

CONTINUOUS MONITORING OF BLOOD GLUCOSE BY USING THE IPRO2 SYSTEM IN A PERSONALISED APPROACH IN TREATMENT OF PATIENTS WITH ERECTILE DYSFUNCTION AND COEXISTING DIABETES MELLITUS

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Annotation: The results of examination and treatment of 17 patients with erectile dysfunction (ED) with coexisting diabetes mellitus (DM). In order to achieve in-depth detail of fluctuations in blood glucose levels, a multi-day monitoring technique has been introduced, followed by further therapy adjustment. During examining with means of functional diagnostic methods, all patients were diagnosed with serious disorders of regional, organ hemodynamics and innervation, in the absence of significant hormonal changes.

During daily monitoring of glucose fluctuations, there were noted uncontrolled, frequently repeated jumps of the given indicator, especially during sexual intercourse, with long trace of fluctuations. Uncontrolled and formidably predictable episodes of hyperglycemia are regarded as the immediate cause of progressive regional pelvic microangiopathy and neuropathy, which are worsening the prognosis of the diseases course.

Keywords: erectile dysfunction, diabetes mellitus, daily monitoring of glucose, iPro2, innervation of the pelvic floor, penile vessels Doppler.

Introductions: With an increase in the number of patients with type 1 and type 2 diabetes who are undergoing insulin therapy amongst men of young reproductive age, issues of treatment of erectile dysfunction become especially urgent, taking into account the inevitable development of diabetic neuropathy, micro- and macroangiopathy. Standard multiple measurements of blood glucose by an individual glucometer during the day do not reflect the whole picture of glycemic fluctuations, especially at night, during sexual arousal and sexual intercourse.

Disorders of the pelvic functions are typical in patients with DM, moreover, firstly impaired sensation of filling the bladder, which leads to prolonged pauses in between urinations. Further disruptions relate to the contractility of the detrusor leading to its atony.

Due to impaired urination, incontinence with overflow is often noted. Disruption of the sympathetic innervation of the internal sphincter of the bladder leads to retrograde ejaculation, as a result of which in a number of cases determines male factor infertility.

The process mechanism of erectile dysfunction alongside of DM, in addition to disorders of organ hemodynamics due to the emerging microangiopathy, is associated with a disruption of the parasympathetic innervation of the Corpus cavernosum.

Often in patients with long-term diabetes, there are disorders of the innervation of the colon, which leads to its atony with the development of constipation. With a combined lesion of the autonomic system innervation of the small and large intestines, interchangeable bouts of diarrhea and constipation are often observed. Violation of the autonomic system innervation of the anal sphincter can be displayed by inability to retain intestinal gases and fecal masses, which especially can accrue at night.

The need to maintain sexual health, pelvic protection to a large degree determines the key to a successful treatment of patients with diabetes mellitus.

In accordance with the most authors research, the vascular cause of ED was diagnosed in 34-80% of the cases, and in 44.4% it is arteriogenic in nature and in 28.6% it is venogenic. The psychogenic causes of ED were established in 19-42% of the cases, neurogenic - 5-34%, hormonal disorders were detected in 5-7% of the cases. In about 15-19% of all cases, a combination of organic and psychogenic factors were noted.

Taking into account the statistical data that show significant fluctuations in the prevalence of ED forms, with values sometimes varying by dozens of times, the inconsistency and imperfection of modern diagnostic tools and technologies becomes obvious, as a result of which the diagnosis is made purely on the basis of intuition, preferences, theoretical inclinations, and knowledge of the research specialists [1, 2, 5, 11, 12, 21].

The most accurate to date data appears to be on pathogenesis and prevalence of hormonal ED. It is the violation of hormonal status and a physiological decrease in the level of sex hormones (absolute and / or relative) that determines the development of ED in old age. The problem of age-related androgen deficiency in men is extremely important not only because of its prevalence, but also because of the significant contribution that testosterone deficiency adds to disruption of the metabolic processes within the organism. Androgen deficiency leads to complex changes in the body of a man, causing an increased risk of cardiovascular disease, diabetes mellitus, and obesity [4, 9, 13, 15].

The frequency of clinically apparent age-related androgen deficiency in men older than 30 years is from 7 to 30% [4, 5, 9]. It is however of importance to note the relative androgen deficiency- in other words decrease in testosterone levels, taking into comparison the previous years, occurs in all men, but not beyond ordinary values and is perceived by the body not less strained than absolute [4, 13, 19, 21].

The traditional therapy of androgen-deficient conditions is based on hormone replacement therapy, the use of which is limited in a sufficiently large number of age-related patients [2, 4, 9, 13, 15, 19]. Among these contraindications include: hyperplasia and prostate cancer, impaired liver function and cancer of the testicles [19].

The main diagnostic method for vasogenic ED is Doppler of the penile vessels and pharmacological erection test with the use of vasoactive drugs. The main disadvantages of echography methods is the lack of an accurate criteria for the separation of moderate changes in the endothelial function in the artery (dilatation of the arteries in response to an increase in shear stress on the vascular wall) and most defiantly pathological decrease in the said function. Ultrasonic methods are notable for low resolution when measuring blood flow of deep-lying arteries. Doppler data largely depends on the relative position of the emitter-receiver axis and the artery axis, which is important for the results of the study. Differences in the geometry of the vascular bed in different patients limit the accuracy of blood flow estimations obtained by ultrasound methods [1, 3,4, 9, 12, 13, 15].

One of the objective methods for studying penile hemodynamics is penile impedance rheography, this method is currently at exploration stage, standardising the protocol for performing rheophallography and clarifying the normative quantitative indicators of penile blood flow [1, 3, 12].

Penile MRI and pelvic MR angiography - are modern highly informative diagnostic methods that provide a high-resolution, contrast image of any organ without the use of ionizing radiation and administration of radiopaque substances, the mentioned beforehand are especially informative in the diagnosis of Peyronie's disease, traumatic penile injuries, as well as atherosclerotic lesions of the pelvic trunk vessels. With all the advantages of MRI, one should remember the high level of false-positive results (up to 28%) and the high costs of the study [5, 6, 8].

In recent years, there has been increased interest in neurourology. The development and improvement of neurophysiological methods for assessing the state of muscles and peripheral nerves of the pelvic floor and corticospinal tract. This has significantly expanded the idea of possible causes of erectile dysfunction [1, 5, 7, 10, 17].

Unfortunately, an analysis of the literature indicates that today the concept of neurogenic ED is perceived by most medical specialists, researchers and patients themselves as an erectile dysfunction, which is a manifestation of severe diseases of the central and / or peripheral nervous system (injuries, tumors, vascular disorders, demyelinating and metabolic diseases of the peripheral nervous system, degenerative diseases of the spine, congenital anomalies). At the same time, absolutely no attention was paid to latent neurogenic disorders of erectile function that occur in borderline, covert, latent neurological diseases [1, 3, 7, 10, 11, 17, 18].

It should be noted that so far there is no consensus on the whereabouts of the cortical "sexual centre". The centres controlling the erection include sections of the cerebral cortex, the thalamus, the limbic system, and the medullary nuclei of the medulla oblongata. The spinal and peripheral regulation of erection has been studied somewhat better and are represented by the sympathetic (Th 11 - Th12) and parasympathetic (S2 - S4) spinal segments of the spinal cord and peripheral nerve plexuses.

Of a particular importance in the diagnosis of peripheral neuropathy in diabetes mellitus is the electromyography technique (EMG). The generality of innervation of the lower extremities and perineal muscles allows us to determine the degree of prevalence of the pathological denervation process by performing EMG of the lower extremities, and the use of transcranial magnetic stimulation (TMS) allows us to determine the time of central motor conduction, the main parameter characterising corticospinal conduction [1,3,10,11 , 17,18,19].

The tonus violation of the autonomic nervous system is observed in almost all of the patients with diabetes mellitus and ED. The results of the examination of the patient's cardiac background, the patient's main indicators of central hemodynamic (HR, BP), the nature of skin dermographism determine the prevailing type of patient's autonomic reactions (vagotonia and sympaticotonia). An analysis of electrodermal activity (EDA), reflects the change in the skin resistance to the directly applied current, which allows us to assess the state of the sympathetic division of the autonomic nervous system [1,2,6].

Cardiointervalography evaluates the propagation of a pulse wave and blood supply to the organs, makes it possible to objectify the state of the autonomic nervous system and the presence of a functional shift. The study of the segmental autonomic nervous system is possible by evaluating electrodermal activity (EDA) on the surface of the penis. The main characteristic is the decrease in the amplitude of this reflex and the shortening of the latent period [6].

Clarification of the contribution of latent neurological changes caused, in particular, by fluctuations in blood glucose levels during the day, to the pathogenesis of ED can be a link that determines the true causes of erectile dysfunction and contributes to an increase of treatment efficiency for patients in this category [5,6,8].

Continuous glucose monitor (CGM) is a method of recording changes in blood glucose concentration, which makes it possible to obtain a complete picture of glycemic fluctuations during the day, to identify episodes of latent hyperglycemia and hypoglycemia, which is not possible with self-monitoring of blood glucose, whilst using an individual glucometer. It also becomes apparent how various foods and various types of physical activity (including sexual intercourse) have an effect on fluctuations in blood glucose levels, being ever of this results helps us to choose the most optimal therapy for the given patient.

Objective: to study blood glucose fluctuations, using the method of Continuous glucose monitor (CGM) in the "blinded" mode using the iPro 2 (Medtronic, Nederland) system for the duration of 6 days. Correct insulin therapy in accordance with the results obtained, thereby improving the results of treatment and rehabilitation of patients with diabetes mellitus and ED.

Material and methods.

Presented below are the results of examination and treatment of 17 patients with diabetes and ED aged 23 to 46.

The signs of androgen deficiency were evaluated using the AMS questionnaire (Aging Males Symptoms), and the Morley Androgen Reduction Rating Scale was also used to assess the severity of androgen deficiency. Examination all of the patients, without a fail included an assessment of skin sensitivity, sacral reflexes, ultrasound studies.

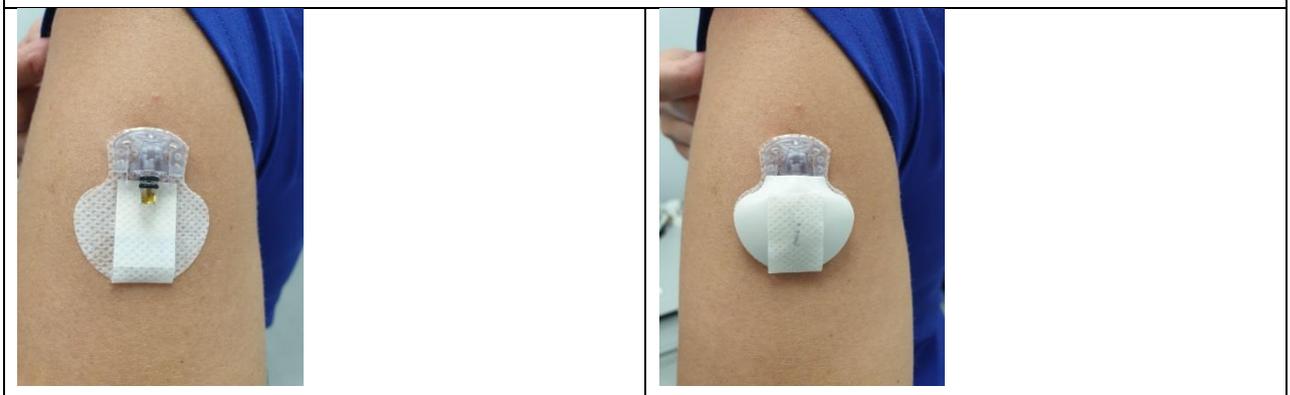
To identify hidden neurogenic disorders, we used the technique of perineal needle electromyography (EMG) developed by us with an estimate of the average duration and amplitude of the action muscle units potential (MUP), the number of polyphase potentials, as well as the fixation of fibrillation potentials and positive acute waves. To assess the symmetry of denervation changes, EMG was performed both on the right and left sides. In order to assess the prevalence of denervation processes and the involvement of large nerve trunks and somatic muscle structures in the process, neurophysiological studies of the muscles of the lower extremities were performed corresponding to the studied segments of the spinal cord.

To assess the conductive ability of the corticospinal tract, transcranial magnetic stimulation (TMS) was performed with registration of the motor Reaction Time from the muscles of the lower extremities and perineum and the calculation of central motor conduction time (CMCT)

Continuous monitoring of blood glucose levels was carried out using an iPro 2 (Medtronic, Nederland) device connected to a hypodermic sensor that records the results of measuring blood glucose levels, every 5 minutes during the day (288 measurements per day).



Pic. 1. iPro2 device



Pic 2. Method of sensor installation

Results

Using the AMS questionnaire (Aging Males Symptoms), the examined patients revealed an average degree of androgen deficiency ($38 \pm 6,4$ points). When analysing the Morley androgen reduction rating scales, similar data was obtained.

All of the examined patients in accordance with modern conceptualisations, in order to determine the severity of erectile dysfunction, an intracavernous test with use of Vasaprostan 10 mcg was performed. The results of this test are presented in table 1.

When assessing the main indicators of the mentioned above test, a 4.5-fold increase in the time of tumescence was established against the background of an increase in the time of onset of rigid erection and the duration of tumescence by 2.5 times and 2 times, respectively. One of the indicators confirming ED in the observed patients was a 2.34-fold decrease in the duration of their own erection and a 2.3-fold decrease in the duration of detumescence.

Table 1. Dynamics of indicators of the intracavernous test with the use of Vasaprostan in patients with diabetes mellitus before and after treatment.

Values	Time of tumescence onset, min	Duration of tumescence, min	Time of onset of rigid erections	Duration of erection, min	Duration of detumescence in min

Groups					
Initialdata	28,5±1,4 P1*	8,3±0,3 P1***	20,1±1,0 P1*	35,2±1,9 P1**	41,7±3,1 P1*
Duringthetr eatment	24,7±1,6 P2*	8,0±0,4 P2**	19,6±1,3 P2*	39,0±1,5 P2*	46,5±1,2 P2**

Note: significance of differences -P1 – comparison to norm; P2 –comparison to the main group;
* - P<0,05 ; ** - P<0,01; *** - P<0,001.

The results obtained objectively confirm the moderate severity of ED in the observed patients. Dopplerexamination of the vessels of the prostate in patients with ED (Table 2) revealed a significant decrease in blood flow velocity both in arterial vessels, which is especially important in venous vessels (1.49 times and 1.61 times).

Table 2 Dynamics of prostate vesselsDoppler studies in patients with ED and diabetes mellitus before and after treatment.

Values groups	Average max blood flow velocity in the arteries of the prostate, m / s	Averagemaxbloodflowinprostaticveins, cm/s	Ri (index resistance) along the capsular branches of arteries	Ri (index resistance) along urethral arterial branches
Initialdata	5,7±0,9 P1**	2,6±0,1 P1*	0,79±0,03 P1*	0,93±0,04 P1**
Duringthetreatment	5,9±0,6 P1*,P2*	2,6±0,14 P1*,P2*	0,77±0,04 P1*,P2**	0,92±0,02 P1*,P2**

Note: P1 – comparison to norm:P2 –Comparison before and after treatment; * - P<0,05 ; ** - P<0,01; *** - P<0,001

A similar pattern was observed when examining penile vessels (Table 3), in which a 1.6-fold decrease in systolic blood flow rate was observed, which was also indicated by a 1.2-fold decrease in the pulse index (Pi). The phenomena of vascular circulation disorder in the arterial link in the observed patients were due to a significant increase in vascular resistance, both in the cavernous arteries and the dorsal arteries (an increase in the index value in Ri 1 and Ri 2 by 1.17 and 1.15 times, respectively).

Table 3 Dynamics of penile blood vessel Doppler values in patients with ED before and after the treatment

Values	Maximum systolic rate of the	Pi (pulsation index), cm/s	Ri (resistance index) in the cavernous	Ri 1 Ri 2 (index resistance) in dorsal
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Groups	flow cm /s		arteries	arteries
Initialdata	22,5±1,4 P1*	1,4±0,07 P1**	0,96±0,03 P1**	1,1±0,08 P1**
Duringthetreatment	23,6±1,2 P1*,P2*	1,46±0,04 P1*,P2***	0,93±0,02 P1*,P2***	1,06±0,05

Note: P1 – comparison to norm: P2 – Comparisen before and after treatment, * -P<0,05 ; ** - P<0,01; *** -P<0,001

When studying the neurogenic mechanisms of ED formation, we studied the functional activity of the pelvic floor muscles using needle EMG (Table 4). During the study, in all patients, violations of the functional activity of the pelvic floor muscles were found, in the form of a decrease in the average duration of motor unit potentials by 1.96 times against the background of a decrease in the average amplitude of motor unit potentials by 2.2 times. The presence of severe polyphasy and spontaneous muscle activity indicate hidden reinnervation disorders of the perineal muscles.

Table 4 Dynamics of indicators of needle electromyography (EMG) of the pelvic floor muscles in patients with ED and diabetes before and after treatment

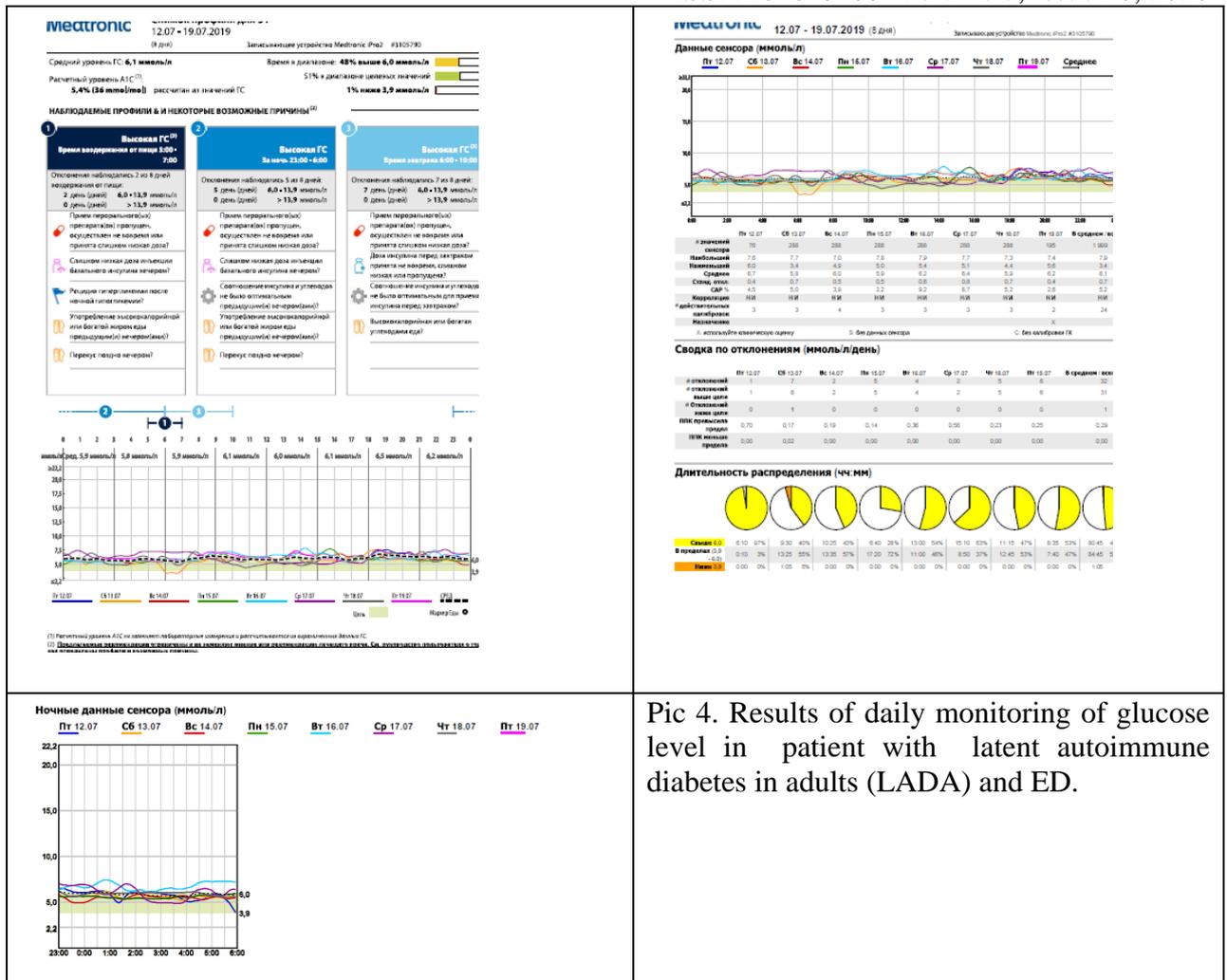
Values Groups	Average duration of motor unit potentials (ms)	Average amplitude of motor unit potentials (mV)	Polyphasy %	Spontaneous muscles activity
Initialdata	9,4±0,3 P1*	0,59±0,02 P1**	40	N=5
Results of thetreatment	11,0±0,2 P1*,P2**	0,75±0,02 P1*,P2***	30	N=5

Note: P1 – comparison to norm: P2 – Comparisen before and after treatment; * -P<0,05 ; ** - P<0,01; *** -P<0,001

With TMS in patients with ED, corticospinal tracts conduction disorders were observed in the form of an increase in latency of the cortical and segmental layers by 11%, prolongation of central motor conduction time in all patients by more than 46% (Table 5).

Table 5 The results of the study of the corticospinal tract for m. bulbocavernosus in patients with ED and diabetes mellitus

Values Groups	Latency cortical motor response time, ms	Latency segmental spinal motor response time, ms	Central motor holding time, ms
Initial data	45,1 ±1,2 P1*	32,8 ±1,1 P1*	16,3 ±1,2 P1*
After the treatment	44,2±1,1 P1*,P3*	31,1±1,0 P1*,P3*	13,1±1,0 P1*,P3*



Pic 4. Results of daily monitoring of glucose level in patient with latent autoimmune diabetes in adults (LADA) and ED.

The revealed critical glucose peaks required a change in the regimen of insulin therapy with the use of an additional injection of an ultrashort-acting forms of drug immediately before sexual intercourse. In 8 cases, patients were transferred to the pump insulin therapy, which greatly facilitated the adjustment of blood sugar levels. 6 months' observation showed a noticeable improvement in erectile function in all of the subjects, confirmed by Doppler control and the absence of undesirable increases in blood glucose levels recorded earlier.

When assessing the regional blood circulation of penile and prostatic blood vessels during treatment correction, an increase in systolic blood flow velocity and a decrease in vascular resistance in the cavernous and dorsal penile arteries were noted. Repeated EMG studies in patients with diabetes mellitus and ED demonstrated restoration to normal values of the average duration and amplitude of motor unit action potential, a decrease in polyphasia and spontaneous muscle activity, which indicates the minimization of latent denervation and reinnervation disorders of the perineum and extremity muscles revealed during the initial examination.

Neurogenic mechanisms of sexual function regulations make a significant contribution to the elimination of ED in diabetes mellitus cases, as evident by the results of the study on the state of the corticospinal tract for m. bulbocavernosus. We can see that in the study subjects the time of cortical and segmental response and central motor conduction time decreased to the level of a healthy individuals, the asymmetry of central motor conduction time almost disappeared.

To summarise:

- With continuous daily monitoring of glucose levels, directly during sexual intercourse there were multiple cases of rising blood glucose levels, while maintaining such indicators for 3-5 hours after ending coition and during sleep.
- Episodic peaks of glucose require a change in the mode of insulin therapy, this entitles using an additional injection of ultrashort-acting forms of drug immediately before sexual intercourse.
- Uncontrolled and difficultly predicted episodes of hyperglycemia are likely to be the cause of progressive regional pelvic microangiopathy and neuropathy which are detected during special functional diagnostic studies.
- Continuous daily monitoring of blood glucose levels using iPro 2 provides valuable insight in to uncontrolled and long-lasting surges in blood glucose levels during the examination and treatment of patients with ED along with diabetes mellitus.
- Some patients with uncontrolled episodes of fluctuations in glucose levels during intercourse need to be transferred to a pump insulin therapy.
- The introduction of daily glucose monitoring in patients of this category is a new and effective step towards a personalised approach to the treatment of patients with diabetes mellitus on insulin therapy.

Conclusion:

Overall, in the examination and treatment of patients with ED with diabetes mellitus, continuous daily monitoring of blood glucose using iPro 2 allows us to obtain valuable information about uncontrolled and long-lasting fluctuations in blood glucose levels, which probably largely determine damage to the penile microvascular and nerve structures. The effectiveness of treatment within the group of the said patients is significantly improved with adequate and timely adjustment of insulin therapy.

The method of daily glucose monitoring in this group of patients is an extremely important, sensitive diagnostic tool that allows, on the one hand, to improve the quality of the sexual life, effectiveness of erection, it allows to create background for sexual longevity, and on the other hand, it allows for the treatment to be adjusted and to reduce the risk of developing chronic complications of diabetes mellitus. Examination and treatment of patients with ED in combination with diabetes mellitus in all cases requires an individual, personalised approach.

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