an entire series of parameters of water-salt metabolism, including demineralization of the bone tissue [10]. As a target organ and the site of degradation of most calcitropic factors, the kidneys significantly affect calcium homeostasis and vitamin D metabolism, and renal disorders are undoubtedly considered a risk factor for the development of secondary osteoporosis [11–14].

Since diabetic nephropathy is one of the leading causes of renal failure among the numerous chronic complications that constantly develop against the background of DM, regardless of its type and duration, it is reasonable to clarify the role of renal dysfunction in the development of mineral metabolism disorders in the case of DM.

The objectives of the research were to study the peculiarities of the intrarenal mechanisms of calcium and phosphate homeostasis regulation and their connection with the disorders of kidney functional state under the condition of experimental diabetes.

Material and methods

The experiments were carried out on 54 white non-linear mature male rats, weighted 0.18–0.20 kg, kept under identical standard vivarium conditions. Experimental diabetes mellitus (EDM) was induced in 24 animals by a single intraperitoneal administration of a diabetogenic dose of alloxan (Alloxan monohydrate, "Acros Organics", Belgium) – 160 mg/kg of body weight – after the preceding 12-hour deprivation of food with preserved access to water ad libitum. 10, 25 and 45 days after alloxan administration, the diabetic rats (8 animals in every subgroup) and 30 control (intact) animals (10 at each stage of the experiment) were loaded with water in the volume of 5% of the body weight. Urine was collected for 2 hours; euthanasia was performed by decapitation under light ether anesthesia.

The level of glucose in the blood samples was determined by a One Touch Ultra glucometer (LifeScan, USA), and only the data of rats with persistent hyperglycemia exceeding 7.0 mmol/L were considered.

After assessment of water-induced 2-hour diuresis (in ml/100 g of body weight for 2 hours), urine creatinine concentration (in a reaction with picric acid according to Folin`s method) and plasma creatinine concentration (according to A.K.Merzon`s method) were determined [15], GFR was calculated based on endogenous creatinine clearance [15]. The concentration of sodium in urine samples was detected by flame photometry method, the calcium urine content – by the intensity of coloration in the presence of o-cresolphthalein complexone, and the level of phosphates in urine – by photometry of the phosphoromolybdate complex. The calculation of electrolyte excretion was carried out, correlated with the unit of functioning nephron [its absolute values were calculated per 100 µl of glomerular filtrate (GF)] [15, 16], as well as the calculation of calcium-phosphorus, calcium- and phosphorus-creatinine ratios to assess the degree of calciuria and phosphaturia, sodium-calcium and sodium-phosphorus ratios in urine – to evaluate sodium-dependent mechanisms of tubular transport of cations.

The data obtained were statistically processed, with the mean value and standard errors determined. The non-parametric Mann-Whitney rank test, provided by the software Statistica for Windows, Version 8.0, was used to assess the probability of difference between the studied groups [17].

The research was carried out in compliance with the provisions of the EU Directive No. 609 (1986) and the Order of the Ministry of Health of Ukraine No. 690 of 09/23/2009 "On measures to improve further organizational norms for work with the use of experimental animals".

Results and discussion

Assessment of intrarenal calcium and phosphates transport in rats with alloxan-induced diabetes showed that urinary calcium and phosphorus concentration, as well as the urinary calcium-phosphorus ratio, did not undergo significant changes at the initial stage of diabetic renopathy development in comparison with the corresponding indices of intact rats, demonstrating a tendency to decrease – by 8.7 and 6.5% as to urinary calcium and phosphorus concentration and by 6.9% as to the ratio of their urinary concentrations, correspondingly (Table 1).

However, the excretion of calcium and phosphorus increased unreliably – by 7.3% and 10.7%, respectively. Consistently, an assumption arises of a possible association between the increase of renal excretion of cations and both the increase of their filtration charge

 https://doi.org/10.46389/rjd-2024-1736

Table 1: Characteristics of tubular transport of calcium and phosphates in rats with 11-day aloxane-induced experimental diabetes (X±Sx).

Indices	Groups, number of animals	
	Control, n=10	11-day EDM, n=8
Calcium concentration in urine, mmol/L	1.26±0.03	1.15±0.11 p>0.3
Excretion of calcium, µmol per 2 hours	3.72±0.24	3.99±0.49 p>0.6
Standardized excretion of calcium, µmol/100 ml of GF	1.05±0.04	0.84±0.14 p>0.1
Phosphates concentration in urine, mmol/L	4.64±0.48	4.34±0.48 p>0.6
Excretion of phosphates, µmol per 2 hours	13.48±1.44	14.92±1.76 p>0.5
Standardized excretion of phosphates, µmol/100 ml of GF	3.86±0.40	3.09±0.50 p>0.2
Calcium-phosphorus ratio in urine, un.	0.304±0.038	0.283±0.037 p>0.8
Calcium-creatinine ratio in urine, un.	1.34±0.05	0.77±0.12 p<0.01
Phosphorus-creatinine ratio in urine, un.	4.93±0.50	2.82±0.34 p<0.05
Sodium concentration in urine, mmol/L	0.72±0.05	3.94±0.16 p<0.001
The sodium-calcium ratio in urine, un.	0.57±0.04	3.62±0.32 p<0.001
Sodium-phosphorus ratio in urine, un.	0.171±0.024	0.991±0.111 p<0.001

Note: Intergroup differences were assessed using the non-parametric Mann-Whitney test; p – the probability of discrepancy of indices relative to the control group; n – number of animals.

and the decrease of their reabsorption in the tubules. Excessive filtration load of calcium and phosphorus can also be assumed, considering the signs of hyperdynamic excretory activity of the kidneys we have established earlier in the specified period of EDM [18]. The significant reduction of calcium-creatinine and phosphorus-creatinine urinary ratio in animals with 11-day EDM *vs.* controls – by 74.0% and 74.8%, respectively – was accompanied by reliably high urine creatinine of rats in this group (by 69.2% higher than the corresponding index in rats of the control group) and does not exclude the possibility of calcium and phosphates hyperfiltration on 11th day of EDM.

When analyzing the tubular transport of calcium and phosphate, it is important to consider the specific characteristics of their renal reabsorption. Thus, calcium is reabsorbed all along the nephron, but the contribution of certain segments of the nephron to preserving the cation's level in the body differs [19–21]. The main areas of calcium reabsorption are the proximal convoluted and straight tubules (reabsorbed 60–70% of filtered calcium), the thick ascending part of the Henle's loop (additional absorption of 20% of filtered calcium) and distal tubules (5–10% of calcium reabsorption). The final correction of calcium excretion is achieved in the collecting tubules, where calcium transport can be both reabsorptive and excretory in type [22]. Thus, only 0.5–1.5% of calcium is excreted in the urine under normal conditions [21, 23, 24].

While the process of calcium ultrafiltration in the glomerulus is passive (the glomerulus does not belong to the area of calcium homeostasis regulation), the transtubular transport of calcium and its reabsorption varies significantly in certain segments of the tubular apparatus of the kidneys [21, 24–26]. Calcium reabsorption in the proximal sinuous and straight tubules

occurs primarily through the energy-passive transport by the paracrine type, which is isoosmotic – calcium, sodium and water are reabsorbed simultaneously, and the driving force of reabsorption is initially (in the more proximal segment) concentration gradient, and then electrochemical one [21, 26, 27]. Approximately 1/5 of calcium is reabsorbed transepithelially [28].

Calcium transport in Henle's loop's thin descending and ascending segments is practically absent due to the low cell permeability for it. Meanwhile, in the thick part of Henle's loop, the reabsorption of filtered calcium occurs in both the medullar and cortical parts, although with different intensities. In the medullar part of the thick ascending segment of the Henle's loop, in general, basal calcium absorption occurs as its passive transport through the intercellular spaces, and in the cortical part, its active transport takes place [20, 27]. Calcium reabsorption in the distal convoluted tubules is driven entirely by active transcellular transport, which begins with calcium entry to the tubular cell through calcium channels in the apical cellular membrane by potent concentration gradient and ends with the removal of calcium from the tubular cell through the basolateral membrane due to the cooperative function of Ca2+-ATPase and Na+/Ca2+ countertransporter, which moves three sodium ions to cells in exchange for one calcium ion from cells to the interstitium [29–31]. Therefore, the direction and volume of sodium and calcium reabsorption in this nephron segment are inversely related [24, 30–32]. Considering the above, a significant (6.4 times *vs*. the control value) elevation of the sodium-calcium urinary ratio in rats with 11-day EDM due to a 5.5-fold increase in urinary sodium concentration *vs*. the control indicates that it is the distal sodium-dependent tubular reabsorption of calcium ensures its effective homeostasis. Calcium reabsorption in the proximal renal tubules occurs simultaneously with sodium reabsorption [21, 24, 26, 27, 30], and the latter remains unchanged when standardized per unit of the functioning nephron in 11-day EDM, as we have established earlier [33]. Furthermore, due to the overloading of the distal segments of the nephron by ultrafiltrate with a high sodium content and the functional weakening of the tubulo-tubular balance, the distal reabsorption of sodium, standardized by GF, is reliably reduced in EDM of this duration [33], and therefore the distal calcium reabsorption in this part of the nephron rises. The latter is confirmed by the reduction (by 20.0% *vs*. controls) of calcium excretion standardized by GF, indicating the effective cation reabsorption by every single nephron. Moreover, a significant decline of sodium content in the renal cortex of rats with 11-day EDM, as we have established previously [34], allows us to assume that it is the work of the Na+/Ca2+ counter transporter of the distal tubule of the kidneys that provides the preservation of the renal mechanisms of calcium homeostasis.

Meantime, 80% of the filtered phosphorus is reabsorbed in the proximal tubules, 10% – in the distal tubules, and only 10% is excreted with the urine [35, 36]. Reabsorption of phosphates has saturation mode until the capacity of the transport system is exhausted, characterizing its maximal reabsorption. The excess of filtered phosphates exceeding this value is excreted with the urine [35, 37, 38]. The entry of phosphates to the proximal tubule cell is carried out through the mediation of apical sodium-dependent (Na/P) cotransporters of types I and II, which are mostly identical in structure. The main function of reabsorbing phosphate belongs to Na/P type II [38–41]. Type II Na/P cotransporter is capable of transporting both mono- and bivalent phosphates (HPO4—/3Na+, HPO4—/2Na+) through the apical membrane of proximal tubular cells [39, 40, 42]. In contrast to Na/P cotransporter type II, type I Na/P cotransporter carries out energy-dependent transport only at high extracellular phosphate levels [39–42].

The above-mentioned features of tubular reabsorption of phosphates along with a reliable augmentation of the phosphorus-creatinine urinary ratio of rats with 11-day EDM is indicative of an increase in the filtration charge of phosphates as the reason for the intensification of their excretion with urine. Accompanied by the intensification of natriuresis and reduction of sodium reabsorption, typical for this stage of alloxan-induced EDM [33, 43], a 5.8-fold elevation of the sodium-phosphorus urinary ratio can be considered as a filtration exceeding of the reabsorptive potential of the proximal tubules. At the same time, the absence of an increase in the urinary phosphorus concentration is indicative of sufficiently effective renal mechanisms of phosphate preservation using, probably, distal tubules, confirmed by a decline of their excretion, scaled to the unit of the functioning nephron (by 20.0% as compared to the corresponding index of the control group).

On the 26th day after administration of the diabetogenic substance, the calciuric response of the kidneys of rats reached statistically reliable values (the calcium content in the urine of animals of this group exceeded that of intact animals by 12.0%, and its excretion – by 24.6%) and was accompanied by a significant intensification of phosphates excretion – the urine concentration of phosphorus of animals with 26-day EDM exceeded

 https://doi.org/10.46389/rjd-2024-1736

the control level by 88.0%, phosphates excretion – by 2.1 times) (Table 2). Furthermore, the greater intensity of phosphate excretion has led to a decline of the calcium-phosphorus urine ratio of animals in this group by 70.6% as compared to the control level. In addition, on the background of an increase of urine creatinine by 81.9% [18], the calcium-creatinine urinary ratio of animals in this group reduced by 60.2%, and the phosphorus-creatinine urinary ratio practically did not change (only by 4.2% differed from control). Analyzing the sodium-dependent mechanisms of disturbance of the tubular calcium and phosphates transport, it should be taken into consideration that at this duration of alloxan-induced EDM we have established a tendency to the reduction of sodium urinary content (by 9.5%) accompanied by an increase of the total reabsorption potential of the proximal tubules [33]. It resulted in the 2.2-fold decline of the sodium-phosphorus urinary ratio in animals with a 26-day EDM, evidencing the predominant contribution of proximal reabsorption to the retention of phosphates in the animal's body. Phosphate excretion standardized by GF, 2.1-times decreased as compared to the control index, was also evidence of effective reabsorption of phosphates by single nephrons, proving their structural integrity at this stage of the experiment. Therefore, the increase in phosphate filtration charge leads to the overloading of tubular transport systems by them at the level of the proximal tubule. The elevation of the phosphates content in the final urine is probably associated with their exceeding the proximal tubule reabsorptive capacity and the lack of their distal reabsorption accompanied by a significant decline of the distal sodium reabsorption standardized by GF [33].

Moreover, a 25.0% reduction of the sodium-calcium urinary ratio and a 3.4-fold decrease in standardized calcium excretion indicates the efficacy of the reabsorptive

Table 2: Characteristics of tubular transport of calcium and phosphates in rats with 26-day aloxane-induced experimental diabetes (X±Sx).

Indices	Groups, number of animals	
	Control, n=10	26-day EDM, n=8
Calcium concentration in urine, mmol/L	1.25±0.03	1.40±0.05 p=0.05
Excretion of calcium, µmol per 2 hours	4.27±0.20	5.32±0.21 p<0.01
Standardized excretion of calcium, µmol/100 ml of GF	1.02±0.03	0.30±0.02 p<0.001
Phosphates concentration in urine, mmol/L	4.90±0.40	9.21±0.87 p<0.001
Excretion of phosphates, µmol per 2 hours	16.84±1.54	34.83±3.09 p<0.001
Standardized excretion of phosphates, µmol/100 ml of GF	3.99±0.34	1.94±0.17 p<0.01
Calcium-phosphorus ratio in urine, un.	0.273±0.025	0.160±0.014 p<0.01
Calcium-creatinine ratio in urine, un.	1.33±0.04	0.83±0.04 p<0.001
Phosphorus-creatinine ratio in urine, un.	5.22±0.42	5.45±0.47 p>0.8
Urine concentration of sodium, mmol/L	0.74±0.03	0.67±0.07 p>0.5
The sodium-calcium ratio in urine, un.	0.60±0.03	0.48±0.05 p>0.1
Sodium-phosphorus ratio in urine, un.	0.165±0.021	0.076±0.010 p=0.001

Note: Intergroup differences were assessed using the non-parametric Mann-Whitney test; p – the probability of discrepancy of indices relative to the control group; n – number of animals.

potential of the renal tubular apparatus, mainly in the distal part, in maintaining calcium homeostasis in rats with 26-day long alloxan diabetes despite the augmentation of the calcium filtration charge. Suggestions concerning a key role of sodium-dependent distal counter-transport of calcium in ensuring calcium reabsorption are consistent with our previous findings of lowered sodium content in the renal cortex in animals of this group [44].

The trends established on the 26th day of alloxan-induced EDM persisted hereinafter. On the 46th day of the experiment, calcium and phosphorus ions were detected in the urine of alloxan-diabetic rats in amounts significantly exceeding the control values, in particular, by 1.2 and 2.1 times, respectively, with an almost two-fold decrease of the calcium-phosphorus urinary ratio in animals of this group (Table 3).

Moreover, the excretory fractions of these ions increased significantly as well: calcium excretion exceeded the corresponding index in the group of intact animals by 27.2%, and phosphate excretion – by 2.3 times. Their standardization to a unit of the functioning nephron demonstrated opposite changes: standardized calcium excretion lessened by 2.3 times *vs*. control value, phosphorus – by 22.4%. Thus, despite the augmentation of the filtration charge of cations, the reabsorptive capacity of the tubular apparatus of the kidneys effectively preserving them in the body on the 46th day of the experiment. However, the urinary calcium-creatinine ratio of animals in this group was reduced by 57.7%, and the urinary phosphorus-creatinine ratio tended to increase by 11.2%. Considering the previously found elevation of urinary creatinine concentration by 81.9% and pronounced renal hyperfiltration at this stage of alloxan-induced EDM [18], it can be suggested that the renal mechanisms of phosphate homeostasis are overstrained. The decline of the sodium-phosphorus

Table 3: Characteristics of tubular transport of calcium and phosphates in rats with 46-day aloxane-induced experimental diabetes (X±Sx).

Indices	Groups, number of animals	
	Control, n=10	46-day EDM, n=8
Calcium concentration in urine, mmol/L	1.27±0.04	1.48±0.08 p=0.05
Excretion of calcium, μmol per 2 hours	4.19±0.34	5.33±0.40 p<0.05
Standardized excretion of calcium, μmol/100 ml of GF	1.01±0.05	0.44±0.04 p<0.001
Phosphates concentration in urine, mmol/L	5.08±0.44	10.50±0.66 p<0.001
Excretion of phosphates, μmol per 2 hours	16.68±1.77	37.99±3.10 p<0.001
Standardized excretion of phosphates, μmol/100 ml of GF	4.06±0.41	3.15±0.37 p>0.1
Calcium-phosphorus ratio in urine, un.	0.272±0.029	0.142±0.004 p<0.001
Calcium-creatinine ratio in urine, un.	1.23±0.06	0.78±0.04 p<0.001
Phosphorus-creatinine ratio in urine, un.	4.91±0.49	5.53±0.36 p>0.3
Urine concentration of sodium, mmol/L	0.56±0.06	1.12±0.16 p<0.01
The sodium-calcium ratio in urine, un.	0.45±0.06	0.77±0.10 p<0.01
Sodium-phosphorus ratio in urine, un.	0.121±0.019	0.110±0.016 p>0.7

Note: Intergroup differences were assessed using the non-parametric Mann-Whitney test; p – the probability of discrepancy of indices relative to the control group; n – number of animals.

https://doi.org/10.46389/rjd-2024-1736

urinary ratio (by 10.0%) is probably related to the oversaturation of the ultrafiltrate with phosphates since the urinary concentration and excretion of sodium ions in animals of this group, as we have detected earlier [33, 43], significantly raised. Given the reliable reduction of the intensity of standardized by GF proximal and distal sodium reabsorption in rats with 46-day EDM [33, 43], we can suggest the defect of maximal reabsorption of phosphates in the proximal and distal tubules of the kidneys as a probable reason for the increase in their content in the final urine.

At the same time, a reliable rise of the sodium-calcium urinary ratio by 41.6% certifies the preserved renal mechanisms of calcium homeostasis during 46-day-long alloxan-induced hyperglycemia. However, it is an alarming fact that along with the development of tubulointerstitial disorders we have found earlier for this duration of EDM [45], and inevitable structural changes in the tubular apparatus of the kidneys and interstitium, the depletion of the reabsorptive capacity of the tubular apparatus of the kidneys, reflected both on the proximal and on distal tubules, will cause a redistribution of the content of cations between the vascular, tubular and interstitial compartments of the kidneys. An increase in the entry of calcium into the tubular cells and a reduction of the activity of the basolateral Na/Ca exchanger can lead to the elevation of the intracellular concentration of free calcium. The latter, due to the activation of phospholipases, proteases, hydrolases and disturbance of cytoskeleton functions, will promote the damage and even death of cells [21, 27, 46, 47], thereby exacerbating the manifestations of tubulointerstitial syndrome. This emphasizes the importance of changes in the tubular transport of calcium and phosphates in the progression of tubulointerstitial disorders against the background of diabetic renopathy, and the character of disorders of the intrarenal circulation of cations allows the identification of a possible mechanism and level of structural or functional reorganization of the kidneys.

Undoubtedly, calcium-phosphorus homeostasis is regulated by a complex mechanism that, in addition to the renal compartment, includes intestinal absorption and bone circulation of cations, and the stability of each component of this mechanism is ensured by well-coordinated hormonal regulation [1, 48, 49]. However, in our opinion, in diabetes mellitus, it is the renal regulation of mineral metabolism and the peculiarities of transtubular transport of cations that determine the course of the pathological process in the kidneys, its intensity and the rate of renal failure progression.

Conclusions

The development of calcium-phosphorus homeostasis disturbances in the dynamics of experimental diabetes is a consequence of an imbalance of calcitropic factors and of kidney dysfunction in response to metabolic processes induced by hyperglycemia. Transtubular transport of calcium and phosphates in the case of alloxan-induced experimental diabetes mellitus is characterized by changes in the intensity of tubule-specific reabsorption of cations, including sodium-dependent ones, and depends on the duration of the experiment. The increase of sodium-dependent excretion of calcium and phosphates is mainly hyperfusional in nature on the 11th day after the administration of a diabetogenic substance and, due to the filtration overload of the proximal tubules, is provided by the distal parts of the tubular apparatus of the kidneys against the background of the functional overstrain of the tubulo-tubular feedback. A similar tendency regarding the predominance of sodium-dependent distal counter-transport of calcium is preserved on the 26th day of the experiment, while phosphates reabsorption relates mainly to the proximal tubules in case of this duration of the experiment. Reabsorptive defect of phosphates in the proximal and distal tubules of the kidneys is a probable reason for the increase of their content in the final urine and for the maximal strain of the mechanisms of phosphate homeostasis in the case of 46-day alloxan-induced hyperglycemia accompanied by their preservation concerning calcium. Furthermore, the identified peculiarities of intrarenal cation transport evidence the preserved compensatory and functional autoregulatory renal mechanisms for calcium and phosphate exchange and, at the same time, enables the identification of a possible mechanism and level of structural or functional reorganization of the kidneys in diabetes, the prognostication of the intensity and augmentation rates for tubulointerstitial disorders in case of diabetic renopathy.

Conflict of interest

The authors declare no conflict of interest.

References

1. Kyryliuk ML, Atanova YaO. Phosphorus-calcium metabolism in postmenopausal women with diabetes mellitus. Journal of Education, Health and Sport 5(12): 544-554, 2015 (in Ukrainian).

2. Safonova OV, Safonov AS. Changes in bone mineral density in women with diabetes. International Journal of Endocrinology 6(54): 123-124, 2013 (in Ukrainian).
3. Kurra S, Siris E. Diabetes and bone health: the relationship between diabetes and osteoporosis-associated fractures. Diabetes Metab Res Rev 5: 430-5, 2011. doi:10.1002/dmrr.1197.
4. Turne RB, Vagula M, Devi SS. Osteoporosis: An Understated Complication of Diabetes. US Pharm 34(5) [Diabetes suppl]: 14-16, 2009.
5. Janghorbani M, Van Dam RM, Willett WC, et al. Systematic review of type 1 and type 2 diabetes mellitus and fracture risk. Am J Epidemiol 166(5): 495-505, 2007. doi:10.1093/aje/kwm106
6. Vestergaard P. Diabetes and bone fracture: risk factors for old and young. Diabetologia 57(10): 2007-2008, 2014. doi:http:/dx.doi.org/10.1007/s00125-014-3338-1.
7. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes a meta-analysis. Osteoporos Int 18(4): 427-44, 2007. doi:10.1007/s00198- 006-0253-4.
8. Kostyuk O, Stepanova I, Kostyuk PG. Changes in the mutual regulation of intracellular calcium-regulating structures in diabetes. Pathologia 5(2): 8, 2008 (in Ukrainian).
9. Gozhenko AI, Zubkova LP, Dolomatov SI. Age-dependent peculiarities of mineral metabolism in man. Nephrology 6(3): 60-63, 2002. doi.org/10.24884/1561-6274-2002-6-3-60-63.
10. Gallant KMH, Spiegel DM. Calcium Balance in Chronic Kidney Disease. Curr Osteoporos Rep 15: 214-221, 2017. doi:10.1007/s11914-017-0368-x.
11. Alpern RJ, Hebert SC. In: The Kidney. Seldin and Giebisch's, Academic Press (4th ed) pp 1851-1890, 2007.
12. Felsenfeld AJ, Levine BS, Rodriguez M. Pathophysiology of Calcium, Phosphorus, and Magnesium Dysregulation in Chronic Kidney Disease. Seminars in Dialysis 28(6): 564-77, 2015. doi:10.1111/sdi.12411.
13. Milovanova L, Milovanov Y, Plotnikova A. Phosphorus and Calcium Metabolism Disorders Assosiated with Chronic Kidney Disease Stage III—IV (Systematic Review and Meta-Analysis). Chronic Kidney Disease and renal Transplantation. Ed. by Manisha Sahay, INTECH, 2012. doi:10.1037/0003-066x.59.1.29.
14. Schwarz S, Trivedi BK, Kalantar-Zadeh K, et al. Association of disorders in mineral metabolism with progression of Chronic Kidney Disease. Clin J Am Soc Nephrol 1: 825-831, 2006.
15. Mahalias VM, Mikhieiev AO, Rohovyi YuYe, et al. Modern methods of experimental and clinical studies of the central research laboratory of Bukovinian State Medical Academy. Medical Academy, Chernivtsi, 42p, 2001 (in Ukrainian).
16. Schuck O. Examination of kidney function. Avicenum, Prague, 344p, 1981.
17. Korda MM, Kashuba OM. Basics of medical statistics and conducting computer statistical analysis of data with statistical programs. TNMU «Ukrmedknyha», Ternopil, 120p, 2021 (in Ukranian).
18. Olenovych OA. Renin-angiotensin system in the regulation of renal excretory function in caseof experimental diabetes mellitus. International Journal of Endocrinology 16(8): 76-82, 2020. (in Ukrainian). doi.org/10.22141/2224-0721.16.8.2020.222880.
19. Felsenfeld A, Rodriguez M, Levine B. New insights in regulation of calcium homeostasis. Curr Opin Nephrol Hypertens 22: 371–376, 2013.
20. Friedman PA. Calcium transport in the kidney. Current Opinion in Nephrology & Hypertension 8(5): 589-595, 1999.
21. Friedman PA. Mechanisms of renal calcium transport. Exp Nephrol 8: 343-350, 2000.
22. Boros S, Bindels RJ, Hoenderop JG. Active Ca2+ reabsorption in the connecting tubule. Pflügers Arch 458: 99-109, 2009.
23. Frick KK, Bushinsky DA. Molecular mechanisms of primary hypercalciuria. J Am Soc Nephrol 14(4): 1082-1095, 2003.
24. Loffing J, Loffing-Cueni D, Valderrabano V, et al. Distribution of transcellular calcium and sodium transport pathways along mouse distal nephron. Am J Physiol Renal Physiol 281: F1021-F1027, 2001.
25. Lambers TT, Bindels RJ, Hoenderop JG. Coordinated control of renal Ca2+ handling. Kidney Int 69: 650-654, 2006.
26. Mensenkamp AR, Hoenderop JG, Bindels RJ. Recent advances in renal tubular calcium reabsorption. Curr Opin Nephrol Hypertens 15: 524-529, 2006.
27. Moor MB, Bonny O. Ways of calcium reabsorption in the kidney. Am J Physiol Renal Physiol, 310: F1337-F1350, 2016. doi:10.1152/ajprenal.00273.2015.
28. Hoenderop JG, Nilius B, Bindels RJ. Molecular mechanism of active Ca2+ reabsorption in the distal nephron. Annu Rev Physiol 64: 529–549, 2002.
29. Bonny O, Edwards A. Calcium reabsorption in the distal tubule: regulation by sodium, pH, and flow. Am J Physiol Renal Physiol 304: F585-F600, 2013.
30. Loffing J, Kaissling B. Sodium and calcium transport pathways along the mammalian distal nephron: from rabbit to human. Am J Physiol Renal Physiol 284: F628-F643, 2003.
31. Loffing J, Vallon V, Loffing-Cueni D, et al. Altered renal distal tubule structure and renal Na+ and Ca2+ handling in a mouse model for Gitelman's syndrome. J Am Soc Nephrol 15: 2276-2288, 2004.
32. Weidong W, Chunling L, et al. Reduced expression of renal Na+ transporters in rats with PTH–induced hypercalcemia. Am J Physiol Renal Physiol 286: 534-45, 2004.
33. Olenovych OA. Peculiarities of ionoregulatory renal function of rats in the dynamics of experimental diabetes mellitus development with underlying pharmacological blocade of renin-angiotensinaldosterone system. Clinical and experimental pathology 19(4): 42-52, 2020. (in Ukrainian). doi:10.24061/1727-4338.XIX.4.74.2020.7.
34. Olenovych OA. Mechanisms of formation of tubulointerstitional renal impairment at the initial stages of experimentaldiabetes mellitus. Medicine Today and Tomorrow 4(89): 13-19, 2020. (in Ukrainian). doi.org/10.35339/msz.2020.89.04.02.
35. Blaine J, Weinman EJ, Cunningham R. The regulation of renal phosphate transport. Adv Chronic Kidney Dis 18: 77-84, 2011.
36. Marks J, DebnamES, Unwin RJ. Phosphate homeostasis and the renal-gastrointestinal axis. Am J Physiol Renal Physiol 299: F285-F296, 2010.
37. Biber J, Hernando N, Forster I, Murer H. Regulation of phosphate transport in proximal tubules. Pflugers Arch 458: 39-52, 2009.
38. Forster IC, Hernando N, Biber J, Murer H. Proximal tubular handling of phosphate: A molecular perspective. Kidney Int 70: 1548–1559, 2006.
39. Biber J, Hernando N, Forster I. Phosphate transporters and their function. Annu Rev Physiol 75: 535-550, 2013.
40. Murer H, Hernando N, Forster I, et al. Proximal tubular phosphate reabsorption: molecular mechanisms. Physiol Rev 80(4): 1373-1409, 2000.

 https://doi.org/10.46389/rjd-2024-1736

41. Virkki LV, Biber J, Murer H, et al. Phosphate transporters: A tale of two solute carrier families. Am J Physiol Renal Physiol 293: F643-F654, 2007.
42. Breusegem SY, Takahashi H, Giral-Arnal H, et al. Differential regulation of the renal sodium-phosphate cotransporters Na-Pi-IIa, NaPi-IIc, and PiT-2 in dietary potassium deficiency. Am J Physiol Renal Physiol 297: F350-F361, 2009.
43. Olenovych OA. Peculiarities of ionoregulatory renal function of rats in the dynamics of experimental diabetes mellitus development. International Journal of Endocrinology 19(2): 118-24, 2023. doi.org/10.22141/2224-0721.19.2.2023.1256.
44. Olenovych OA. Pathogenetical aspects of tubulointerstitial syndrome development in alloxaninduced experimental diabetes mellitus. Reports of Vinnytsia National Medical University 25(1): 17-21, 2021. (in Ukrainian). doi.org/10.31393/reports-vn-medical-2021-25(1)-03.
45. Olenovych OA. Influence of chronic hyperglycemia on thedevelopment of tubulointerstitial syndrome inexperimental diabetes mellitus. Bulletin of Medical and Biological Research 1(7): 80-86, 2021. (in Ukrainian). doi:10.11603/bmbr.2706-6290.2021.1.12091.
46. Hoenderop J, Nilius B, Bindels R. Calcium Absorption Across Epithelia. Physiol Rev 85(1): 373-422, 2005.
47. Scwaderer A, Srivastava T. Complications of hypercalciuria. Front Biosci (Elite Ed) 1: 306-315, 2009.
48. Blaine J, Chonchol M, Levi M. Renal Control of Calcium, Phosphate, and Magnesium Homeostasis. Clin J Am Soc Nephrol 10: 1257-1272, 2015. doi: 10.2215/CJN.09750913.
49. Taylor JG, Bushinsky DA. Calcium and Phosphorus Homeostasis. Blood Purif 27: 387-394, 2009. doi:10.1159/000209740.