



Paper Accepted*

ISSN Online 2406-0895

Original Article / Оригинални рад

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Low-intensity extracorporeal shock wave therapy of vasculogenic erectile dysfunction – three-week treatment in a cohort of north Italian patients

Екстракорпорални ударни таласи ниског интензитета за третман васкулогене еректилне дисфункције – тронедељна терапија на групи пацијента из североисточне Италије

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Received: May 16, 2018

Accepted: June 7, 2018

Online First: June 14, 2018

DOI: <https://doi.org/10.2298/SARH180516043A>

* **Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. *Srp Arh Celok Lek*. Online First, February 2017.

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Low-intensity extracorporeal shock wave therapy of vasculogenic erectile dysfunction – three-week treatment in a cohort of north Italian patients

Екстракорпорални ударни таласи ниског интензитета
за третман васкулогене ерекtilне дисфункције – тронедељна терапија
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SUMMARY

Introduction/Objective Although phosphodiesterase 5 (PDE 5) inhibitors represent the gold standard for medical treatment of erectile dysfunction (ED), they are not curative. Over recent years, low-intensity extracorporeal shock wave therapy (LI-ESWT) has been proposed as a valid non-invasive therapy approach for erectile dysfunction. The aim of our work is to assess the shortened, three-week low-intensity extracorporeal shock wave treatment of vasculogenic erectile dysfunction.

Methods The study involved a total of 32 patients with an International Index of Erectile Function (IIEF) score between 5 and 20, and whose vasculogenic ED had been proven through doppler ultrasound. All patients had a washout period of 1 month after previous therapy and agreed to discontinue the PDE5-I therapy during the follow-up. The LI-ESW therapy was applied for 3 weeks, twice weekly, without repeating. The patients were evaluated at baseline, after 1, 3 and 6 months, with the IIEF, Doppler ultrasound and the Beck Depression Inventory (BDI).

Results All investigated parameters (International Index of Erectile Function, Beck Depression Inventory and penile doppler ultrasound parameters) showed statistically significant improvement just one month after the treatment, compared to pre-treatment values, in all investigated domains. The international index of erectile function passed from baseline values of 12.75 ± 4.62 to 14.87 ± 5.04 at one month after treatment ($p < 0.01$). This trend remained positive in IIEF and all the parameters tested at the 3-month and 6-month follow-up.

Conclusion The shortened three-week low-intensity shock wave treatment of vasculogenic erectile dysfunction proved to be clinically effective.

Keywords: erectile dysfunction; low-intensity extracorporeal shock wave therapy; international index of erectile function (IIEF); Doppler ultrasound, Beck depression inventory (BDI)

САЖЕТАК

Увод/Циљ Инхибитори фосфодиестаразе типа 5 (*PDE5-Is*) представљају златни стандард у медикаментозној терапији ерекtilне дисфункције. Упркос томе медикаментозни третман не представља терапију којом се може трајно излечити ерекtilна дисфункција. Циљ наше студије је испитати скраћену тронедељну терапију екстракорпоралним ударним таласима ниског интензитета васкулогене ерекtilне дисфункције.

Метод Студија је укључила 32 пацијента са међународним индексом ерекtilне функције између 5 и 20 са потврђеном васкулогеном ерекtilном дисфункцијом на доплер ултразвуку. Пацијенти су имали паузу у трајању од 1 месеца од претходне терапије и били су сагласни да прекину терапију *PDE5* инхибиторима у периоду праћења након третмана. Применили смо екстракорпорални ударне таласе ниског интензитета у трајању од 3 недеље, два пута недељно, без понављања. Пацијенти су оцењивани пре терапије, 1 месец, 3 и 6 месеци после терапије међународним индексом ерекtilне функције, доплер ултразвуком и Бековим упитником за депресију.

Резултати Сви испитани параметри (Међународни индекс ерекtilне функције, Беков упитник за депресију, параметри доплер ултразвука пениса) показали су позитивну статистицики значајну промену само након једног месеца након терапије. Међународни индекс ерекtilне функције је забележио пораст после првог месеца након терапије и попео се са основних вредности од $12,75 \pm 4,62$ на $14,87 \pm 5,04$ ($p < 0,01$). Овај позитиван тренд се задржао како на Међународном индексу ерекtilне функције тако и на свим тестираним параметрима и након 3 и 6 месеци праћења.

Закључак Скраћена тронедељна терапија екстракорпоралним ударним таласима ниског интензитета примењена на васкулогену ерекtilну дисфункцију показала се клинички ефективном.

Кључне речи: ерекtilна дисфункција; екстракорпорални ударни таласи ниског интензитета; међународни индекс ерекtilне функције; доплер ултразвук; Беков упитник за депресију

INTRODUCTION

Erectile dysfunction (ED) is a problem of the male population with both high prevalence and incidence worldwide. The Massachusetts Male Aging Study has reported a prevalence of ED between 5% and 35% (Northern Europe) [1]. ED is commonly associated with aging and age-related health problems, such as vascular, hormonal, neural, psychogenic factors, and side effects of therapeutic drugs [2].

Phosphodiesterase-5 (PDE-5) inhibitors, although not curative, have become a standard way of treating ED [3–6]. However, there are still some significant shortcomings of this treatment, such as side effects, drug intolerance, etc.

Low-Intensity extracorporeal shock waves therapy (LI-ESWT) was introduced by Vardi et al. in 2010, as an innovative and promising curative treatment of ED [7, 8], with the possibility of avoiding side effects and drug intolerance. The majority of therapy protocols studied with non-linear LI-ESWT were based on treatments lasting six weeks, with a three-week pause in between [8–11].

The aim of this pilot study was to investigate the effects of a three-week LI-ESW therapy in a cohort of patients from north-eastern Italy, all with vasculogenic erectile dysfunction.

METHODS

An open-label, single-arm, prospective pilot study was performed in a private urological care structure (FG studio urologico) in accord with the Helsinki Declaration. 32 patients were enrolled in the study after obtaining their written informed consent. The inclusion criteria were: history of ED for at least 6 months, an International Index of Erectile Function ED (IIEF-ED) domain score between 5 and 20, responders and non-responders to PDE5-therapy and vasculogenic ED proven by Doppler ultrasound. All patients had a washout period of 1 month after previous therapy and agreed to discontinue the PDE5-I therapy during the follow-up.

The exclusion criteria were: psychogenic ED, neurologic comorbidities, documented hypogonadism (total testosterone serum levels under 10 nmol/L), prior radical prostatectomy, and recovery from any cancer within the past 5 years.

Treatment protocol

Low-intensity shock wave therapy was delivered using a special probe attached to a compact electrohydraulic unit with a focused shockwave source (Omnispec ED1000, Medispec Ltd,

Germantown, MD, USA). Only standard ultrasound gel was applied between contact surfaces. The penis was manually stretched, and the prepuce retracted; the shockwaves were delivered to the distal, mid, and proximal penile shaft, and to the left and right crura.

Each LI-ESWT session lasted for 20 minutes, and comprised 300 shocks per treatment point (a total of 1500 per session), at an energy density of 0.09 mJ/mm² and a frequency of 120/min. The volume of penile tissue that was exposed to shockwaves at each site was cylindrical (diameter: 18 mm; height: 100 mm). The treatment protocol consisted of two treatment sessions per week, for 3 weeks, without repeating the treatment after 3 weeks, which is the key difference compared to the previous study protocols with non-linear LI-ESWT [11, 12].

During the treatment period, no psychological intervention or support was provided, and patients were required to maintain their normal sexual habits.

Study protocol

The International Index of Erectile Function (IIEF) was used for the symptomatic evaluation of patients with ED, as this is a widely accepted measurement tool with a high degree of sensitivity and specificity for detecting treatment-related changes in the erectile mechanism [13, 14]. A standard tool was used for the psychological evaluation of patients, the Beck Depression Inventory (BDI) score, and a clinical evaluation was performed on all patients [15]. A grey scale ultrasound followed by a penile Doppler dynamic ultrasound with Alprostadil 10 mcg intracavernosal injection was performed. Measurements of peak systolic (Q_{max}) and end-diastolic velocities were obtained in each cavernosal artery at 5-min intervals for a total of 30 minutes. A peak systolic velocity of less than 35 cm/sec was used as the threshold for arterial insufficiency. An end-diastolic velocity of greater than 5 cm/sec was used to predict venous incompetence. Moreover, a resistance index (RI) was evaluated and considered to be pathologically reduced when lower than 0.75. A complete study protocol was carried out before the treatment and during the follow-up. A follow-up was carried out 1 month, 3 months and 6 months after treatment, using IIEF-5 and BDI questionnaires and recording changes in dynamic Doppler ultrasound parameters.

Statistical analysis was performed with a repeated measures analysis of variance (ANOVA). Linear regression analysis was used to prove the correlation between the variables. Statistical difference was considered significant when $p < 0.01$.

RESULTS

The study protocol was applied to 32 middle-aged men (mean: 57.62 ± 7.98 ; range: 38-68 years) with vasculogenic ED for a mean of 35.2 months. The data regarding pre and post therapy IIEF, Duplex Doppler ultrasound, RI and BDI are shown in Table 1.

A statistically significant improvement in all the investigated parameters can be seen one month after treatment, compared to the pre-treatment values, in all investigated domains. The international index of erectile function passed from baseline values of 12.75 ± 4.62 to 14.87 ± 5.04 at one month after treatment ($p < 0.01$). The BDI basic values passed from 6.59 ± 5.70 to 4.59 ± 0.57 after the first months from the treatment ($p < 0.01$). As of penile color doppler ultrasound parameters, both Q max and RI values showed a statistically significant improvement at first month after treatment ($p < 0.01$). There was no deterioration of the investigated values during the follow-up.

There is a significant correlation between the improvement in IIEF and Qmax (Figure 1), and a negative correlation between IIEF and BDI (Figure 2). Multiple significant correlations between IIEF, Qmax and RI are shown in Figure 3.

DISCUSSION

Our results show a significant change in both IIEF and BDI scores, and an improvement in Qmax and RI. Significant improvement remained during the follow-up.

Low intensity shock wave therapy is promising, although the exact mechanism used by LI-ESWT to induce the tissue changes is not known. Thanks to the release of neo-angiogenic factors and the subsequent neovascularization of the treated tissue, LI-ESWT therapy leads to tissue regeneration [16]. Indeed, it has been shown that this low-intensity energy acts on vascularization, inducing a non-enzymatic production of physiologic amounts of nitric oxide [17]. Thus, the latest studies show that IIEF scores increase after treatment with LI-ESW [18]. Even though PDE-5 inhibitors represent the first-line therapy for erectile dysfunction by increasing the IIEF score, they do not represent a curative approach. The increase in IIEF does not last over time but, rather, is strictly limited to the assumption of PDE-5 inhibitors. In addition, some ED patients respond poorly to PDE-5s and need other, more invasive treatments [9, 11, 12].

After the pilot study by Vardi and colleagues, which took into consideration the patients who had previously responded to phosphodiesterase type 5 inhibitor (PDE5i) therapy, Gruenwald and Vardi applied LI-ESWT to patients who had responded poorly to PDE5i therapy. By using the same

protocol as in the first study on 29 patients, they concluded that LI-ESWT was again beneficial for this kind of patient, as it had a physiological effect on the erectile mechanism [10].

After those preliminary studies, others were done, but almost all studies on low-intensity extracorporeal shock wave therapy for erectile dysfunction had the same duration and applied the same treatment doses. The treatment protocol mostly considered the application of LI-ESW twice a week for three weeks, with re-treatment for another three weeks after a three-week pause. The number of shocks applied were almost always 300 per treatment point with an energy flux density of 0.09 mJ/mm². (9)

A very recent study carried out at Mayo Clinic applied low-energy shockwave therapy to alleviate renal dysfunction in renovascular disease. They treated pigs' kidneys with renal-artery-stenosis using low-energy shockwaves twice a week for only three consecutive weeks, without repeating. 26 pigs were randomized to atherosclerotic renal artery stenosis (ARAS) or normal controls, treated or untreated with LI-ESWT. The results were amazingly positive. A 3-week low-intensity shockwave therapy attenuated renovascular hypertension, normalized stenotic kidney microvascular density and oxygenation, stabilized function and alleviated fibrosis. This was associated with upregulation of VEGF expression that was decreased by ARAS, with increased angiopoietin-1 and downregulation of hypoxia-induced factor (HIF-1). Moreover, LI-ESWT improved the expression of endothelial nitric oxide synthase (eNOS) that was diminished in ARAS. No detectable injury to the kidney was observed [19].

The encouraging results from this and all the previous studies led us to conduct a prospective pilot study, applying the three-week low-intensity shockwave therapy to patients with erectile dysfunction in order to examine if the shortened therapy could have the same effect as the repeated three-week therapy.

Our primary end points were the change in IIEF-5 and in the penile colour Doppler values given through the Qmax and resistance index (RI) values, as well as the Beck Depression Inventory (BDI) score.

The IIEF-5 questionnaire is a widely accepted measurement tool with a high degree of sensitivity and specificity for detecting treatment-related changes in the erectile mechanism [13, 14].

The Beck Depression Inventory (BDI) is one of the most widely used psychometric tests for measuring the severity of depression. The BDI was originally developed to provide a quantitative assessment of the intensity of depression. As it is designed to reflect the depth of depression, it can monitor changes over time and provide an objective measurement for judging improvement and the effectiveness of treatment methods [15]. A systematic review by McCabe showed how erectile

dysfunction leads to poor sexual relationships and poor sexual satisfaction, diminished confidence, low self-esteem, and symptoms of depression. After any kind of treatment, there were significant improvements for the baseline regarding most of these parameters, except for overall life satisfaction and overall relationship satisfaction [20]. Although the BDI has its limitations, as do all questionnaires, considering that the person completing it may exaggerate or minimise their score, we considered BDI as an important aspect of treatment success. As far as we know, this is the first study to date that uses BDI in evaluating the results of low-intensity shock wave therapy to treat erectile dysfunction.

The immediate, statistically significant increase in all variables after the 1-month follow up showed that this shortened therapy was efficient in improving the erectile function, and that the effects of angiogenesis could be clinically important after the three-week therapy, without repeating.

The fact that the basic BDI values did not show the presence of depression in our patients, excluded the fact that ED was due to depression in our cohort. This also excluded the possible placebo effect that could be expected from our study protocol. The BDI score, although in the normality range at basic values, lowered even more at the 6-month follow-up. The mean BDI scores passed from 6.59 ± 5.70 before treatment, to 2.96 ± 3.58 at the 6-month follow-up which was statistically significant. Patients sometimes need time to develop self-confidence and improve general well-being after suffering depression-like symptoms for a long time before the therapy. This could be especially true for those patients who did not respond to PDI-5 therapy previous to the LI-ESW treatment, and who had lost faith in clinical improvement, considering that, to date, PDI-5 therapy is the gold standard for treating erectile dysfunction. Our results showed an immediate effect on BDI scores after 1 month which was maintained after 6 months without any additional active intervention.

A positive physiological effect on cavernosal tissue is certainly proven by hemodynamic values. As with the Doppler findings, we witnessed an increase in Qmax at the 1-month follow-up. This increase was greatest the first month after treatment, with a slightly greater value at the 3-month and 6-month follow-up. This represents direct proof that the shortened course of therapy with low-intensity shock waves improves the hemodynamic values of the penis, and that this effect can be observed quite soon after treatment. Vardi et al. stated that most of the treated men reported improvement in erectile function between treatment sessions 6 and 8, which is probably the time needed for LI-ESWT to induce the physiological changes [7, 8]. Nevertheless, those values remained the same with a small but significant increase over 3 and 6 months, which is indicative of the durability of the shortened treatment.

We used a scientifically tested machine that had already been proven through 'sham control' to have certain positive effects on penile hemodynamics over a longer follow-up period. Recently,

Fojecki et al. showed that exposure to two cycles of linear ESWT to treat ED was not superior to one cycle at the 6-month and 12-month follow-up. Although they used a different machine with a linear probe and a 5-week treatment session, the number of shockwaves and the energy flux density were the same [21].

Our patient cohort was mostly homogenous when considering cardiovascular risk factors. Three men had arterial hypertension in medical therapy, one had insulin-dependent diabetes mellitus and one of the patient's erectile dysfunction was due to previous pelvic trauma. We included patients who had responded, partially responded or had not responded to previous PDI-5 therapy. This is based on previous studies which showed that LI-ESWT could have beneficial effects on both PDI-5 responders and non-responders [7, 10].

The main limitations of our study were certainly the low number of patients and the lack of a sham-controlled arm. Although the study population was comprised of only 32 men, this was sufficient to determine whether or not our shortened treatment could have a positive physiological effect on cavernous tissue. Bearing in mind that this was a pilot study, and that Vardi's first study was carried out on a smaller patient cohort, without a sham-controlled arm, these limitations should be considered relative. We would like to emphasize that the most striking clinical observation was that almost every participant gave highly positive feedback on the treatment.

CONCLUSION

The efficacy of a short course of LI-ESWT therapy to manage erectile dysfunction was confirmed. LI-ESWT was successful in improving symptomatic, vasculogenic and psychological aspects of vasculogenic ED. Although additional investigations are necessary, the initial results of our study are promising, improving the position of LI-ESWT in the guidelines for curative treatment options for patients with vasculogenic erectile dysfunction.

NOTE:

This paper forms a part of a doctoral thesis.

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Table 1. Qmax, RI, BDI and IIEF values before and after treatment

Baseline values and follow-up (mean value \pm SD)					
Variables	Baseline	1 month	3 months	6 months	Significance*
Qmax	27.59 \pm 12.55	37.39 \pm 17.81	39.43 \pm 17.22	39.71 \pm 17.74	< 0.001
RI	0.67 \pm 0.08	0.76 \pm 0.08	0.79 \pm 0.06	0.79 \pm 0.05	< 0.001
BDI	6.59 \pm 5.70	4.59 \pm 0.57	4.06 \pm 4.56	2.96 \pm 3.58	< 0.003
IIEF	12.75 \pm 4.62	14.87 \pm 5.04	17.06 \pm 4.04	17.64 \pm 4.34	< 0.004

Qmax – maximal velocity of arterial systolic flow; RI – resistance index; BDI – Beck's Depression Inventory score; IIEF – International index of erectile function

*Significance was calculated between pre-treatment and post-treatment values after 1 month. No significant differences were noted between the 3-month and 6-month follow-up, except from BDI.

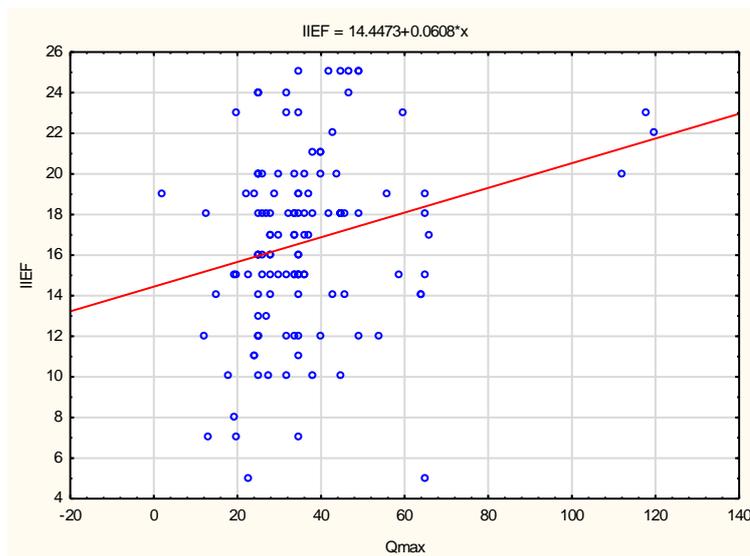


Figure 1. Correlation between the adjusted Qmax parameters and the changes in IIEF scores

Qmax – maximal velocity of arterial systolic flow score;

IIEF – International index of erectile function

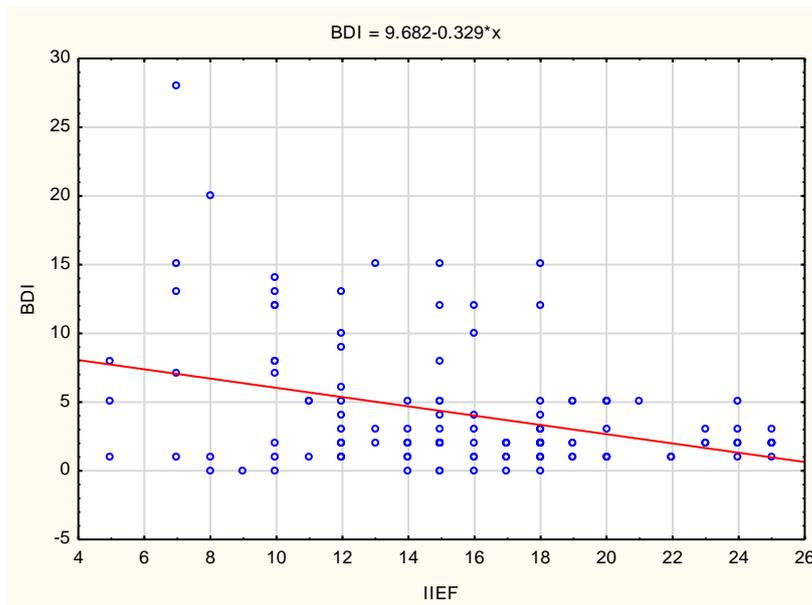


Figure 2. Correlation between the adjusted BDI scores and the changes in IIEF scores

BDI – Beck's Depression Inventory score; IIEF – International index of erectile function

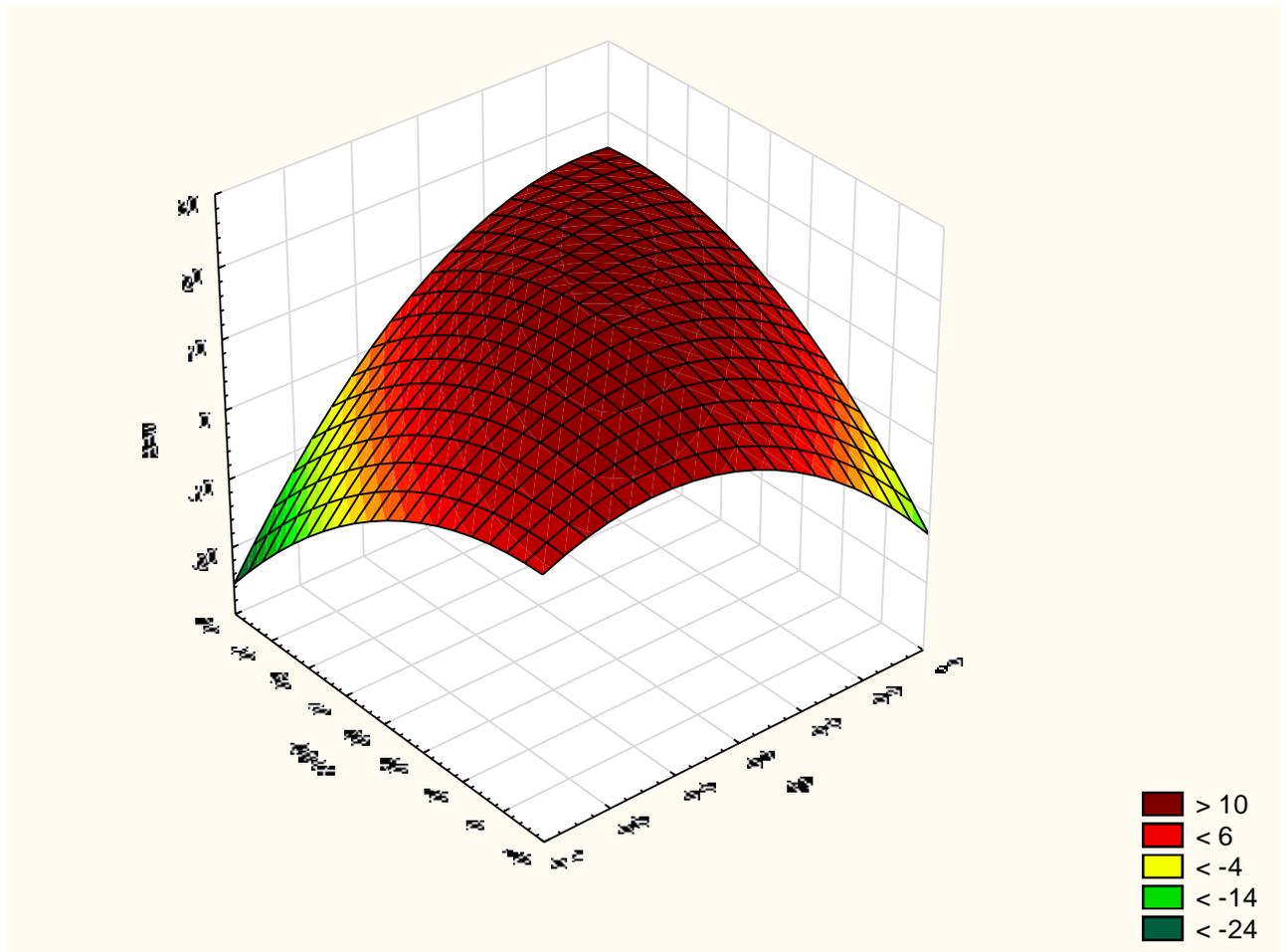


Figure 3. Multiple correlation between the changes in Qmax and RI values and the changes in IIEF scores

Qmax – maximal velocity of arterial systolic flow; RI – resistance index; IIEF – International index of erectile function