

Diabetes Mellitus (Type 2), Erectile Dysfunction and Diabetic Neuropathy: Georgian Point of View and Experience for Treatment of such Patients

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Erectile dysfunction (ED) is typically defined as the inability to achieve an erection sufficient for penetration or to maintain an erection following intromission. ED is fairly common problem, affecting as 30 million US men and approximately 5-50% of all men depending on their age group [1].

Because erectile response assumes well-functioning vascular and neural systems, the prevalence of ED increases with age. The prevalence may be as low as 10% in men under 40, with increasing prevalence to over 50% in men over 70 [2].

In 80% ED is caused by somatic and not psychogenic factors. Among organic diseases, most often, over 30% of cases, the cause of ED is diabetes Mellitus (DM) [3].

Diabetic men have a more than 3-fold increased prevalence of ED compared with no diabetic men [4]. The prevalence of ED among diabetic men may be as 20% in young man and 85% in elderly men [5, 6].

DM is one of the largest global health emergencies of the 21st century. Each year more and more people live with this condition, which can result in life changing complications. In addition to the 415 million adults who are currently estimated to have diabetes, there are approximately 318 million adults with pre diabetes, which predicts the development of the disease in the future. In 2015 according to the International Diabetes Federation, 415 million people are diagnosed with this condition. Its incidence is increasing rapidly and by 2040 the number of diabetic patients will be approximately 642 million [7].

Erectile function is primarily a vascular phenomenon, triggered by neurologic controls and facilitated by appropriate hormonal and psychological components. Recent advances in the understanding of the physiology of penile vasculature and its role in male sexual performance have influenced the clinical approach to ED in men with DM. The etiology of ED in type 2 DM is often multi-causal [8]. The patho-physiological alterations leading to ED in diabetic men include neurogenic, vasculogenic, and hormonal etiologies [9].

However, despite the fact that cardio-vascular diseases, dyslipidemia, testosterone deficiency, hepato-renal diseases and diabetic angiopathy are the risk factors of ED, the main cause for the development of ED among patients with type 2 DM is Diabetic Neuropathy (DN) which can also gradually decrease in men sexual response and sex drive [10].

DN may complicate type 1 and type 2 diabetes more than 50% of causes [11] and usually it increases with duration and poor diabetic control. Among several risk-factors of DN age plays very important role [12, 13]. 1460 men with type 2 DM were observed and more often DN was discovered. Besides DN above-mentioned men had retinopathy, nephropathy, atherosclerosis and all of them were treated by insulin. At the same time, much less risk of DN was observed among patients with type 2 DM, which was conducted by diet therapy only [14].

Both metabolic and ischemic mechanisms may play a role in DN. The thickening and hyalinization of the walls of small blood vessels suggests a role in DN [15]. The role of accumulation of polyols observed in animals also occurs in humans but whether this accumulation in nerves leads to neuropathy is not established. The reduction of protein synthesis and transport has been

found in animal models and may account for the occurrence of dying-back fibers in the nerve. Impairment of axonal elongation and caliber growth of regeneration fibers has been found in diabetic rats. A number of other factors and mechanisms may also play a role [16, 17]. Anyway, hyperglycemia is the common factor for DN and structural damage of neural fibers [18, 19].

A micro vascular deficit in the Vasa Nervorum of nerve trunks and ganglia is a major trigger for a cascade of events that eventually lead to DN. ED is a consequence of these events and if not treated early may become irreversible. Restoring diminished blood flow to the Vasa Nervorum as early as possible before irreversible changes such as fibrosis and neuronal degeneration occur should be a key aim of medical management of DN [20] as well as ED. Consequently, early diagnostic of ED in diabetic men with the purpose of beginning the treatment of DN as early as possible plays very important role in the successful management of ED.

Very often ED is the first manifestation of type 2 DM in men. All the more important is active identification of the first symptoms of ED [21]. At the same time not rare cases when the patient expects much more questions from the medical doctor to identify possible ED, since the diabetic men himself avoids recognizing problems with erection. According to some authors, only 30-35% of patients with type 2 DM decide to tell his doctor about the presence of ED [22]. Thus, a terrible consequence of such passivity of the medical doctors in the process of management for DM may be the patient's "silent suffering" for the long time and even forever [23].

The first step in the process of management for ED among men with type 2 DM requires identifying of the specific problems. Those are usually effective as an initial screen that helps establish where the specific problem lies. Optimally, each question should be augmented with further questioning to affirm the ED. Such quantification may include estimate rigidity and the rate of successful attempts of sexual intercourses. The second step is a clinical work-up, including a thorough history and physical examination, is an important aspect of ED management in diabetic men. Biochemical evaluations to rule out secondary causes are also suggested. Medical assessments may be limited, moderate, or extensive. In addition to the physical examination a family/medical history, including the use of prescription and medications and recreational substances, is typical. Laboratory tests and psychiatric assessment for mood disorders can help determine whether the ED is secondary to another disease or condition. More extensive evaluations, including assessment of vascular problems, sleep-related erections and hormone profiles [24], including first of all evaluation the total testosterone, prolactine and prostate-specific antigen levels are also should be implemented.

Based on the analysis of modern data regarding the efficacy, safety and relevance to patients and professionals several methods of treatment ED it is clear that there is a great need for technology that will allow you to restore the structure and function of the cavernous tissue [25] especially in case of severe form of ED like in men with type 2 DM.

Oral medications acting through Phospho-Diesterase 5 (PDE 5) inhibition in penile vasculature have revolutionized treatment of ED. Because of a high success rate in treating ED of various etiologies including type 2 DM, these agents are the treatment

of choice for most patients. Acceptability of vacuum-constriction devices, intracavernous injections or intra-urethral suppositories of alprostadil as well as penile prosthesis surgery in diabetic men because of high risk of complications is still discussable [26].

Diabetes-induced ED is one of the most difficult to treat [27, 28]. Despite the known associations between DM and ED, the influence of type 2 DM on the treatment of ED remains poorly understood. Some authors hypothesized that DM-associated ED may be more severe and therefore may require the utilization of more invasive therapies to achieve satisfactory erections [29]. Besides, ED among diabetic men is more often resistant to PDE 5 inhibitor treatment, thus there is a need to discover targets that may lead to novel approaches for a successful treatment [30]. In this context it seems very important to reduce the risk of resistance to PDE 5 inhibitors treatment. Above-mentioned goal could be achieved by early treatment of DN as an important preparing step of therapy of ED for men with type 2 DM.

Treatment of DN usually is based on: 1. aiming at near-normoglycemia, 2. pathogenically oriented therapy, 3. symptomatic therapy, and 4. avoidance of risk factors. If we take into consideration that alpha lipoic acid (ALA) as a safe medication has an effect on glucose uptake, thereby increasing polyol path-way activity as well as increasing pyruvate dehydrogenase and alpha-ketoglutarate activity in a number of non neural tissues [31, 32], and at the same time has additional actions such as stimulating nerve growth factor with promoting fiber regeneration and improving motor nerve conduction velocity with protection peripheral nerves from ischemia [33, 34] it is clear that ALA is a best choice for the etio-pathogenic treatment for DN among men with type 2 DM. Clinical dates also indicates activity of ALA among patients with DN. An oral dose of 600 mg once daily seems to provide the optimum risk-to benefit ratio in the SYDNEY 2 trial [35]. Per oral treatment with ALA for five weeks improved neuropathic symptoms in 187 diabetic patients [36].

As a first stage of treatment for ED in diabetic men ALA can be combined with Yohimbin Hydrochloride (YH) that is alpha-adreno blocker. Treatment of ED by YH is based on selective blockade of alpha – adreno receptors located in the penile arteries [37]. Despite the fact that effectiveness of YH is not indisputable some authors are sure regarding safety and possibility to use of this medication as an useful preparing step before PDE 5 inhibitors therapy [38, 39].

Combined therapy of diabetic-induced ED with ALA and YH may be also effective because in case of hyperglycemia in rats the role of alpha-adreno blockers as a promoting factor for nerves fiber regeneration was described. Besides, should be useful to include L-arginin in this stage of treatment of ED for patients with type 2 DM because this medication may increase concentration of endothelial NO in the penile arteries [40] and in the result of this it can increase probability of positive erectile response after PDE 5 inhibitors treatment.

Testosterone level have been reported to be lower in patients with type 2 DM as compared with healthy controls, which suggests testicular impairment in diabetes [41]. Moreover, diabetic men tend to be middle-aged or older and are prone to the physiological decline in androgen production associated with aging, known as an andropause [42] in the other words Aging Male Syndrome (AMS). Testosterone replacement therapy is advocated in the treatment of AMS [43]. Therefore, some authors suppose that testosterone undecanoate treatment in type 2 diabetic men with androgen deficiency improved several features of glucose homeostasis, improved symptoms of androgen deficiency such as ED, reduced libido, nervousness, insomnia and fatigue [44].

39 men with type 2 DM were included in our study. To be considered for inclusion, subjects had to be aged between 43 and 65 years, be married or living in a stable relationship with a female sexual partner for at last 6 months, have symptoms of ED. Patients were recruited from the men with type 2 DM referred to

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Assessments were performed at baseline after 3 months of treatment. All patients underwent a structured clinical (sexological) interview (including measurement of sexual constitution - the scale of the vector definition of the male's sexual constitution, defined as: weak, medium, upper-medium and strong by G.S. Vasilchenko) [45] and thorough medical examination at the start of the study as well as psychological examination by Eysenck Personality Questionnaire to assess the personality traits of a person as two biologically based independent dimensions of temperament: extraversion and introversion [46].

Medical evaluation included assessment of age at onset duration of diabetes, glicemic control (glycated hemoglobin – HbA1c), diabetic treatment and complications.

Special attention was paid to history of, or clinical evidence of, peripheral and autonomic neuropathy. Total serum testosterone concentrations were determined as well as prostate specific antigen and routine laboratory tests like blood biochemistry, hematology and urine analysis.

ED was assessed using the 15-item version of International Index of Erectile Function (IIEF-15) [47]. Statistical significance was set at $p < 0,05$. The different variables at baseline and the end of the study were compared by two-sided t tests for paired and independent samples.

The results of the psychological examination of 39 elderly men with type 2 DM induced ED by Eysenck Personality Questionnaire. Introversion was indicated in 60% of our patients and extraversion in 40%.

Most patients (67%) had a medium or strong sexual constitution and only 33% of the men studied could identify a weak sexual constitution.

The analysis of the data obtained by us showed that the mean duration of the diabetic condition at the time of the study was 5,3 years (range 1–16 years). Mean age at diagnosis of type 2 DM was 51,8 years. Diabetic treatment in 89% was with oral hypoglycemic agents only (metformin). Other patients recieved insulin monotherapy or oral hypoglycemic agents in combination of insulin therapy. All of 39 men were with evidence of peripheral/autonomic neuropathy. 15,5% showed evidence of coronary heart disease.

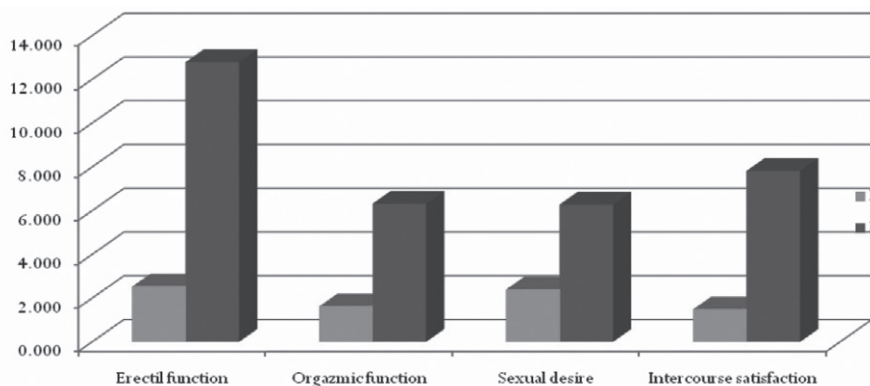
Glycemic control ($HbA1cAl = 7,7 \pm 0,5\%$) in the all of patients was satisfactory as well as the concentration of prolactin ($6,3 \pm 0,9$ ng/ml) and prostate specific antigen ($1,4 \pm 0,07$ ng/ml). Results of routine laboratory tests like blood biochemistry, hematology and urine analysis were within the normal framework.

However, total testosterone level has been reported to be lower in 69% of patients with ED induced by type 2 DM.

Results of special neuropathy tests like monofilament, camerton and temperature tests together with clinical symptoms (paresis, muscle weakness and chronic pain in the toe area) indicated the presence in all patients peripheral/autonomy diabetic neuropathy.

Before treatment all characteristics of IIEF-15 (mean score) in: erectile function (2,5), orgasmic function (1,7), sexual desire (5,8) and intercourse satisfaction (1,2) have been reported to be lower in all of 39 patients.

The complex stage-by-stage treatment of our patients with type 2 induced ED included: **As a first step:** strict glycemic control; treatment of peripheral/autonomic neuropathy with daily intravenous transfusions of ALA solution for 10 days and afterward with a long-time daily oral administration of 600 mg of ALA; 5 mg YH three times a day for a month and daily oral administration of 600 mg L-arginin for a month; **69% of patients who had testosterone deficiency** – replacement therapy with intramuscular injection of 4 ml 250 mg/ml testosterone undecanoate. **As a second step:** Treatment with sildenafil citrate for two or three months in a dose of 50 mg or 100 mg (depending on the severity of ED) before each sexual intercourse with a gradual decrease in dose.



The effects of the complex treatment

The effects of the complex stage-by-stage treatment of 39 patients with type 2 induced ED are presented in table 1.

In the result of this treatment among all of our patients has been indicated statistically significant (P<0,05) improving of all characteristic of IIEF-15 in comparison of baseline scores.

For instance: erectile function has been increased to 13.2 score, orgasmic function to 5.9, sexual desire to 5.8 and intercourse satisfaction to 7.5 scores.

Therefore, we can conclude that:

1. Among men with type 2 DM the resistance to PDE 5 inhibitors more often is observed and therefore these require the

utilization of more active, complex and combined therapies to achieve satisfactory erections;

2. The complex, combined stage-by-stage treatment of ED for men with type 2 DM includes glicemic control, early treatment of DN with ALA in combination of YH, L-arginin and replacement androgen-therapy. This is the first step of treatment that may reduce for the second step of treatment the presence of resistance to PDE 5 inhibitors (sildenafil citrate) therapy.

3. Above-mentioned algorithm is the ensuring the success of recovery of erection and could be supposed as a “golden standard” among men suffering with ED induced by type 2 DM.

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