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STRUCTURAL AND FUNCTIONAL CHANGES IN THE PROSTATE GLAND IN DIABETES MELLITUS

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Ultrasound scanning, colour ultrasound angiography, histology, morphometrics, and statistics were used to study the features of hemodynamics and the structural and functional state of the prostate gland in adult men with a history of insulin-dependent diabetes mellitus. Under these conditions, it was found for the first time that the peak arterial velocity in the central zone decreases to 6.20±0.38 cm/sec against 18.30±3.20 cm/sec in control and the peripheral area – to 2.70±0.01 cm/sec against 5.30±0.03 cm/sec. It was found that due to the proliferation of connective tissue in the prostate gland, its volume increases to 29.5±1.0 cm^3, and weight – up to 27.4±1.5 g against 22.4±1.6 cm^3 and 21.5±1.2 g, respectively, in men of the control group. The ratio between glandular parenchyma and muscular-elastic structure is 56 % and 44 % versus 69.8 % and 30.2 % in control, respectively. Histologically, prostate biopsy samples contained atrophic changes with a decrease in the lumen of the terminal glands, flattening of secretory epithelial cells, and proliferation of collagen fibres of the stroma. The testosterone concentration decreases to 380.0±12.0 ng/dL against 650.0±10.0 ng/dL in men of the control group.

Key words: insulin-dependent diabetes mellitus, prostate gland, structural and functional changes.

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СТРУКТУРНО-ФУНКЦІОНАЛЬНІ ЗМІНИ В ПЕРЕДМІХУРОВІЙ ЗАЛОЗІ ПРИ ЦУКРОВОМУ ДІАБЕТІ

Методами ультразвукового сканування, кольорової ультразвукової ангіографії, гістології, морфометрії і статистики досліджено особливості гемодинаміки та структурно-функціонального стану передміхурової залози у чоловіків зрілого віку, в анамнезі яких виявлено інсулінозалежний цукровий діабет. За цих умов вперше встановлено, що пікова швидкість артеріального кровотоку в центральній зоні передміхурової залози знижується до 6,20±0,38 см/с, проти 18,30±3,20 см/с у чоловіків контрольної групи, а в периферичній зоні – до 2,70±0,01 см/с проти 5,30±0,03 см/с. Виявлено, що за рахунок розростання сполучної тканини в передміхуровій залозі її об'єм збільшується до 29,5±1,0 см^3, а маса – до 27,4±1,5 г проти 22,4±1,6 см^3 і 21,5±1,2 г відповідно у чоловіків контрольної групи. Співвідношення між залозистою паренхімою і м'язово-еластичною строю складає 56 % та 44 % проти 69,8 % і 30,2 % відповідно у контролі. Гістологічно в біоптатах передміхурової залози наявні атрофічні зміни зі зменшенням просвіту кінцевих відділів залоз, сплощенням клітин секреторного епітелію, розростанням колагенових волокон строми. Концентрація тестостерону в крові знижується до 380,0±12,0 нг/дл проти 550,0±10,0 нг/дл у чоловіків контрольної групи.

Ключові слова: інсулінозалежний цукровий діабет, передміхурова залоза, структурно-функціональні зміни.

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According to the scientifical literature, diabetes mellitus is one of the most common diseases diagnosed in the population [1, 9]. In recent years, the number of people of mature age with insulin-dependent diabetes mellitus is constantly growing, becoming an epidemic. Impaired carbohydrate metabolism in the body caused by insulin deficiency leads to diabetic macro- and microangiopathy in many organs, including the organs of the male reproductive system [2, 3]. Previous studies conducted by other specialists in adult men diagnosed with diabetes have shown a probable decrease in testicular volume, decreased hemodynamic parameters, and reduced layers of germinal epithelial cells in tortuous seminiferous tubules. Also, in the ejaculate, there was a decrease in the total number of spermatozoa and the number of living and actively moving spermatozoa. The number of pathological forms of spermatozoa has doubled and the number of Immobile spermatozoa has increased fivefold. There was a decrease in the volume of interstitial Leydig cells, and in the blood, there was a probable decrease in testosterone levels [4, 5]. Given the fact that the prostate is a target organ for sex hormones, reducing their concentration in the blood, of course, affects its structural and functional state [12].

It is known that the prostate gland in the male reproductive system is important, which consists in both exocrine and endocrine functions [8]. As for its endocrine function, the glandular epithelium of lobules, particularly its basal cells, secrete prostaglandins into the blood, which are biologically active substances that stimulate testosterone production and spermatogenesis [6, 7]. The exocrine function of the prostate gland is that its alveolar glands produce mucosal secretions that not only dilute the ejaculate but also increase sperm motility [7].

Prostate diseases are an important problem not only in urology, but also in andrology, since chronic prostatitis and prostate adenoma are the most common diseases of men of reproductive age [10].

According to the literature, there are three main theories of the development of pathological processes in the prostate gland: a) hormonal, b) changes in the primary epithelial cells, and c) stromal-epithelial effects. The hormonal theory is based on the action of dihydrotestosterone, which leads to the proliferation of epithelial cells of the prostate. Regarding the change of basic epitheliocytes, the theory explains the normal and pathological growth of the prostate by the presence in these cells of androgen-sensitive receptors that respond to changes in the age-related hormonal background by proliferative processes [7, 10]. The stromal-epithelial theory proves the influence of stromal elements of the prostate on the differentiation and proliferation of epithelial cells through the mechanism of paracrine response. Therefore, studies of the nature of hemodynamic features and structural and functional changes in the prostate gland with hormonal imbalance in the body remain relevant.

The purpose of the study was to establish the features of hemodynamics and the nature of structural and functional changes in the prostate of infertile men of mature age in conditions of insulin-dependent diabetes mellitus of moderate severity.

Materials and methods. Ultrasound scanning and colour ultrasound angiography of the prostate gland of 12 mature infertile men (22–35 years), who were diagnosed with insulin-dependent diabetes mellitus of moderate severity, were performed at the Clinical Diagnostic Center using SIEMENS G60S apparatus (Siemens AW, Germany) with a 5–10 MHz rectal sensor. The following morphological parameters of the prostate were determined: length, width, thickness (in mm), volume (in cm^3) and weight (in g). In the colour Doppler mapping mode, we evaluated the nature of vessels and their pattern, the course of vessels, their diameter, and the number of vessels in symmetrical parts of the organ, followed by a graphical representation of the Doppler shift spectrum frequency in the selected vessel. A quantitative assessment was carried out by the Vascular Plexus Density (VPD) – the number of vessels per 1 cm^2 and the vessel diameter (VD). Qualitative parameters of hemodynamics were: peak velocity – PV (cm/s), diastolic velocity – DV (cm/s), resistance index – RI (relative units, RU), volume flow – VF (mL/min). In accordance with the cooperation agreement, the Urology Department of the Regional Clinical Hospital of the Ivano-Frankivsk Regional Council examined the tissues of 9 prostate biopsy samples of adult men with this pathology. Histological examination of prostate tissues of seven patients was performed by S. B. Stefanov's method. In histological sections stained with hematoxylin and eosin, the relative areas of the epithelial and muscular-elastic components and the height of the cells of the glandular epithelium of the lobules were determined using a periodic morphometric calculator in 20 sections. The testosterone concentration in the blood was determined by enzyme-linked immunosorbent assay using an automatic analyser IMMULITE-2000 (Siemens Healthcare Diagnostics Inc., USA). The control was the data of echometric studies of the prostate gland of 5 mature men with no history of diabetes mellitus.

The study's violation of moral and ethical norms was not detected (Minutes No. 1 of February 2, 2022, Vasyl Stefanyk Precarpathian National University).

Data processing. Statistical processing of morphometric parameters was performed using the Statistica 10 software. We determined the mean value – M, root mean square error – m, coefficient of variation – CV, Student's test – t and the reliability of the difference of comparative values – p. The difference was considered significant at $p<0.05$.

Results of the study and their discussion. In men of mature age (22–35 years) in the control group, the echostructure of the prostate gland, as a rule, is homogeneous, and its parameters: width, length, volume and mass, which are examined during ultrasound examinations of the prostate gland, correspond to the accepted standards (table 1).

Table 1

Echometric parameters of the prostate gland in mature men (22–35 years) of the control group and with diabetes mellitus (m±m)

	Prostate parameters				
	Width (mm)	Thickness (mm)	Length (mm)	Volume (cm^3)	Mass (g)
Control group	37.4±2.0	24.5±1.8	22.8±2.2	22.4±1.6	21.5±1.9
Diabetes mellitus	40.8±1.7	26.5±1.8	26.9±1.7	29.5±1.0	27.4±1.5

Even in mature men, in some cases, prostate tissue heterogeneity is manifested by alternating small areas of increased and decreased echogenicity in both the periurethral and peripheral regions.

In men of the control group, colour Doppler mapping gave a clear image of the blood vessels of the prostate (fig. 1).

Capsular blood vessels in cross-section are represented by point individual colour signals with a diameter of 3.0±0.2 mm. The most significant number of vessels penetrating the capsule is visualised in the projection of the peripheral zone near the apex and base of the prostate gland. The smallest is in the middle part. The urethral arteries and periurethral veins are straight and symmetrically located in the periurethral area. Capsular arteries are localized in the peripheral zone and run parallel to the surgical capsule of the gland, which is visible on echotomograms in β-mode. Along with the prostate gland, the vascular structures of the venous plexuses are determined along the anterior and lateral contours in the form of tubular structures. The diameter of the veins preferably does not exceed 4.0±0.1 mm.

According to colour ultrasound angiography of the prostate gland of infertile men of mature age (22–35 years) with a history of diabetes mellitus, the peak arterial velocity in the central zone decreases to 6.20±0.38 cm/sec against 18.30±3.20 cm/sec in control, and the diastolic velocity – to 2.55±0.30 cm/sec, against 5.80±0.25 cm/sec in the control group (fig. 2). In the peripheral zone of the prostate gland, peak arterial velocity decreases to 2.70±0.20 cm/sec, compared to 5.30±0.03 cm/sec in the control group.

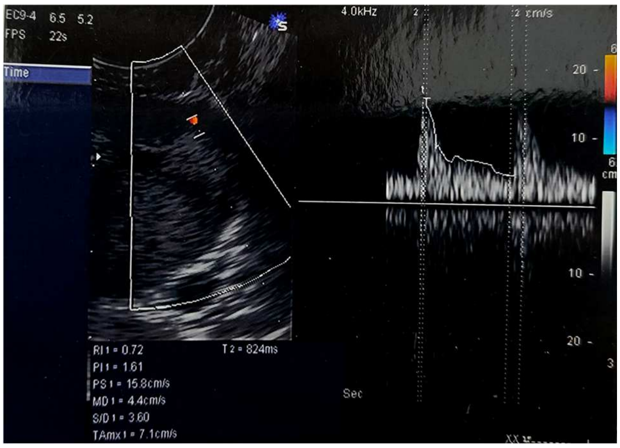

Fig. 1. Ultrasound colour flow angiography of the prostate gland of a 30-year-old man (control group).

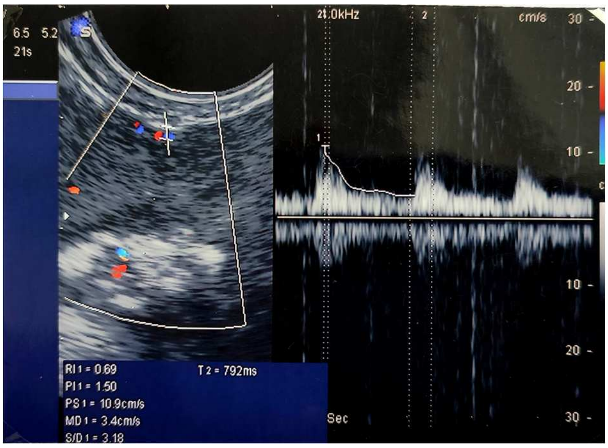

Fig. 2. A decreased peak systolic velocity in the prostate of a 32-year-old man with diabetes.

Under these conditions, the volume flow in the prostate's central and peripheral areas changes significantly. The nature of hemodynamic parameters of blood flow in the prostate is due, in our opinion, to changes in its echometric parameters. In particular, not only the increase in volume to 29.5±1.0 cm^3, but also the weight of the organ up to 27.4±1.5 g against 22.4±1.6 cm^3 and 21.5±1.9 g in the control group.

Features of the structure of the tissue components of the prostate gland in men aged 22–35 years (control group) indicate that it is well developed and has a pronounced lobular structure (fig. 3).

The prostate lobules' secretory parts are alveolar-tubular and in different phases of the secretory cycle. The epithelium of the terminal glands is prismatic or cubic. In the lumens of individual secretory departments, there is an amorphous secretion and single prostatic nodules of different sizes. The excretory ducts of the glands are covered with prismatic epithelium, which becomes cubic in the distal parts. Loose connective and smooth muscle tissue is present in the stroma of the prostate. The prostate capsule is well defined and contains a vascular, fibrous and muscular layer. The relative area of the glandular component is, on average, 69.9 %, and the size of the muscular-elastic stroma is 30.1 %. In some cases, in mature men, the number of terminal parts of the glands with a normal structure decreases, the secretory epithelium flattens. The fibrous-muscular-elastic stroma of the prostate gland expands.

Structural restructuring of the prostate is to change the ratio of the relative area of the glandular parenchyma and stroma. According to our data, in mature men with diabetes mellitus, the relative area of the glandular parenchyma decreases to 56.2 % compared to 65.8 % in the control group. Histologically, prostate biopsy samples contained atrophy of the lobules and proliferation of the muscular and elastic stroma. The epithelium of the terminal secretory parts of the parenchyma is flattened, and the nuclei are pyknotic (fig. 4). The concentration of testosterone in the blood of men in the study group decreases to 380.0±12.0 ng/dL against 650.0±18.0 ng/dL in the control group.

It is known that prostate disease is an essential problem in urology and andrology. According to the literature [10], hemo microcirculation disorders play a significant role in their aetiology. The latter is often due to macro- and microangiopathy, which develop in insulin-dependent diabetes mellitus. Our analysis shows changes in hemodynamics in the prostate and the impact of these changes on its histostructural restructuring. Under these conditions, the peak arterial velocity in the prostate's central and peripheral areas is likely to decrease. This leads to atrophic changes in it with the development of connective tissue, which is confirmed by an increase in the volume and weight of the organ. Under these conditions, the glandular parenchyma atrophies, which is manifested, in particular, by flattening of the glandular epithelium. The histostructural changes in the prostate gland of adult men described by us could negatively affect both exocrine and endocrine function, in particular the production of biologically active substances – prostaglandins, which affect the secretion of male sex hormones by the testes. According to our data [5], the concentration of testosterone in the blood of men in the study group decreases to 380.0±12.0 ng/dL against 650.0±18.0 ng/dL, which adversely affects reproductive function.

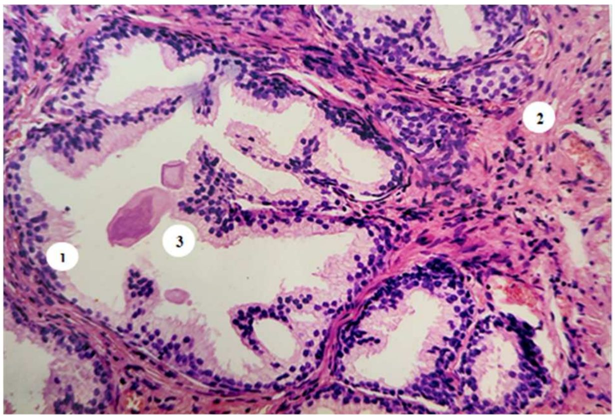

Fig. 3. Lobular structure of the prostate gland of a 30-year-old man (control group): 1 – secretory parts of the glandular lobules; 2 – muscular-elastic stroma; 3 – nodules. Staining with hematoxylin and eosin. Magn.: x200.

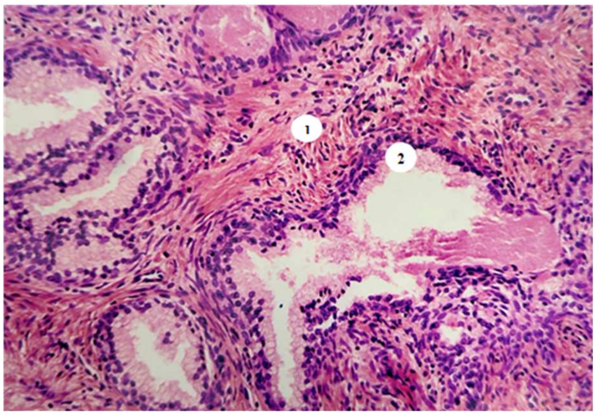

Fig. 4. Histological changes in the prostate gland of a 35-year-old man with a history of diabetes mellitus: 1 – stroma proliferation; 2 – flattening of glandular epithelial cells. Staining with hematoxylin and eosin. Magn.: x200.

In colour ultrasound transrectal angiography of the prostate gland of mature men (the first period) with diabetes mellitus, we found depletion of the vascular pattern and its disorganization. We also found a significant decrease in peak linear velocities, vascular plexus density, decreased vascular lumen diameter, and volumetric blood flow due to diabetic macro- and microangiopathy, manifested by sclerosis and hyalinosis of blood vessel wall elements of different diameters. Our data are largely comparable to the literature data on age-related morphofunctional changes in the prostate gland in men [5]. We found that in men aged 36–60 years (the second period of maturity) in the grey-scale mode, all parameters of the prostate gland are significantly increased, in particular, width – up to 28.3±1.2 mm, thickness – up to 27.8±0.12 mm, length – up to 30.1±1.0 mm. Accordingly, the volume of the prostate gland is significantly increased by 31.9±1.2 cm^3, and its mass is 34.7±1.3 g [5]. The ratio of the area of the glandular parenchyma to the muscular-elastic component ranges from 57 % to 43 %. That is, the area of the glandular parenchyma decreases, and the size of the muscular-elastic part increases statistically significantly ($p<0.05$). In the latter, the number of muscle fibres decreases, and connective tissue proliferates.

Histologically, in this age group, the mucous membrane of part of the terminal parts of the alveolar-tubular glands is represented by prismatic epithelium. Clusters of squamous epithelial cells and prostatic bodies are found in the lumens of the glands. Under these conditions, the vascular pattern on Doppler images is disorganized; the peak velocity in the arteries is 7.9±0.5 cm/sec and the blood flow rate in the veins is 2.6±0.3 cm/sec. The volume of blood flow in the prostate gland of men of this age decreases to 0.01±0.002 l/min, which may be due to changes in the muscular-elastic stroma of the organ [3].

It was found that in elderly men (61–75 years), the linear size of the prostate, compared with the previous age group, increases significantly. So, the width of the prostate was 49.2±2.0 mm, thickness – 48.5±1.5 mm, and length – 34.5±1.5 mm. There is an intense increase in the volume of the prostate gland by 50.0±1.9 cm^3, and its mass was 53.5±2.0 g [7]. In the histological preparations of the prostate tissue in men of this age, we found an increase in the frequency of initial structural changes characteristic of benign hyperplasia compared with men of the second period of mature age (36–60 years) and a decrease in hemodynamics.

Other researchers [12] also noted an increase in stromal components of the prostate in benign hyperplasia up to 70–90 % and a decrease in the relative volume of the glandular part of the prostate.

In this age group, compared to the previous one, the relative area of the glandular parenchyma decreases statistically significant ($p<0.05$), and, accordingly, the relative stroma area of the organ increases.

In old age, histologically pronounced age-related changes in the prostate gland are observed, manifested by atrophy of the parenchyma. The glandular epithelium of peripherally located small particles becomes cubic, and individual glands are cystically expanded with exfoliated cells and prostatic bodies of different sizes. There is also fibrosis of the smooth muscle fibres of the stroma and an increase in the number of collagen fibres.

According to color Doppler, hemodynamics in the prostate deteriorates significantly. The peak velocity in the arteries was 5.6±0.5 cm/sec, velocity in the veins – 2.7±0.3 cm/sec, and volumetric flow – 0.01±0.002 L/min [6].

Thus, the results of changes in hemodynamics, the ratio of the parenchyma and stroma of the prostate gland, indicate that with age, the number of glandular parenchyma decreases in it and the number of stroma increases.

According to the literature [5], physiological (age-related) and pathological changes in the hormonal balance (sex and pituitary hormones) in men and dystrophic changes in prostate tissue that develop against their background play an important role in prostate pathology. Hormonal disorders that cause anatomical and functional changes in the prostate gland contribute to a sharp decrease in its barrier function. It has been shown that destructive changes in glandular tissue, muscle and connective tissue elements occur in patients with secondary androgen deficiency due to metabolic disorders of testosterone metabolism in the prostate [8].

It is known [12] that at the age of 30–60 years in men in the prostate, there are significant changes in the relationship between the stroma and epithelial components due to hormonal changes in the body. This often leads to the development of benign prostatic hyperplasia. It was also found that violations of epithelial-stromal ratios are the leading cause of the development of epithelial prostate tumours.

Conclusions

1. In adult men with insulin-dependent diabetes mellitus, the peak arterial velocity in the central zone decreases to 6.20±0.38 cm/sec against 18.30±3.20 and 17.90±1.80 cm/sec in the control group.

2. Under these conditions, the volume of the prostate gland increases to 29.5±1.0 cm^3 and its weight increases to 27.4±1.5 g, compared to 22.4±1.6 cm^3 and 21.5±1.9 g in men of the control group, and the relative area of the glandular parenchyma decreases to 56.2 % versus 65.8 % in the control group.

3. Atrophic changes are present in prostate biopsies in a significant part of glandular lobes. The epithelium of the terminal parts is flattened, the cell nuclei are pyknotic, and collagen fibres predominate in the muscular-elastic stroma.

Prospects for further research are to study structural and functional changes in the prostate gland in men of different age groups with diabetes mellitus.

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