Editor in chief
Prof. V. Mitev, MD, Ph. D., DSc

Editorial board
Prof. K. Tsachev, MD, Ph. D., DSc
Prof. M. Marinov, MD, Ph. D., DSc
Prof. D. Ziya, MD, Ph. D., DSc
Prof. N. Lambov, Mag. Ph., Ph. D.
Prof. W. Bossnev, MD, Ph. D., DSc
L. Tacheva, MD
PERIARTICULAR CALCIFICATIONS IN NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM

M. Panchovska¹, E. Firkova², H. Georgiev¹, A. Gosmanov¹ and R. Makuleva¹

¹Clinic of Internal Diseases, Military Hospital – Plovdiv, Bulgaria
²Department of Periodontology and Oral Diseases, Medical University – Plovdiv, Bulgaria

Summary. We report the case of a 63-year-old female patient referred to the clinic for further diagnostic specification. The patient had complained of periodically increasing pain in the left knee joint and thigh muscles for a year and a half. The X-rays studies of both knee joints revealed degenerative changes consistent with those of osteoarthritis. There were calcifications in the patellar tendons and in m. quadriceps femoris sin. The lab studies and imaging techniques showed that the patient had increased levels of blood ionised calcium (with total calcium within norm), increased concentrations of parathyroid hormone and hyperplasia of one of the parathyroid glands. Extended investigations found generalised osteoporosis, bilateral renal microlithiasis and cholelithiasis. The case of primary hyperparathyroidism we report excited our interest because of the endocrine disorder diagnosed in connection with the pain in the soft tissues caused by the periarticular calcifications established in the X-ray study.

Key words: periarticular calcification, primary hyperparathyroidism, chondrocalcinosis

Calcifications in the joints, the periarticular structures and soft tissues can be the presenting symptoms in quite a lot of diseases, including endocrine, metabolic, systemic, and neoplastic disorders [1, 2]. Heterotopic calcifications can manifest themselves with pain and restricted functional capacity. In patients with hyperparathyroidism, there are various musculoskeletal events that can be observed – generalized osteoporosis, bone cysts, periosseous bone resorption, and muscle weakness [1, 3]. The normocalcemic forms of the disease found in 3 to 4% of the cases are of some interest. The disease commonly presents as an asymptomatic disorder or with isolated manifestations in the locomotor apparatus, with renal microlithiasis, and arterial hypertension. Gastrointestinal tract and nervous system involvement is seen relatively rarely [3, 4, 5]. 11% of all patients with hyperthyroidism have a concomitant secondary chondrocalcinosis. Radiologically, calcifications are found in the articular cartilage, meniscuses, bursae, ligaments and soft tissues [6, 7, 8].
The organs most frequently affected are the joints and pelvis but there have been reports of sacroiliac joint involvement in a case report [9].

**CASE REPORT**

A 63-year-old female patient was referred to the clinic for more accurate diagnosis. She had had constant pains for a year, with periods of intensifying the pain in the left knee and the adjacent thigh muscles. The patient did not report a previous trauma or a swelling of the joint. She reported also mechanical pains in the proximal and distal interphalangeal joints of the hands. She had not received any thiazide diuretics, nor had she had any calcium or vitamin D3. At physical examination, the patient’s hand revealed Heberden’s nodes and Bouchard’s nodes with the functional capacity still intact. Movements in the left knee were painful and considerably limited. There was no evidence of hydrops. *M. quadriceps femoris sin.* was painful at palpation. The lab studies found normal concentrations of total calcium – 2.39 mmol/l (reference values 2.12 – 2.62 mmol/l), increase of the ionised calcium – 1.59 mmol/l (reference values – up to 1.33 mmol/l); the other biochemical parameters were within reference limits (including the alkaline phosphatasis, the complete ionogram, and creatinphosphokinase). We found elevated levels of parathormone – 148.1 pg/ml at reference values between 8.8 and 76.6 pg/ml.

The X rays of hands and the two knee joints revealed degenerative changes similar to osteoarthritis – a narrowed articular gap, subchondral osteosclerosis, and osteophytes. There were, however a considerable number of calcifications in the left knee joint – in the patellar tendon and in m. quadriceps femoris.

![A. X-ray of left knee joint – front view](image1)

![B. X-ray of left knee joint – side view](image2)

*Fig. 1. A, B. An X-ray of left knee joint – front and side views*
Doppler sonography and high resolution MRI studies found changes in one of the two parathyroid glands. Alongside the lower contour of the left lobe of thyroid gland we observed parasagittally the second parathyroid gland 12 mm in size (Figs 2, 3). The thyroid gland was normal in size and echogenicity.

A – Adenoma with perinodular blood stream
B – Parathyroid adenoma in the left part of the thyroid gland

Fig. 2. A, B. Ultrasonography of the thyroid and parathyroid glands

Fig. 3. MRI of the cervical region with the parathyroid glands
The computerised axial tomography of the abdominal organs found bilateral renal microlithiasis and cholelithiasis. X-rays of teeth and alveolar bones revealed horizontal resorption, which is typical for the chronic periodontal disease the patient had.

Bone density measurements were indicative of generalised osteoporosis (T score – 2.9 SD).

**DISCUSSION**

Presence of calcifications in the joints and periarticular structures is usually manifested with pains and restriction in movements. Heterotopic calcifications are characteristic of various endocrine, systemic, neoplastic, blood and metabolic diseases. The complaints from locomotor system make patients look for relief at various specialists: rheumatologists, orthopedists, surgeons, neurologists.

In the presented case, calcifications were found at radiography of the knee joints and were concomitant with the degenerative changes in them. The abnormalities in the lab tests results (elevation of blood ionised calcium and the parathyromone) necessitated further studies which revealed hyperplasia in one of both parathyroid glands [10, 11]. In 80% of the cases, hyperparathyroidism is caused by benign adenomas, in 10 to 15% – by diffuse hyperplasia of the parathyroid glands, and in 0.5 – 2% – by carcinomas with a severe clinical course.

Primary hyperparathyroidism generally presents with characteristic skeletal changes – generalized osteoporosis, osteitis fibrosa cystica, thinning of the lamina dura of dental alveoli, periosseous bone resorption, and a ground glass appearance of the skull on radiographs (a skull in a classic radiographic appearance called “ground glass” skull) [4, 5].

Calcifications in the joints and periarticular structures in primary hyperparathyroidism have been reported by a number of authors [12, 13, 14]. Our patient complained from chronic pain in the left knee and in m. quadriceps femoris that periodically intensified; her functional capacity was progressively getting restricted. There have been reports in the literature of patients with primary hyperparathyroidism and a rupture of the tendons as complications due to crystal depositions of calcium pyrophosphate dihydrate [12, 13]. Diagnostically, we considered also the option of secondary chondrocalcinosis although the X-ray study showed no calcium depositions in the articular cartilage and meniscuses. Articular puncture was not done because of absence of liquid in the joint. The patient however reported a periodical intensification of the pains in the knee region and in m. quadriceps. In 11% of patients with hyperparathyroidism screening radiographs of the knee joints, wrists, and pelvis usually reveal secondary chondrocalcinosis. In addition to the articular cartilage, the disease affects also the tendons, the bursae and soft tissues [6, 7, 8].

Generalised osteoporosis in primary hyperparathyroidism can present with fractures of the spinal vertebrae or in the femoral neck [14]. The osteoporosis found
in our patient is considered to be related to the underlying disease as well as to the onset of menopause nine years previously. A surgical treatment was considered in our patient because of future complications due to calcinosis and according to the generally accepted criteria of parathyroidectomy [5, 15]. The patient refused the surgical treatment. She is now being followed up regularly by a rheumatologist and an endocrinologist. Conservative therapy including biphosphonates (Fosamax), furosemid and non-steroid anti-inflammatory agents is being administered to her.

CONCLUSIONS

We would like to emphasize the following points in the reported case:

1. Musculoskeletal complaints can be the prodromal symptoms of an endocrine disorder (primary hyperparathyroidism in the reported case).

2. The normocalcemic forms of hyperparathyroidism run usually an asymptomatic course or present with isolated skeletal manifestations.

3. Secondary chondrocalcinosis in primary hyperparathyroidism can present with no involvement of the articular cartilage and meniscuses (with bouts of pseudogout) but with involvement of the tendons and soft tissues.

4. There is still this possibility of overlap of the manifestation of primary chondrocalcinosis in adults with that of normocalcemic primary hyperparathyroidism.

REFERENCES


Address for correspondence:
Maria Panchovska, MD, PhD
10, Alen Mak str., fl. 1, ap. 3
4003 Plovdiv
Bulgaria
35932609837
e-mail: panchovska@abv.bg
DEANXIT SELF-POISONING IN A PATIENT WITH FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY – A CASE REPORT

A. Loukova¹ and J. Radenkova-Saeva²

¹Sector of Psychiatry,  
²Toxicology Clinic,  
Emergency Hospital “N. I. Pirogov” – Sofia, Bulgaria

Summary. The authors report a case of deanxit self-poisoning in a 18-year-old female with accompanying hereditary degenerative disease – facioscapulohumeral muscular dystrophy, confirmed by molecular genetic investigation in the mother and the grandmother of the patient. It was to lay great emphasis on the necessity of interdisciplinary approach and utilization of means and instruments by different clinical specialists in examination of rarities in medical practice.

Key words: deanxit, self-poisoning, hereditary degenerative disease

Deanxit (Flupenthixol) is a mixture of two psychoactive agents, flupentixol and melitracen. It is used in the treatment of nervous, mental, and emotional conditions. Improvement in such conditions is thought to result from the effect of the medicine on nerve pathways in specific areas of the brain.

A non-fatal case of deanxit self-poisoning in a 18-year-old female is presented. She has been managed in the Toxicology Clinic, Emergency Hospital “N. I. Pirogov”.

The history included facioscapulohumeral muscular dystrophy (FSHD), diagnosed 5 years ago.

FSHD is a distinct type of muscular dystrophy, expressed both clinically and genetically. When fully developed, it presents with a characteristic pattern of muscle weakness, including, as the name implies, weakness of the facial muscles, the scapula, and the upper arms. The onset of noticeable symptoms usually occurs in childhood or young adulthood, but may rarely occur in middle life. An infantile onset form of FSHD has also been described.

In most cases, facial weakness is the first sign of the disease. The weakness results in an expressionless appearance. Patients soon develop inability to
smile, whistle, or fully close the eyes. The lips appear full and are often everted. The eyes may seem prominent and patients may also appear to sleep with their eyes partially open.

Unlike many of the other muscular dystrophies, FSHD is not associated with disease of other organ systems. Specifically, the heart is not involved and there is no association with mental retardation. There is an association with labile hypertension, although the reason for this is not understood. There is also increased incidence of sensorineural hearing loss and Coats’ disease, a disorder which includes detachment of the retina and telangiectasias.

FSHD is an autosomal dominant disorder with a prevalence of 1 in 20,000. Sporadic cases without a family history usually represent new mutations. FSH is due to a deletion which has been localized to the distal portion of the long arm of chromosome 4 (4q35). Expression of the FSH gene is variable. Although penetrance is 95% by age 20, there is a wide range of severity, even within families.

**CASE REPORT**

Patient was admitted to the hospital around 4 hours after accident with following diagnosis: Tentamen suicidii. Intoxicatio medicamentosa cum deanxito. Encephalopathia toxica. Somnolentio toxica.

On physical examination the patient was drowsy, with pale skin. The pupils were of normal width. Lungs had clear breath sounds. Heart sounds – with no murmur, or rub; blood pressure 110/70 mm Hg; Abdomen was soft, no guarding or rebound. No hepatosplenomegaly was noted. Extremities – without edema.

Neurological state was presented by myopathic syndrome: myopathic face; hypotonia of proximal musculature to extremities. Weakness of the shoulder girdle more on the right. Axial muscle weakness for flexion to the head. Peroneal weakness more on the left. Myopathic walking with rocking to the right. Scapular winging. Thoracolumbal scoliosis.

Diagnosis of FSHD in this patient was confirmed by genetic test in Department “Human and Clinical Genetics” at University Medical Center, Lyden, Holland. The disease was confirmed in the mother, grandmother and grandmother’s two sisters. All they had pathologic fragment by size 18 kylobasis from type “A”.

As a result of the investigation of psychiatric status, there was established the following: Psychomotor processes – externally tranquil. Completely oriented towards oneself, accessible to verbal contact. Formally – critical towards self-condition and the incident. Mental process – correct to rate and grammatical structure. Felt a touch of slip out to the associations in side course. In the contents – discovered lack of prospects. Shared internally pressure, bad temper, sleeplessness (insomnia). Felt better in the afternoon. Expressed ideas for hopelessness, which she associated with the own illness, as well as with deteriorating state of her mother (suffering from FSHD). There were no data for perception disorders, hypobulia,
emotional instability, pointed passive attention. Memory and intellect were on the level of educational and social experience.

After psychiatric investigation, we assumed that the patient presented intentional selfpoisoning in the condition of moderately expressed depressive episode in the state of somatic suffering.

Treatment consisted of fluid infusion 1500 ml, Pyramem 3x1 g/24 h, Vit B compl. 3x1 amp/24 h, Quamatel 1fl, kinesitherapy – passive-active exercise to extremities.

The patient remained in the hospital for two days. She was dehospitalized in a good state and was administered consultation with neurologist and psychiatrist.

This case represents interest because of necessity for active cooperation between different medical specialists – toxicologist, neurologist, psychiatrist and kinesitherapist, in order to overcome life-threatening state. In our opinion, it is necessary to apply interdisciplinary approach to a big part of toxicological traumatism. The good coordination between different specialists is a guarantee of success in multidisciplinary pathology.

The involvement of different medical specialists is requirement of modern science thinking – each phenomenon of medical nature should be examined by interdisciplinary approach.

REFERENCES

1. Бужов, Б. Ц. и др. Диференциалнодиагностични насоки при верифицирането на пациент с нов атипичен фенотип на фациоскапулухумерална мускулна дистрофия, 41, 2005, 3.
2. Маринов, П. Фармакопсихиатрия и психодофармакология. С., Пропелер, 1999.

Adress for correspondence:
Dr. Anelia Loukova
Toxicology Clinic – Psychiatry Sector
Emergency Hospital “Pirogov”
21 Totleben blvd.
1606 Sofia Bulgaria
9154409
e-mail: aloukova@yahoo.com
Summary. The aim of this study is to describe the epidemiological characteristics, physical findings and morphological signs of pseudoexfoliative glaucoma. This is a prospective, observational case-control study, which includes a 7-year period of observation of 893 patients (1786 eyes) with pseudoexfoliation glaucoma (PeG) and 52 patients with Primary Open Angle Glaucoma (POAG). Color Doppler Ultrasonography (CDU) of carotid and ophthalmic artery of 18 eyes with PeG was performed. Peak systolic and end diastolic velocities were measured. Mean flow velocities, resistive and pulsative indices were calculated. Transmission electron microscopic (TEM) study of 24 eyes with PeG and 12 eyes with POAG was performed. Specimens from conjunctiva, trabecular meshwork and iris were obtained during surgery. The results show high prevalence of PeG (37.19% of all glaucoma types). The patients were predominantly men and the recessive type of inheritance was proposed. PeG was diagnosed more frequently in elderly (60-80 years). CDU showed that the hemodynamic parameters were altered. It was observed by TEM that all cell types are involved in the pathological process.

Key words: pseudoexfoliation syndrome, glaucoma

The number of individuals diagnosed with PeG increases in recent years. Many researchers look for new data concerning etiology, pathogenesis and systemic manifestations. The questions of clinical epidemiology, physical findings and morphological signs of pseudoexfoliation syndrome (PeS) and glaucoma are still actual.

AIM

The aim of this study is to describe the epidemiological characteristics, physical findings and morphological signs of pseudoexfoliative glaucoma.
DESIGN

Prospective, observational case-control study.

METHODS

A) Clinical study.
The clinical epidemiological study includes a 7-year period of observation of 893 patients (1786 eyes) with pseudoxfoliation syndrome (PeS) and glaucoma (11.43 % of 7815 patients in the clinic). The case-control study includes a 5-year period of clinical observation of 309 patients (618 eyes) with glaucoma. Besides were examined 261 patients with PeS without glaucoma for the need of systemic disease analysis. Data were obtained for a long period of time (from 7 months till 25 years after diagnosing glaucoma), m=59.1489. To avoid mistakes in the selection of patients we checked all official and unofficial documents referring to history of illness. The basic inclusion criteria were: patients with glaucoma and clinically visible PeS at least in one of the both eyes.

The control group consisted of 52 patients with POAG (104 eyes). To avoid the system mistake we randomized the two groups by age (5 years interval).

The order of examination was: history of illness, visual acuity, Schirmer I test, perimetry, slit lamp examination, tonometry, gonioscopy, direct fundoscopy after mydriasis.

All data are analyzed by statistical package Statgraphics Plus for Windows.

B) Transmission electron microscopy of trabecular meshwork, iris and conjunctiva

The specimens were obtained after informed consent, during filtration surgery of 24 patients. The tissues were processed using a standard procedure for electron microscopy and observed by Tesla-SB 500 electron microscope.

C) Color Doppler Ultrasonography (Imaging) – CDI

We examined 18 eyes in patients with PeG (mean age 71.69). 5 of them were locally treated with medications and in 13 trabeculectomy was performed (6 months ago at least). The IOP in all eyes was below 18 mmHg because of treatment. Previous or current history of any topical or systemic drugs was recorded. All patients were referred from internal disease services. Exclusion criteria were: other eye diseases besides glaucoma and cataract; diabetes mellitus; severe cardiovascular diseases – history of ischemic attacks or stroke; systolic pressure >150 mmHg and diastolic pressure > 90 mmHg during the time of examination; hemodynamically significant carotid occlusive disease (> 75%). Eye examination and color Doppler imaging were performed on the same day. The mean arterial pressure was registered immediately before the ultrasound examination.

Color Doppler imaging (Fukuda Denshi, Tokyo, Japan) was performed using a 7.5-MHz transducer with acoustic gel in a supine position and closed eyes of the patient. The study was double blinded. The mean peak systolic (PVs) and
the mean end diastolic velocity (PVd) of a common and internal carotid artery were measured (approach in front of m.sternocleidomastoideus), and ophthalmic artery (transorbital approach). The mean velocity (MV), resistive (Pourcelot-RI) and pulsative (Gosling-PI) indices were calculated. The optic nerve was the most useful landmark for the identification of the retrobulbar vessels. Because the PVd and PVs are both dependent on the Doppler angle, they were both regarded to a degree, as operator-dependent. The RI is known as an angle-independent index and was regarded to be good mark to quantify the vascular resistance of the circulation.

RESULTS

A) Clinical epidemiology

The relative part of patients with PeG from all the patients with glaucoma was high – 37.19%. The fluctuations during years were statistically insignificant.

– Sex distribution

PeG involved males predominantly (64.36%) in comparison with POAG where the involved are mostly females.

– Heredity

We obtained glaucoma history only in 20.36% of 275 patients. Differences between the groups with glaucoma (suffering mother or father) were statistically insignificant. Analysis in the group of indirect relatives showed involvement predominantly of males.

– Age

The mean age of PeG patients was 70.08 years vs. 64.54 years in POAG.

– Laterality

We analyzed retrospectively the data of 275 patients with PeG and examined 130 of them. In 29.29% of previously unilaterally involved eyes we discovered clinically visible PeS in the second eye. In 68.98% this happened for less than 5 years and in 31.02% for more than 5 years. Probably in the first group the early PeS was misdiagnosed or unregistered in the past. The second group confirmed the thesis that the syndrome was bilateral and asymmetrical.

B) Ultrastructural characteristics of EG

Cornea

Ultrastructural examination of three corneal specimens obtained intraoperatively during trabeculectomy, showed transformation and endothelial detachment of Descemet’s membrane, oval shape of endothelial cells, and encircling of their nuclei. Actually, degenerative changes were cytoplasmic and mitochondrial vacuolization. Phagocytized melanin granules, which were incorporated in vacuoles were found. Endothelium was irregular with a lot of desquamated cells covered by proliferating neighbour cells. Areas of basal lamina splitting and pseudoexfoliation (Ex) fibres were also observed.
**Anterior chamber angle**

Disorganization of normal trabecular meshwork structure was demonstrated with the help of electron microscope. Collagen fibers were irregularly orientated with regions of fragmentation. Ex material was observed as different sized deposits with high electron density. In some areas Ex material was seen as a pre trabecular layer. Migration and proliferation of cornel endothelial cells on the trabecular meshwork was also seen. (Fig. 1).

![Fig. 1. Trabecular meshwork – separated basal lamina with endothelial cell, X 2400](image)

The evidence of active production and degeneration was of great interest. Enlarged and round nuclei, developed Golgi apparatus and elongated endoplasmic reticulum were found in one and the same time with vacuoles containing destroyed mitochondria, a great number of residual bodies, and vacuoles with phagocytized melanin granules. Endothelial cells laying trabecular meshwork were irregular in shape. Their junctions were broken at some places because of desquamation.

**Iris and pupil**

Several groups of signs were observed showing evidence of vascular pathology—changes in blood vessels (fig. 2) and neovascular vessels (fig. 3).

We classified vascular pathologic changes in four stages according to electron microscope observation:

I stage – Deposition of Ex material in a focal manner

II stage – Deposition of Ex material associated with degenerative changes in pericytes

III stage – Deposition of Ex material and changes in pericytes associated with degenerative changes in endothelial cells

IV stage – Destruction of blood vessels and consequent fibrosis
Changes in lamina basalis of blood vessels were interesting. In one and the same model we observed thickened basal laminas (which is a characteristic for glaucoma process) and destroyed ones (which is a characteristic feature of ES).

All cell types showed evidence of dystrophy. The result was epithelial desquamation and fibrosis of dilatator and sphincter. Membrane ruptures were observed in epithelial cells and liberation of melanin granules in the stroma was found (fig. 4).

Fibrotic changes in iris musculature were also found. There were intracellular signs for active production and degeneration at one and the same time (enlarged round or segmented nuclei, cytoplasmic vacuolization, a plenty of residual bodies, lost of mitochondrial cristae and vacuolization, elongated endoplasmic reticulum).
**Conjunctiva**

Morphologic changes were similar to those in the iris. Ex deposits were distributed within the stroma and around blood vessels, which were in a different stage of obliteration. Neovascular vessels could be easily seen giving evidence of ischemia (fig. 5).

C) Ocular microcirculation

During the examination of blood flow through the ophthalmic artery, it was noted that the speed of blood flow was so slow, so was not possible to register it. At the same time the speed of blood flow through internal carotid artery was within normal range (the speed was measured infront of sternocleidomastoid muscle and transor-
bitally). All the patients had IOP within the normal range after filtrating surgery. After these data were obtained, we supposed that vascular pathology in EG could play an important role for further glaucomatous damage in patients with normal IOP. The group of selected patients showed evidence of progression of glaucoma process (worsening of parameters describing optic nerve head, visual field, and visual acuity) although the values of IOP were low after trabeculectomy. Worsening of blood supply was in correlation with the stage of glaucoma process.

Systemic diseases
Analysis of data showed a higher incidence of arrhythmias, stroke, heart failure, ischemic heart disease, gastritis or stomach/duodenal ulcer in patients with EG as compared to patients with POAG and ES without glaucoma. The percentage of arthritic changes was relatively high in patients with ES with or without glaucoma.

DISCUSSION

A) Epidemiology
Data show that EG is more frequently observed in men and probably gender has modulating effect on this disease. Whether this hypothesis is true could not be stated for sure, because of several reasons: unexplored demographic characteristics of the studied region, lack of population based epidemiological studies about gender distribution of patients with EG. Other factors, which could have an effect are the established dependencies by Moreno-Montanes. According to them men with ES develop glaucoma more frequently and earlier than women and the disease is taking its course with higher IOP and more prominent visual field loss. A recessive type of inheritance of EG could be supposed because of the large group of patients with healthy parents.

Our hypothesis is that ES is age-dependent systemic process, which unlocks after breaking of unknown compensatory mechanism or it has so slow subclinical course that takes decades for development of the disease. Exfoliation glaucoma is diagnosed in later age when the symptoms become obvious, but the syndrome has developed earlier.

B) Ultrastructural characteristics of EG
Cornea
Based on our research data we assume the presence of the specific for ES corneal damage called by Naumann pseudoexfoliative keratopathy [2]. It includes endothelial defects and active cells production of Ex material, which lead to corneal endothelial decompensation.

The question about primary or secondary character of the corneal damage is without answer.
Anterior chamber angle (trabeculum)

The question concerning the stage of damage in the trabecular meshwork from ES is discussed for decades. Richardson and Epstein [4] state that besides Ex deposits, they do not find any other pathological changes in the trabeculum. According to us, the disturbed trabecular architectonic is the cause of trabecular obstruction. The effect of endothelial growing which is responsible for the pre trabecular obstruction of the flow is additionally added. Therefore another factor which obstructs the flow is the peeling of endothelium.

According to us, the active secretion of extracellular Ex material, dead cells and pigment granules “block” the trabecular meshwork and lead to increase of IOP. We can not say for sure that these are the only causes for rising of IOP and development of glaucoma, because we observed many eyes with ES without glaucoma.

Iris

The main question is whether vasculopathy is the cause or the result of ES. It leads to tissue ischemia. Obviously it is the main reason for development of neovascularization. We clearly see a different stage of vessel obliteration in all cases. This produces dystrophic changes in all cell types and results in epithelium desquamation and a process of fibrosis of the dilator and sphincter. The releasing of melanin granules in the stroma appears clinically with pigment dispersion and iris cheterochromia. Fibrotic changes in the iris muscles lead to asymmetric enlargement of the pupil, myosis and difficult pupil dilation.

There is no clear explanation for the ultrastructural finding – the existence of active production and degeneration.

Conjunctiva

The vasculopathy leads to degenerative changes in the Goblet cells, which explain the reduced lacrimal secretion in patients with EG (in 70% reduced lacrimal secretion in men with EG). We recommend careful application of β-blockers, due to a potential danger for development of dry eye syndrome.

C) Ocular microcirculation

According to excitotoxic theory, ischemia is an important factor for the development of the glaucoma process. Its influence leads to reduction of the axoplasmatic flow so the growing factors can not react with ganglion cells in the retina. Worsening of the metabolism in the retina results in accumulation of neuromediators (glutamate) leading to apoptosis. The established organic damages of the vessels in the PeG (pericyte and endothelial proliferation, distraction of basal membrane, obliteration of the vessel lumen to total occlusion of the vessels) and the presence of neovascularization demonstrate development of a chronic process of tissue ischemia.
According to us, the decrease of blood flow in the ophthalmic artery, measured with Color Doppler Ultrasonography (CDU), is a result of organic damage of the vessel muscles because of Ex deposits. According to our results we can offer the following hypothesis (fig. 6).

\[
\text{Organic changes in the vessels} \\
\downarrow \\
\text{Reduced blood flow} \\
\downarrow \\
\text{Ischemia} \\
\downarrow \\
\text{Releasing of endothelin-1} \\
\downarrow \\
\text{Constriction of blood vessels}
\]

*Fig. 6. Pathophysiology of the microcirculatory damages in PeG*

**Systemic diseases**

According to Hollo and all. [6], the ischemia is common to the whole body in patients with PeG. Data from CDU and the morphological signs of local ischemia give evidence to look for changes in blood vessels in the body. How much Ex deposits influence other diseases, disturb their clinical course or they are part of systemic process, is up to know. It is necessary to clear up the role of ischemia as a cause or result of ES in the future.

**CONCLUSION**

In recent years, the interest in PeG is growing. This leads to more precise registration and long term evaluation of the patients.

**REFERENCES:**


Address for correspondence:
Dr. Hristina Blagoeva
“St.Sofia” Hospital, Sofia
104 Bulgaria str.
0888 46 28 90
e-mail: ch_blagoeva@abv.bg
He-Ne low level laser therapeutic applications for treatment of acute iridocyclitis

K. Koev¹, E. Borisova² and L. Avramov²
¹Clinic of Ophthalmology, University Hospital “Alexandrovska” – Sofia
²Institute of Electronics, Bulgarian Academy of Sciences

Summary. This investigation is carried out in two groups of patients with acute anterior uveitis (acute iridocyclitis). In every group, there were included 20 eyes. In the first group, eyes were irradiated every day during a ten-day-period with He-Ne low level laser (Mediray 04, Optella Ltd., Sofia, Bulgaria) at emission wavelength of 632 nm and power density 0,1 mW/cm². Second group was used as a control. In both groups, there was applied standard anti-inflammatory treatment of iridocyclitis in equal number of applications of the following: Tobradex, Ophthalar, Midrum, antibiotics drugs per os and non-steroid anti-inflammatory drugs per os, Dexamethazone para bulb. We observed significant suppression of the inflammatory reaction, stronger decrease of the ciliary flush, photophobia, epiphora, faster disappearance of the fibrinous exudate and posterior synechiae in the anterior chamber, as well as faster disappearance of the keratic precipitates, in the treated by low-level laser therapy (LLLT) eyes. For irradiated eyes by LLLT, we have found that the healing period is shortened significantly by 40 % (p<0,001). Our results revealed that LLLT application is appropriate and perspective for acute iridocyclitis treatment.

Key words: low level laser therapy, acute iridocyclitis, inflammatory reaction, eyes.

Introduction

Uveitis is the third leading cause of preventable blindness in the developed world. Most ophthalmologists are not trained in the diagnosis and treatment of difficult to control uveitis. Iritis is inflammation predominantly located in the iris of the eye. Inflammation in the iris is more correctly classified as anterior uveitis. The ciliary body can also be inflammed and this would then be called iridocyclitis [1].

Causes of anterior uveitis can be related to autoimmune disorder (juvenile rheumatoid arthritis, ankylosing spondylitis, Reiter’s syndrome, ulcerative colitis,
psoriasis, sarcoidosis), infections (syphilis, tuberculosis, herpes zoster, herpes simplex, adenovirus), malignancy (masquerade syndrome-retinoblastoma, leukemia, lymphoma, malignant melanoma), trauma, gout, idiopathic or other [2].

Acute iridocyclitis is usually unilateral and is characterized by a history of pain, photophobia, epiphora, blurring of vision, a red eye (circumcorneal flush) without purulent discharge, and a small, variably irregular shaped pupil. The presence of keratic precipitates on the posterior surface of the cornea as well as flare and cell in the anterior chamber can be seen with the slit lamp [2].

Low-level laser therapy (LLLT) – also known as cold or soft laser, used for bio-stimulation, or photobiomodulation – is an emerging therapeutic approach in which cells or tissue are exposed to low-levels of red and near – infrared light from lasers. It might either stimulate or (less likely) inhibit cellular function, leading to reduction of cell and tissue death, improved wound healing, increasing repair of damage to soft tissue, nerves, bone, and cartilage, and relief for both acute and chronic pain and inflammation [3].

Low-energy laser irradiation produces significant bioeffects. These effects are manifested in biochemical, physiological and proliferative phenomena in various enzymes, cells, tissues, organs and organisms [4].

After burning the corneas with alkali, without stimulating the regeneration, some authors (5) find out that in the front epithelium and the stroma of the cornea the activity of lactatdehydrogenase, malatedehydrogenase, glutamatdehydrogenase, and glucose-6-phosphate-dehydrogenase is sharply reduced, and at the same time the activity of flavin-dependent succinatdehydrogenase is increased, which was estimated as a protective adaptation phenomenon which helps the tissues preserve their viability in extreme conditions, and conduces to decrease the deficiency of macroenergy compounds.

It was established that after a chemical burn of the cornea, the activity of some phosphatases – adenosinetriphosphatase, was permanently decreased [6], and the activity of other phosphatases – the acidic phosphatase, varies within certain limits [7].

**MATERIALS AND METHODS**

Inflammation of the uveal tract has many causes and may involve one or all three portions (iris, ciliary body and choroids) simultaneously. The most frequent form of uveitis is acute anterior uveitis (also termed as iridocyclitis acuta). A randomized study was carried out which included 34 patients (40 eyes) with active acute iridocyclitis. The patients were divided into two groups each including 20 eyes. The first group included idiopathic acute anterior uveitis (8 eyes), sarcoidosis (2 eyes), herpes simplex (2 eyes), juvenile rheumatoid arthritis (2 eyes), and one eye each of tuberculosis, Crohn’s disease, ankylosing spondylitis, Behcet’s, Reiter’s syndrome, Fuchs heterochromic.
The second group included idiopathic acute anterior uveitis (8 eyes), herpes simplex (3 eyes), Reiter’s syndrome (2 eyes), and one eye each of juvenile rheumatoid arthritis, ankylosing spondylitis, Fuchs heterochromic, tuberculosis, Crohn’s disease, Behcet’s, sarcoidosis.

Both groups included patients with acute iridocyclitis with the following symptoms: painful red eye, ciliary flush, marked photophobia, epiphora, posterior synechiae. Slit lamp showed anterior chamber reaction manifested by inflammatory cells, flare (protein leakage), keratic precipitates, fibrinous exudate in the anterior chamber. In cases with acute herpes simplex keratoiridocyclitis, the test with fluorescein stain was applied to rule out corneal abrasion and herpes simplex dendrite. In both groups, visual acuity was investigated.

For the investigation, there was applied a new ophthalmologic system for bio-stimulation and LLL therapy of eye diseases based on the He-Ne laser (Mediray 04, Optella Ltd., Sofia, Bulgaria) with emission wavelength of 632 nm. The system has an opportunity to regulate the size of the laser spot and laser power density from 0,05 to 0,4 mW/cm². The apparatus is developed in Bulgaria by the authors K.Koev, V. Tanev, L. Avramov. The system is compact, portable and with minimal optical losses and high reliability. The device is convenient in exploitation, both for the patients and for the treating personnel. In the first group, eyes are irradiated every day during ten days with Mediray 04 with power density 0,1 mW/cm². Second group is used as a control. In both groups, there was applied standard anti-inflammatory treatment of iridocyclitis in equal number of applications of the following: Tobradex, Ophthalar, Midrum, antibiotics drugs per os and non-steroid anti-inflammatory drugs per os, Dexamethazone para bulb.

RESULTS

We observed a significant suppression of the inflammatory reaction, stronger decrease of the ciliary flush, photophobia, epiphora, faster disappearance of the fibrinous exudate and posterior synechiae in the anterior chamber, as well as faster disappearance of the keratic precipitates in the treated by low-level laser therapy (LLLT) eyes. For irradiated eyes by LLLT, we have found that the healing period is shortened significantly by 40 % (p<0,001).

In cases with acute keratoiridocyclitis herpetica, treated with LLLT, flourescein colorization disappearance and earlier epithelization setting was observed.

In the group with combined LLLT best-corrected visual acuity improved in 20 eyes, of which in 19 eyes (95%) attained final visual acuity was better than or equal to 0,3, mean 0,5.

No improvement in visual acuity was seen in one eye with Behcet’s. In the control group, the final corrected visual acuity was mean 0,1.
The combined LLLT with Tobradex, Ophthalar, Midrum, antibiotics per os and non-steroid anti-inflammatory per os, Dexamethazone para bulb showed significant additional effect on the recovery rate. (Table1).

Table 1. Time needed for recovery in dependence on treatment procedure applied in the case of acute iridocyclitis therapy

<table>
<thead>
<tr>
<th>Group number</th>
<th>Treatment applied</th>
<th>Average days for recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tobradex, Ophthalar, Midrum, antibiotics per os and non-steroid anti-inflammatory per os, Dexamethazone para bulb and LLLT</td>
<td>13,4±0,7</td>
</tr>
<tr>
<td>2</td>
<td>Tobradex, Ophthalar, Midrum, antibiotics per os and non-steroid anti-inflammatory per os, Dexamethazone para bulb</td>
<td>22,3±0,5</td>
</tr>
</tbody>
</table>

DISCUSSION

From the results obtained during this investigation we could ascertain the fact that the combined treatment with the best effect on the patients with acute iridocyclitis was obtained in group one using Tobradex, Ophthalar, Midrum, antibiotics per os and non-steroid anti-inflammatory drugs per os, Dexamethazone para bulb and LLLT. This combination led to earlier disappearing of the inflammatory reaction, in comparison with the control group.

The combined laser treatment shows significant additional effect on the recovery rate.

The mechanisms of positive influence of LLLT are not completely understood. There are various local and systemic medico-biological processes that take place under the influence of LLLT. The action of laser light of optimal parameters has normalizing influence bringing to the total rising of adaptive potential and to the acceleration of treatment. Initial phase of any biological and clinical effect of LLLT is the absorption of quantum energy by biotissues with induction of primary photophysical and photochemical processes. The process of absorption is influenced by the optical properties of the biological object and the parameters of laser irradiation [8].

There exists a strong relationship, first, between light parameters and biostimulation effects on a cellular level, and second, between the moment of irradiation and limits of magnitude of biostimulation effects. Systemic studies with cells clearly indicate that such parameters of light as wavelength, fluence, and intensity play the most important roles in both stimulation and inhibition of cellular metabolism [9, 10].

When the iris is inflammed, white blood cells (leukocytes) are shed into the anterior chamber of the eye where they can be observed on slit lamp examination floating in the convection currents of the aqueous humor. These cells can be counted and form the basis for rating the degree of inflammation. These cells can
accumulate and cause adhesion (posterior synechiae) between the iris and the lens. It is important to make the diagnosis early and to dilate the pupil to prevent the formation of permanent posterior synechiae related to glaucoma [11].

The first law of photobiology states that for low-power visible light to have any effect on a living biological system, the photons must be absorbed by electronic absorption bands belonging to some molecular chromophore or photoacceptor. Cytochrome c oxidase, a subunit in the mitochondrial electron-transport chain, may play a role as a primary photoacceptor in mammalian cells since it has absorption bands up to 1000 nm [12].

Experimental studies on animals and in vitro conditions provide evidence that 633 nm laser light can enhance wound healing. Rigau et al., [13] studied the effects of the 633 nm laser on the behaviour and morphology of a primary fibroblast culture after a central scratch of 0.4-1mm and two irradiations were performed. The effect of the wounding and laser irradiation was studied using colony formation (formation of colonies in the central zone of the wound or on the edge of the scratch), haptotaxis (change of orientation of the edge cells) and chemotaxis-chemokinesis (movement or migration of cells across the wound). The number and intensity of colony formation, the haptotaxis of the edge fibroblasts and the fibroblasts present in the centre of the scratch were rated and the irradiated and non-irradiated controls compared. The group concluded that structural changes like colony formation, haptotaxis and chemotaxis-chemokinesis appear sooner in LLLT irradiated cultures than in non-treated controls. They also confirmed that LLLT induced fibroblast biological effects.

Low-intensity laser therapy is recognized as an effective therapeutic method by the FDA, particularly to improve tissue healing [14]. A large body of evidence from in vitro and in vivo studies has suggested that LLLT enhances collagen synthesis, increases the motility of keratinocytes, releases growth factors, and promotes the transformation of fibroblasts into myofibroblasts [15]. On the other hand, the idea of investigating the early phase of the skin repair process under the influence of anti-inflammatory agents (a corticosteroid or a cyclooxygenase (COX-2) inhibitor) is based on the known pharmacological properties of such drugs and on their broad clinical use and side-effects [14].

Studies have shown that during normal wound healing the inflammatory phase lasts up to two days [16]. Cell proliferation, epithelization, granulation tissue formation, and wound contraction occur during the proliferative phase. Growth of new epithelial cells across the surface of the wound and collagen remodeling occur during the maturation phase of wound healing, which lasts for months or even longer. The present results showed that He-Ne laser irradiation of the skin of mice produced beneficial effects on the macroscopic aspects of the surgical wound, such as reduction of humidity, apparent vascular modulation and effective control of the amount of clot in the injured area, during the first 24 h [17]. These data therefore, suggest that laser therapy increased the healing dynamics compared to control.
Similar results were obtained by [18] in diabetic rats, showing that laser-treated animals healed faster and better than controls. Other studies [19] using He-Ne low-energy laser have indicated that it is mainly the laser energy at 633 nm wavelength that affects the healing dynamics, producing changes in the early phase of the repair process, i.e. the inflammatory phase.

The suggestion that laser affects the early events in the dynamics of wound healing was partially based on the observed low-intensity laser therapy-induced attenuation of reactive oxygen species production by neutrophils in inflammatory models. This was initially suggested by another study where a diminished oxidative stress-induced apoptosis of neutrophils in acute inflammation is described [20]. Nevertheless, the basic aspects of oxidative stress and the mechanisms by which reactive oxygen species modulate physiological and pathological processes, with emphasis on wound healing, are still motive of debate.

It is well known that corticosteroids down-regulate pro-inflammatory proteins and affect gene expression, interfering with almost all phases of the inflammatory process. On the other hand, controlled laboratory trials have reported that laser photostimulation can reduce inflammation through inhibition of inducible COX-2, leading to a reduction in prostanoid levels. Additionally, experiments involving various cell culture stages have shown that laser irradiation at early stages significantly stimulates cell proliferation, alkaline phosphatase activity and osteocalcin gene expression, indicating that laser photostimulation enhances bone formation in vitro [21].

Authors [22] determined that the effects of helium-neon laser irradiation on wound healing dynamics in mice treated with steroidal and non-steroidal anti-inflammatory agents. They made the following experiment: male albino mice, 28-32 g, were randomized into 6 groups of 6 animals each: control (C), He-Ne laser (L), dexamethasone (D), D + L, celecoxib (X), and X + L. D and X were injected im at doses of 5 and 22 mg/kg, respectively, 24 h before the experiment. A 1 cm long surgical wound was made with a scalpel on the abdomens of the mice. Animals from groups L, D + L and X + L were exposed to 4 J (cm²)⁻¹ day⁻¹ of He-Ne laser for 12 s and were sacrificed on days 1, 2, or 3 after the procedure, when skin samples were taken for histological examination. They observed a significant increase of collagen synthesis in group L compared with C (168 ± 20 vs 63 ± 8 mm²). The basal cellularity values on day 1 were: C = 763 ± 47, L = 1116 ± 85, D = 376 ± 24, D + L = 698 ± 31, X = 453 ± 29, X + L = 639 ± 32 U/mm². Their results show that application of L increases while D and X decrease the inflammatory cellularity compared with C. They also show that L restores the diminished cellularity induced by the anti-inflammatory drugs. The authors suggest that He-Ne laser promotes collagen formation and restores the baseline cellularity after pharmacological inhibition, indicating new perspectives for laser therapy aiming to increase the healing process when anti-inflammatory drugs are used.

In two of the observed cases with keratoiritidocyclitis herpetica of group one where LLLT treatment was applied, a decrease of the dendritic lesions was wit-
nessed in comparison to those cases with non-LLLT treatment. In cornea, colorized lesions were found, as in the most cases they appeared in the form of tree branches. In similar previous investigations, we have found out that in patients with keratitis herpetica dendritica in the group treated with He-Ne laser irradiation combined with Pandavir and Acyclovir the earliest answer reaction observed was inflammation suppression and perifocal edema disappearance. Eyes treated only with Acyclovir present mean time of improvement, as the flourescein colorization disappearance and epithelization setting is observed. Similar results were obtained on the eyes treated in double combination, Pandavir and Acyclovir. The best effect was obtained by the triple combination: Pandavir, Acyclovir and He-Ne laser (statistically proved), with the lowest mean time of improvement [23].

The combined treatment with Tobradex, Ophthalar, Midrum, antibiotics per os and non-steroid anti-inflammatory drugs per os, Dexamethazone para bulb and LLLT, is revealed as an efficient method for eye therapy of acute iridocyclitis. Thus the combination with He-Ne laser has strong additive effect, assuring total healing of the affected eyes with pronounced shortening of the mean duration of the disease. These excellent results most probably are related to the conjunction of the drugs and laser irradiation influences. Besides, LLLT has a stimulating regeneration effect.

The therapeutic method proposed as a combination of medicaments and LLLT is a new alternative for treatment of acute iridocyclitis.

REFERENCES:


Address for correspondence:
Dr. Krassimir Koev, PhD
Clinic of Ophthalmology
Aleksandrovskva Hospital
1 Sv. G. Sofiiski str.
1431 Sofia
836-55-04
e-mail: sofia56@abv.bg
PREGNANCY OUTCOMES IN NORMOGLYCEMIC WOMEN WITH HYPERINSULINEMIA TREATED WITH METFORMIN BEFORE AND DURING PREGNANCY – A CASE-CONTROL STUDY

BIGUANID IN PREGNANCY OF HYPERINSULINEMIC WOMEN

K. Todorova – Ananieva¹, E. Konova², D. Iafusco³, O. Palaveev⁵, Al. Emin², M. Atanasova¹ and M. Guenova⁴

¹High Risk Pregnancy Department, Specialized Hospital of Obstetrics and Gynecology, Medical University Sofia, Bulgaria
²Clinical Institute for Reproductive Medicine, Pleven, Bulgaria
³Department of Pediatrics, Second University of Naples, Naples, Italy
⁴Central Department Clinical Laboratory and Clinical Immunology, Medical Faculty, Sofia, Bulgaria
⁵Unipharm AD, Sofia, Bulgaria

Summary. The aim of this study was to evaluate the effects of metformin on maternal and neonatal pregnancy outcome among normoglycemic hyperinsulinemic women with one previous spontaneous abortion (SA). A prospective, two-year case-control study was performed including sixty-six pregnant women with normal carbohydrate tolerance before pregnancies and one SA. A 75-gram Oral Glucose Tolerance Test (OGTT) was performed before pregnancy. The levels of blood glucose (BG) and immunoreactive insulin (IRI) were measured at 0 min, 60 min and 120 min. Women with hyperinsulinemia were treated with metformin (0.75 g/day) before and during pregnancy. OGTT was repeated at 12 and 36 gestational weeks (g.w.) in all pregnant women. Pregnant women were divided into two groups: non-treated with metformin (Group 1; n₁ = 32) and treated with metformin (Group 2; n₂ = 34). The changes in BG, IRI levels during OGTT, live births and SA rates and newborn's body weight were recorded. Statistical comparison was performed between treated and non-treated pregnant women. Logistical regression analysis was used to assess the effect of hyperinsulinaemia and metformin on the risk of pregnancy loss. No statistically significant differences in the mean values for age, body mass index (BMI) and BG levels were found. The IRI was significantly higher in women of n₁ compared to n₂ in early and in late pregnancy. Eleven (34.4%) pregnant women of n₁ and five (14.7%) of n₂ presented impaired glucose tolerance (IGT) at late pregnancy (P=0.03). There was no case of gestational diabetes (GD) in n₂, whereas
four (12.5%) of n1 developed GD in late pregnancy. There were no maternal complications and no birth defects in the group of patients treated with metformin. The body weight of the newborns was similar for both groups. The rate of miscarriage was 18.7% in Group 1, and 8.8% in Group 2. Pregnant women with IRI levels over 50 mIU/ml at 12 g.w. showed a significantly higher risk for SA in comparison with those with normal level of IRI, proved by the model of logistic regression (OR = 4.9; CI. 2.1-19.3). There was no statistically significant effect of metformin on the logistic regression model. Conclusion of our study was that the treatment with metformin during pregnancy was safe, improved metabolic markers and significantly reduced spontaneous miscarriage rates.

Key words: hyperinsulinemia, insulin resistance, gestational diabetes, metformin, pregnancy outcome, spontaneous abortion

INTRODUCTION

Puberty and pregnancy are two physiologic conditions associated with decreased sensitiveness of peripheral tissues to biological action of insulin. Insulin resistance (IR) results from hormonal changes and its severity may be variable. Glucose balance is supported, in normal range, because pancreatic β-cells react by adequate raise in insulin secretion and this way compensates the decreased biological effect of the insulin action. During pregnancy, hormones which decrease peripheral insulin sensitiveness are increased and glucose homeostasis is supported by balanced changes in insulin secretion. This mechanism enhances simultaneously with progress of pregnancy. Hyperinsulinemic IR before pregnancy could be a precondition for the occurrence of pancreatic β-cells dysfunction later [1, 2]. During pregnancy, IR is a risk factor for undesirable maternal-fetal complications. Gestational Diabetes (GD) is the pathological condition of a carbohydrate intolerance of variable severity, which occurs as a result of inadequate β-cell insulin production in response to tissue resistance [3, 4].

The biguanid metformin (diamethyl guanyl guanidine) is usually used in type 2 diabetes (T2D). It reduces plasma insulin levels by reducing hepatic gluconeogenesis and stimulating peripheral glucose uptake. Treatment with metformin improves the defects of the insulin activity, decreases the insulin secretion, reduces the ovarian steroidogenesis and slows the progress of GD in women with polycystic ovarian syndrome (PCOS) [6, 7]. Metformin decreases the weight, preserves β-cell reserves and decreases the risk of future development of T2D in women with PCOS [8, 9]. Metformin is generally considered safe and it has received a pregnancy category B. Glueck at al. reported improvement of the pregnancy outcome after metformin treatment, without teratogenic or other side effects concerning both the physical, the motor as well as the social development of the newborn [10]. Metformin decreases fibrinolysis and enhanced thrombogenesis, resulting from IR by suppressing the action of the tissue plasminogen activator-1 (PAI-1) and de-
creasing the concentration of plasminogen activator type 1 (PAI-1) inhibitors [11]. Jakubowiez at al showed that the frequency of miscarriages decreased after treatment with metformin in pregnant women with PCOS [12].

OBJECTIVE

Assuming that IR may be one of the probable key mechanisms for the miscarriage, we supposed that the therapy with metformin before and during pregnancy decreases the frequency of SA in normoglycemic, hyperinsulinemic women with one previous SA.

STUDY DESIGN

This was a prospective, observational, case-control study type, comparing the pregnancy outcome in metformin treated group versus non-treated group in regard to miscarriages. The study population was ethnic Bulgarian patients, who achieved pregnancy for the second time after one previous SA. All patients attended the Clinical Institute of Reproductive Medicine, Pleven, Bulgaria, from May 2006 to May 2008 (n = 66).

SUBJECTS AND METHODS

Cases and controls. Before the beginning of the diagnostic procedure, all women were informed about the study and signed an informed agreement. The study was approved by the Local Ethic Board. The participants’ selection was done according to the following including criteria: age (range 18-35), BMI \( \leq 25 \) kg/m\(^2\), presence of a second, planed pregnancy with a previous history of one SA, defined as a pregnancy interruption before 12 weeks’ gestation. There were not disturbance of glucose tolerance before pregnancy, hyperandrogenemia, and PCOS. Excluding criteria were: PCOS, hyperglycemia before pregnancy, hormonal treatment of infertility, inherited or acquired thrombophilia, hyperandrogenemia, hormonal or immunological signs of thyroid autoimmune disease. Pregnant women were divided into two groups: non treated with metformin (Group 1; \( n_1 = 32 \)) and treated with metformin (Group 2; \( n_2 = 34 \)).

Diagnostic criteria. All women underwent a 75 g OGTT before pregnancy. The levels of BG in venous plasma and IRI in serum at 0, 60, and 120 min after glucose loading were measured. The BG results were interpreted according to the criteria of WHO [13]. The values of IRI during OGTT were used for diagnosing concomitant hyperinsulinemia. IRI levels at 0 min \( \geq 20 \) mUI/ml, at 60 min \( \geq 50 \) mUI/ml, at 120 min \( \geq 25 \) mUI/ml, were considered a manifestation of IR. All women with normal glucose tolerance and with IR were treated with metformin in a daily dose of 750 mg, administered in three applications of 250 mg. The metformin treatment was performed until the end of the pregnancy. All participants were given dietetic...
instructions for food intake with low rapid carbohydrate and high protein contents. All women took folic acid (1 mg per day) before and during pregnancy until delivery. During pregnancy, the pregnant women were advised to keep the dietetic instructions similar to the ones given before pregnancy.

All pregnancies were planned in advance applying a multidisciplinary team approach – obstetrician, immunologist and endocrinologist. Before the pregnancy, hormonal, immunologic and genetic examinations were performed to exclude the most frequent causes for pregnancy loss. These examinations include a thyroid and sex hormones analysis, including testosterone, anti-phospholipids and anti-thyroid antibodies, as well as DNA mutations, associated with inherited thrombophilia. The 75 g – OGTTs were repeated twice during pregnancy: between the 10–12 g.w. and the 34-36 g.w. Final OGTTs were performed in the women, whose pregnancies were terminated with miscarriage at the moment of pregnancy interruption. The change of BG and IRI during pregnancy, the frequency of miscarriages and the birth weight of the newborns were recorded. BG measurements were performed immediately after blood taking using the glucooxydases method in mmol/l on a gluco-analyzer: the Beckman’s apparatus, at a referent range of 3.7-5.5 mmol/l. The level of IRI was determined using electrohemoluminiscence method (ECLICA) by the analyzer Roche Elecsys 1010 for imunnoassays, in a referent range of 5.0-15 mUI/l. This test showed 0.05% from the crossed reactivity towards the intact human proinsulin and insulin.

All statistic analysis was done with the statistic panel SPSS for Windows version 11.0.1. The results are presented as an average value and their standard deviations (SD), which are to be signed as “mean ± SD” or n (%). The difference between the groups is determined by the two tailed Student’s t test and the Mann-Whithey’s test. ANOVA was applied for multiple comparison. Multivariate logistical regression analysis was used to assess the effect of IR, metformin and other risk factors, including age, BG and BMI. Adjusted odds ratio (OR) and its 95% confidence interval (CI) was calculated on the analysis. Statistical significance level of P < 0.05 was used.

RESULTS

The mean age of the pregnant women was 28.5 yrs, ranging from 23 to 34 yrs without significant difference between both groups. No women were overweights or obeses before pregnancy. The mean BMI in early pregnancy was 21 kg/m² ranging from 19 to 24 kg/m² similar for both groups. Fourteen patients of g₁ (43.8%) and eighteen of g₂ (52.9%) had a family history of type 1 diabetes or type 2 diabetes mellitus in the first and/or in the second generation.

Twenty-six (81.2%) women of g₁ and thirty-one (91.2%) women of g₂ carried their full term pregnancy. The metabolic characteristics evaluating the change in the BG level and IRI before and during pregnancy of women in the first group are
shown in Table 1. The mean values of BG at the end of first trimester were similar to those before pregnancy. The value of IRI increased significantly at beginning of the pregnancy, in 11 women (34.3%) IR was established in early pregnancy. The mean values of BG levels at the end of pregnancy were significantly higher in comparison with those in a non-pregnant state. Fifteen pregnant women (46.8%) have had different stage of carbohydrate intolerance: 11 of them (34.4%) were with IGT and 4 (12.5%) with GD. The IRI values in the late pregnancy increased significantly in all pregnant women compared to the early pregnancy. IR at the end of the pregnancy was proved in 26 pregnant women (81.2%); all of them had history for diabetes.

Table 1 shows also the changes in the mean values of BG and IRI for women of the second group, before and during pregnancy. In early pregnancy, there were no changes in the carbohydrate tolerance or in the IRI concentration in any of the pregnant women. The mean values of BG and IRI in early pregnancy were similar to the levels in a non-pregnant state. At the end of pregnancy, evidence for IGT and increased IR was established in five (14.7%) pregnant women, despite the metformin therapy. There was no case of GD.

The difference in metabolic parameters in the first and in the second group during pregnancy are shown in Table 2. There were no significant differences in BG levels after glucose loading in early and late pregnancy, but the concentrations of insulin were significantly higher in first group until pregnancy. There was significant difference in frequency of carbohydrate intolerance disturbances between both groups – 46.8% n₁ women vs. 14.7% n₂ women (P=0.03).

**Table 2. Changes in metabolic parameters of patients of first and second Group**

<table>
<thead>
<tr>
<th></th>
<th>Early pregnancy g₁ = 32</th>
<th>Early pregnancy g₂ = 34</th>
<th>Significance</th>
<th>Late pregnancy g₁ = 26</th>
<th>Late pregnancy g₂ = 31</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG-0 min.</td>
<td>5.1 ± 0.6</td>
<td>4.3 ± 1.2</td>
<td>NS</td>
<td>6.5 ± 1.2</td>
<td>5.5 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>BG-60 min.</td>
<td>7.9 ± 1.6</td>
<td>6.5 ± 1.8</td>
<td>NS</td>
<td>8.8 ± 1.9</td>
<td>8.1 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>BG-120 min.</td>
<td>7.4 ± 1.2</td>
<td>6.1 ± 0.6</td>
<td>NS</td>
<td>7.9 ± 1.3</td>
<td>7.4 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>IRI-0 min.</td>
<td>16.2 ± 8.5</td>
<td>11.4 ± 3.2</td>
<td>NS</td>
<td>22.2 ±12.9</td>
<td>17.2 ± 9.1</td>
<td>P=0.051</td>
</tr>
<tr>
<td>IRI-60 min.</td>
<td>56.8 ±12.8</td>
<td>23.3±12.4</td>
<td>P=0.02</td>
<td>93.8 ± 15.5</td>
<td>48.4 ±13.5</td>
<td>P=0.001</td>
</tr>
<tr>
<td>IRI-120 min.</td>
<td>37.3 ±10.3</td>
<td>15.3 ± 9.3</td>
<td>P=0.04</td>
<td>85.6 ± 23.7</td>
<td>31.5 ± 17.8</td>
<td>P=0.001</td>
</tr>
</tbody>
</table>

BMI rised in all of the pregnant women during pregnancy. Compared to the first group, the women in the second one had a significantly lower BMI in late pregnancy (g₁ = 31.5 ± 4.2 kg/m² vs. g₂ = 26.8 ±3.6 kg/m²; P = 0.01). The highest weight gain during pregnancy was observed in pregnant women with IGT which belong to first group. The observed differences in the BMI mean values between the pregnant women with IGT in both groups were significant (g₁ = 30.6 ± 2.1 kg/m² vs. g₂ = 28.3 ± 2.4 kg/m²; P = 0.02).
Of all sixty-six observed pregnancies 57 (86.4%) were successfully terminated. There were no observed obstetrical complications as pregnancy induced hypertension, preeclampsia, preterm deliveries or infections in any one of them. The estimated rate of live births of newborns was 86.4%. There was no case of prenatal death or congenital anomalies in both groups. The mean weight of the newborns was $3.580 \pm 381.3$ g. There was no difference between the weight of newborns in both groups ($g_1 = 3.600.9 \pm 343.5$ g.; $g_2 = 3.460.3 \pm 408.9$ g.; $P = 0.6$). There was no newborn with macrosomia (> 4.000 g).

The overall SA rate was 13.6% (9 out of 66). There was a significant difference in miscarriage rate between the two groups: 18.75% (6 out of 32) in the first group and 8.82% (3 out of 34) in the second group ($P=0.02$). Women with miscarriages had equal levels of BG and IRI at the moment of fetal lost (table 3). There was no significant difference in BG levels in early pregnancy between women with miscarriages and women with successfully terminated pregnancy, but the concentrations of insulin measured at 60 and 120 min after glucose loading were significantly higher in women with miscarriages comparing to those without miscarriages [(IRI measured at 60 min in SA group = 72.7 ± 6.6 mIU/ml vs. IRI at 60 min in non SA group = 40.0 ± 12.6 mIU/ml; $P=0.001$ ) and IRI measured at 120 min in SA group = 48.5 ± 12.6 mIU/ml vs. IRI at 120 min in non SA group = 26.3 ± 9.8 mIU/ml; $P=0.001$)].

<table>
<thead>
<tr>
<th></th>
<th>Miscarriage $g_1=6$</th>
<th>Miscarriage $g_2=3$</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG-0 min.</td>
<td>5.6 ± 0.4</td>
<td>5.2 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>BG-60 min.</td>
<td>8.1 ± 0.3</td>
<td>8.8 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>BG-120 min.</td>
<td>7.1 ± 0.6</td>
<td>6.9 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>IRI-0 min.</td>
<td>12.8 ± 6.2</td>
<td>10.3 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>IRI-60 min.</td>
<td>76.6 ± 8.3</td>
<td>68.5 ± 6.3</td>
<td>NS</td>
</tr>
<tr>
<td>IRI-120 min.</td>
<td>49.7 ± 9.5</td>
<td>48.2 ± 4.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Risk factor analysis of the miscarriage occurrence did not determine relationship among the age, the BG levels and the BMI in early pregnancy. A relationship was determined only between the IRI measured at 60 and 120 min in early pregnancy. Pregnant women with IRI levels over 50 mIU/ml at 60 min had a significantly higher risk for SA in comparison with those who had normal level of IRI, proved by the model of logistic regression (OR = 4.9 ; CI. 2.1-19.3). Patients with IRI levels
over 40 mIU/ml at 120 min also have a significantly higher risk for miscarriages (OR =3.4; 95% CI, 1.7- 5.1).

**DISCUSSION**

All pregnancies observed by us were preplanned for excluding the most frequent causes for miscarriages. Familial history for diabetes mellitus and absence of strong reasons for fetal loss established the implementation of OGTT. The results of this study indicated, that the risk for miscarriage is positively related to the IRI levels in early pregnancy. Pregnant women with IRI higher than 40 mIU/ml have a four times higher risk for SA that of those with IRI of 40 mIU/ml or less. IRI is an independent risk factor for pregnancy loss, no matter which BG level and weight gain during pregnancy. The finding that IR is a possible risk factor for SA within the Bulgarian population gave an important information and helped us to propose a new diagnostic and prophylactic approach. The criterion adopted by us for IR – levels of IRI higher than normal during OGTT – is less precise than the euglycemic clamp but is well standardized, economical, not very invasive and easily applicable for outpatients.

Although all the specific pathophysiologies of pregnancy losses in normal women remain unknown, we suggest that decreasing of the glucose-induced insulin secretion by insulin sensitizers such as metformin will reduce the rate of miscarriages among women with one previous SA. The obtained results revealed that the rate of SA could be reduced after medication to 8.8%.

Probably this is only the first of many reports showing the direct relationship between the exact IR levels and the risk of SA. A similar risk definition but with HOMA IR without using euglycemic clamp was performed by Tain Li et al in women with prior sterility and applied assistant reproductive technique [14]. The author reported that HOMA IR higher than 4.5 increased eight times the risk for miscarriage in women with overweight or PCOS.

Chronic hyperinsulinemia in women with PCOS is at the root of obesity, thrombosis of placental capillaries, abnormal endometrial growth and functioning during implantation. Apart of these mechanisms, IR decreases the production of two specific proteins, the glycodelin and the IGR- binding protein-1 (IGF-BP1), which are secreted by endometrium and play an important role in the endometrial receptivity during implantation and early pregnancy. Glycodelin inhibits the immunity response of the endometrium to the embryo by blocking the mixed lymphocyte reaction and the NK (natural killer) cell activity. IGF-1BP accelerates the process of adhesion and maternal-fetal interaction during the preimplantation period [15]. The pathophysiology of miscarriage in insulin resistant women without PCOS is unwell-studied. Hyperinsulinemia increases PAI-1 levels [16, 17] and may cause placental bed thrombosis in women with recurrent pregnancy loss without gene defects for thrombophilia [18].
In conclusion, IR plays a critical role in the etiology of SA in hyperinsulinemic women. Medication with metformin reduces hyperinsulinemia and decreases the frequency of miscarriages to 8.8% without side effects on the fetal growing. In the future, a large, randomized prospective study would be necessary to clarify the possible mechanisms on how IR may cause SA in hypeinsulinemic women without PCOS. Moreover, future studies are needed to determine the equality of different insulin sensitizing drugs in decreasing miscarriage in normoglycemic women without PCOS.

Acknowledgements

We thank all the mothers who collaborated in the study

REFERENCES

19. Velazquez, E. et al. Metformin therapy is associated with a decrease in plasma plasminogen activator inhibitor-1, lipoprotein (a), and immunoreactive insulin levels in patients with the polycystic ovary syndrome. – Metabolism, 46, 1997, 454-457.

Address for correspondence:
Katya Todorova – Ananieva MD, PhD
High Risk Pregnancy Department
Specialized Hospital of Obstetrics and Gynecology
2 Zdrave Str.
1431, Sofia, Bulgaria
00359 2851 7222
00359 2851 7222
e-mail: todorova_kate@abv.bg
PHARMACOECONOMIC ANALYSIS FOR THE FUTURE TREATMENT OF DIABETES MELLITUS AFTER GESTATIONAL DIABETES

Katya Todorova-Ananieva

Specialized Hospital of Obstetrics and Gynecology, Medical University – Sofia, Bulgaria

Summary. The research aims to outline the risk of developing diabetes mellitus (DM) during the first year after giving birth for women with previous gestational diabetes mellitus (GDM), as well as to estimate the social efficiency value of the applied prophylactic method. A study has been performed among 50 women, with GDM for one year after delivery. During that period, a prophylactic program has been applied for DM prevention. The social efficiency of the applied prophylactic method is presented using the “decision tree” model. All indirect costs for future DM treatment are presented, as well as calculations are given for the added years of life with invalidity (DALY). DM has been observed at 13 (or 26%) out of 50 women with previous GDM in the first year after birth delivery. The total costs per women for the applied preventative programme have been calculated at 12.1€. The total annual expenses for treatment and control of a women with T2 DM and good metabolic control are 98.9€, for satisfying metabolic control – 122.1€ and for bad metabolic control – 241.8€. The total annual expenses for treatment and control of one women with T1 DM and good metabolic control are 241.8€, for satisfying metabolic control – 303.7€, and for bad metabolic control – 119.5€. The social cost of late diagnosed or complicated T2 DM is 10,994.80€. The cost for the complicated T1 DM treatment is 20,979.38 € at 5% discount. The rate of DALY also varies according to the rate of diabetic complications. The calculated DALY for women with DM at stage of disability are: – 10.1 year for women with DM with no complications, 12.1 years for women with DM and a mild rate of complications, 13.6. r. – years for women with DM and with moderate complications and 15.1 years for women with DM and a severe rate of complications. Future DM treatment costs depend entirely on the extent of metabolic compensation, probability for later complications and the method of treatment. However, the prophylactic screening of the women with previous GDM can considerably save these costs.

Key words: pharmacoeconomy, gestational diabetes, pregnancy, DALY
INTRODUCTION

Women in reproductive age are known to have higher medical expenses than men. This financial difference is mainly due to the financial expenses women have for the medical care during pregnancy, after birth delivery and in case of possible complications.

Gestational Diabetes Mellitus (GDM) is a heterogenic disease characterised by spoiled carbohydrate tolerance only during pregnancy. Although GDM influences women’s health for a very short period of their lives, it could have extremely harmful effects on their overall and reproductive health conditions.

Research in the field of epidemiology shows that approximately 50% of all women with GDM develop diabetes melitus (DM) within a ten-year period after birth delivery and usually within the first five years of that period. The other 50% with previous GDM may never develop DM [7, 11]. Recent research shows that the risk for developing DM after having had GDM could be lowered by changing the lifestyle of the patients [2, 11]. The frequency of late diagnosed DM and the frequency of not found diabetic malformations and complications in patients with GDM could be decreased by performing an annual DM screening [11].

Recently, there has been a rising interest towards pharmacoeconomic analysis in the field of DM, but there has been hardly research done in the field of costs and expenses for DM prevention after GDM.

There is a need for controlled epidemic and pharmacoeconomic research concerning women with previous GDM. Despite the complexity of such research, it has high prospective due to the provided opportunity for the disease’s diagnosis, evolution and GDM prevention possibilities. This kind of research would provide information about expenses for the DM prevention including prophylactic care, control of the risk factors for DM in the postnatal period and expenses concerning a different lifestyle of the patient [11].

The aim of the following research is to study the frequency of DM during the first year after giving birth of women with previous GDM in order to determine the social effectivity of the applied prophylactic strategy.

MATERIALS AND METHODS

A study has been performed among 50 women, where GDM has been observed; the women have been hospitalized and have given birth at the University Maternity Hospital, Sofia for the period January 2002- January 2005.

The pregnant women with GDM have been divided into two groups according to the treatment method during pregnancy: the first group is of pregnant women treated with a diet (n₁ = 30 women) and the second group is of pregnant women treated with insulin (Humulin R® HM и Humulin N® HM) (n₂ = 20 women).
The observed 50 women have been regularly tested during the first year after giving birth.

**Applied method:** Immediately after having given birth, there has been a prophylactic program applied to all women with found GDM, the aim of which is prevention of type two DM (T2 DM). This prophylactic program has been governed by an endocrinologist and compiles of the following actions: advice of dietary regimen, reduction of body weight and lifestyle alternation. For the prevention of occuring of DM by women with a body mass index (BMI) over 25 kg.m\(^2\) there has been a metformin – prevention therapy applied. There has been a DM-screening performed for all women after the first year after giving birth via oral glucose tolerance test (OGTT) with 75.0 glycosis. The metabolic status has been evaluated according to the criteria of the WHO [12].

The social efficiency of the applied prophylactic strategy is shown via the model “decision tree”, which shows the value of a future DM treatment for women with previos GDM according to the rate of complications, the rate of metabolic control, the possibility of malformations and the financial costs of the treatment.

Two final results have been used for the “decision tree” – treatment efficiency and treatment non-efficiency. The efficiency is determined by the level of the glycosilated hemoglobin (HbA1-c), where the critical limit value has been set to be HbA1-c < 7%. Each branch shows the possibilities of future complications as a function of the metabolic control; the total sum always equals 1. The shown in the model possibilities for treatment efficiency are own results and the possibilities for the development of diabetic complications have been taken from medical literature [5, 6]. The relative risk for the occurance of diabetic cardiac complications, described at the research projects DCCT and UKPDS, observed at patients with 10-12 years of diabetes and treated with intensified and conventional insulin regimen, have been used in the model (32, 44).

In the development process of the prognosing method of diabetes treatment, the whole process of the disease propagation has been followed and the direct medical expenses for each complication have been determined. They include the value of hospital and ambulatory treatment according to prices set by the National Health Insurance Company (NHIC) for the year 2003.

An additional analysis which predicts the possible complications in the following 15 years after birth delivery and the monetary value of their treatment has been done. The indirect costs of the future DM treatment have been determined as well. The calculations are based on the determination of life quality loss due to DM [9, 13]. Additionally, the DALY (disability adjusted life years) due to the predicted DM complications are calculated using two factors: YLL (years lost life) due to early death and YLD (years lost due to disability).
DALY is the sum of YLL and YLD.

YLL is the difference between the expected life span of women with diabetes and the expected death age for the women with DM. This has been done with the help of statistical data representing the expected average life span of women in reproductive age till 20, between 20 and 30 and between 30 and 40 years of age [3].

The YLD is the multiplication of the factor burden (of the pregnancy) and years life with diabetes in the stage invalid. The age limit after which invalidisation inevitably follows is considered to be 15 years [6,13].

The performed analysis shows the perspective of costs and profits from two different points of view: the doctor’s point of view and the society’s one.

To verify the obtained results, there has been a sensitivity analysis performed by which the final result has been reconsidered again after varying the input parameters [10]. The model is considered more reliable when change in the input does not influence the final results.

There is a 5% annual discount considered due to expected changing life standard [1].

For the purposes of this paper and under conditions of a Currency board in Bulgaria, the used fixed exchange rate throughout the text is 1.94 Bulgarian leva for 1 EUR.

**RESULTS**

*Postnatal DM frequency:*

DM has been observed at 13 (or 26%) out of 50 women with previous GDM in the first year after birth delivery.

The number of patients with newly developed DM is 0.14% of the whole number of patients after birth delivery (total 9182) at the University Maternal Hospital for the period 2003-2005.

T2 DM (Non-insulin-dependent DM) has been observed at 7 (23.3%) women, out of 30 with GDM treated with diet. T1 DM (Insulin dependent DM) has been observed at 6 (30%) women out of 20 with GDM treated with insulin ($P=0.74$).

The average age of women with newly found DM is 25.6 ± 1.78 years of age and it statistically differs from the average age of women without DM 24.1 ± 1.02 years of age ($P = 0.04$).

The calculated BMI of women with DM is 26.34 ± 2.12 kg. b. w./m$^2$ and it does statistically differ from the BMI value of women without DM, or 23.56 ± 2.37 kg. b. w./m$^2$ ($P=0.003$). Five of the women with newly observed DM have first – line relatives suffering from DM, the other seven have second- or third–line relatives with DM. For seven of the women, there has been a per oral metformin therapy performed 3 times 425 mg daily, for the other six there
was an intensified insulin therapy performed (Humulin N® и Humalog®) as a basal prandial regime.

Based on the costs of NHIC, the value of the applied preventive program has been calculated. The average cost per woman is 12.1€, resp. 5.9€ for OGTT and 6.1€ for consulting an endocrinologist (for 50 women – 605.6€).

The annual preventive metformin therapy costs – 52.5€ per person.

The annual basis insulin treatment costs – 141.3€ per person.

The cost of consultations by a GP, endocrinologist and ophthalmologist are 23.1€ and their frequency is once to three times a year, according to the rate of metabolic compensation. The laboratory costs are 25.7€ for the women with T2 DM and 38.6€ for the women with T1 DM; and their frequency is once to three times a year, according to the rate of metabolic compensation. The price of a single examination of the eyes at women with T1 DM including fundus-photography is 38.6€.

Table 1 shows the expenses for diabetes treatment and control of the studied women according to the NHIC. These expenses include the consulting and laboratory costs.

Table 1. Annual expenses for DM treatment and control as a function of the metabolic control rate at women with previous GDM

<table>
<thead>
<tr>
<th>Metabolic control</th>
<th>T1 Diabetes mellitus (n = 6)</th>
<th>T2 Diabetes mellitus (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Нв А1-c &lt; 7</td>
<td>725.5€ (n = 3)</td>
<td>395.8€ (n = 4)</td>
</tr>
<tr>
<td>Нв А1-c &gt; 7&lt; 8</td>
<td>841.7€ (n = 2)</td>
<td>244.3€ (n = 2)</td>
</tr>
<tr>
<td>Нв А1-c &gt; 8</td>
<td>365.5€ (n = 1)</td>
<td>93.8€ (n = 1)</td>
</tr>
<tr>
<td>Total</td>
<td>1698.5€</td>
<td>734.0€</td>
</tr>
</tbody>
</table>

The total annual expenses for treatment and control of a woman with T2 DM and good metabolic control is 98.9€, for satisfying metabolic control – 122.1€ and for bad metabolic control – 241.8€.

The total annual expenses for treatment and control of one woman with T1 DM and good metabolic control is 241.8€, for satisfying metabolic control – 303.7€, and for bad metabolic control – 119.5€. The total cost of the complications' treatment and the most probable microvascular and macrovascular complications expected after a 15-year period of DM at women with prior GDM and bad metabolic control has been calculated (Table 2).
### Table 2. Costs for future treatment of DM complications at women with previous GDM

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic treatment</td>
<td></td>
<td>365.5</td>
<td>515.4</td>
<td>628.8</td>
<td>529.7</td>
<td>421.3</td>
<td>969.0</td>
<td>798.9</td>
<td>1768.0</td>
<td></td>
</tr>
<tr>
<td>MAU+DR +ACE</td>
<td>0.27</td>
<td>0</td>
<td>324.7</td>
<td>386.5</td>
<td>0</td>
<td>0</td>
<td>556.7</td>
<td>386.5</td>
<td>0</td>
<td>0.55</td>
</tr>
<tr>
<td>Heart Attack</td>
<td>0.01</td>
<td>2731.9</td>
<td>3056.7</td>
<td>3118.5</td>
<td>3443.2</td>
<td>3144.3</td>
<td>4113.4</td>
<td>3943.2</td>
<td>4912.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.01</td>
<td>2731.9</td>
<td>3056.7</td>
<td>3118.5</td>
<td>3443.2</td>
<td>3144.3</td>
<td>4113.4</td>
<td>3943.2</td>
<td>4912.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Amputation</td>
<td>0.27</td>
<td>721.6</td>
<td>1046.3</td>
<td>1108.2</td>
<td>1432.9</td>
<td>1134.0</td>
<td>2103.0</td>
<td>1932.9</td>
<td>2902.0</td>
<td>0.55</td>
</tr>
<tr>
<td>Uremia</td>
<td>0.41</td>
<td>2577.3</td>
<td>2902.0</td>
<td>3288.5</td>
<td>3479.3</td>
<td>2989.6</td>
<td>3958.7</td>
<td>3788.6</td>
<td>4757.7</td>
<td>0.82</td>
</tr>
<tr>
<td>Blind</td>
<td>0.12</td>
<td>984.5</td>
<td>1309.2</td>
<td>1371.1</td>
<td>1695.8</td>
<td>1396.9</td>
<td>2365.9</td>
<td>2195.8</td>
<td>3268.0</td>
<td>0.24</td>
</tr>
<tr>
<td>Severe Hypoglycaemia</td>
<td></td>
<td>618.5</td>
<td>618.5</td>
<td>1005.1</td>
<td>1329.8</td>
<td>1030.9</td>
<td>2000</td>
<td>1829.8</td>
<td>2798.9</td>
<td></td>
</tr>
<tr>
<td>Ketoasidosis</td>
<td></td>
<td>438.1</td>
<td>438.1</td>
<td>824.7</td>
<td>850.5</td>
<td>850.5</td>
<td>1768.0</td>
<td>1649.4</td>
<td>2618.5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.09</td>
<td>11 169.3</td>
<td>11958.4</td>
<td>13844.8</td>
<td>16204.4</td>
<td>13690.5</td>
<td>13948.1</td>
<td>3479.2</td>
<td>27936.8</td>
<td>2.58</td>
</tr>
</tbody>
</table>

Abbreviations used: D.R. – Diabetic Retinopathy, A.H. – Arterial Hypertension; MAU – Microalbuminuria; ACE – Angiothensin Converting Enzymes Inhibitors
The obtained results have been used for the development of a hypothetical model (fig. 1) that shows the total expenses for a future DM treatment according to the type of DM (T1 DM and T2 DM), the rate of metabolic compensation (good or bad metabolic control) and the presence of vascular complications (diabetic micro- and macrovasculopathy).

![Diagram](image)

**Fig. 1.** Future expenses for DM treatment in the model of “Decision tree”

The two branches of the “decision tree” show the future expenses for the treatment of T2 DM (upper branch) and T1 DM (lower branch). The other upper branches show the possibilities for achieving a good metabolic control and the costs of DM treatment with no complications. The lower branches show the possibilities for bad diabetic compensation and its costs with already presented complications.

The applied to the final result sensitivity analysis does not show any sufficient difference among the final values after varying the possibilities for occurrence of T1 DM or T2 DM. However, the analysis shows difference between the expenses for the best and the worst relative part – 965.70€ and between the expenses for the worst and the present relative part – 850.7€ (table 3).
Table 3. Result sensitivity analysis

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>sensitivity</td>
</tr>
<tr>
<td>P1</td>
<td>P2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>3658.63</td>
</tr>
<tr>
<td>0.9</td>
<td>0.1</td>
<td>3452.31</td>
</tr>
<tr>
<td>0.8</td>
<td>0.2</td>
<td>3246.00</td>
</tr>
<tr>
<td>0.7</td>
<td>0.3</td>
<td>3039.69</td>
</tr>
<tr>
<td>0.6</td>
<td>0.4</td>
<td>2833.37</td>
</tr>
<tr>
<td>0.566</td>
<td>0.434</td>
<td>2763.23</td>
</tr>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>2627.06</td>
</tr>
<tr>
<td>0.4</td>
<td>0.6</td>
<td>2420.75</td>
</tr>
<tr>
<td>0.3</td>
<td>0.7</td>
<td>2214.43</td>
</tr>
<tr>
<td>0.2</td>
<td>0.8</td>
<td>2008.12</td>
</tr>
<tr>
<td>0.1</td>
<td>0.9</td>
<td>1801.81</td>
</tr>
</tbody>
</table>

Expenses difference -965.70

Between the best and the worst relative part

Expenses difference -850.7

Between the worst and the present relative part

In order to keep the data up to date, there has been a discount method applied with a 5% discount rate. After a period of 11 years – time when the DM complications are expected, this would correspond to 61% of the current cost (table 4).

The indirect costs have been calculated through DALY with DM by stepwise determination of YLL and YLD.

The YLL at women with previous GDM due to early death is 9.1 years.

The weight of DM varies with the complication rate. The weight of the disease with no complications is 0.07, of the disease with mild rate of complications is 0.2, of the disease with moderate complications is 0.3 and with a severe rate of complications -0.4 [22].

The lost years of quality life vary as well, according to the metabolic compensation and the rate of diabetic complications.
Women with no complications and good metabolic control would have just a year of quality life lost. YLD of women with DM is 1.0 year for women with DM with no complications, 3.0 years for women with DM and a mild rate of complications, 4.5 years for women with DM and with moderate complications and 6.0 years for women with DM and a severe rate of complications.

The rate of DALY also varies according to the rate of diabetic complications. The calculated DALY for women with DM at stage of disability are: – 10.1 year for women with DM with no complications, 12.1 years for women with DM and a mild rate of complications, 13.6 years for women with DM and with moderate complications and 15.1 years for women with DM and a severe rate of complications (fig. 2).

**Table. 4. Model of Discounting**

<table>
<thead>
<tr>
<th>Total expense</th>
<th>r</th>
<th>0.03</th>
<th>0.05</th>
<th>0.08</th>
<th>0.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>734.18€ year</td>
<td>€</td>
<td>€</td>
<td>€</td>
<td>€</td>
<td>€</td>
</tr>
<tr>
<td>1</td>
<td>1382.86</td>
<td>1356.52</td>
<td>1318.84</td>
<td>1283.20</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2725.44</td>
<td>2648.44</td>
<td>2539.98</td>
<td>2439.23</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4028.92</td>
<td>3878.85</td>
<td>3670.68</td>
<td>3480.70</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5294.43</td>
<td>5050.66</td>
<td>4717.61</td>
<td>4418.95</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6523.08</td>
<td>6166.67</td>
<td>5687.00</td>
<td>5264.23</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>7715.95</td>
<td>7229.54</td>
<td>6584.58</td>
<td>6025.75</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>8874.07</td>
<td>8241.79</td>
<td>7415.67</td>
<td>6711.79</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>9998.46</td>
<td>9205.85</td>
<td>8185.20</td>
<td>7329.86</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>11090.11</td>
<td>10123.99</td>
<td>8897.73</td>
<td>7886.67</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>12149.95</td>
<td>10998.42</td>
<td>9557.47</td>
<td>8388.30</td>
<td></td>
</tr>
</tbody>
</table>

*Fig. 2. Prognosis for YLD and DALY at women with previous GDM*
DISCUSSION

The total cost of our profiling program for women with previous GDM is 12.1€. The cost of late diagnosed or complicated T2 DM is 1097.9€. The cost for the complicated T1 DM – treatment is 20 979.38€. Prophylactic program of women with previous GDM may save these expenses. The expenses for future DM treatment depend on the metabolic compensation, the chance for complication occurrence and the way of treatment.

This is a first-of-the-kind national prognoses pharmacoeconomic research performed within women with previous GDM, in a reproductive age and with a high diabetic risk. It shows the disease’s frequency and the expenses for the applied prophylactic program for DM prevention and early diagnosis. The obtained results show that the possibility for DM occurrence within the observed group depends on three risk factors: over 25 years of age, BMI over 25 kg. b.w./m² and presence of relatives suffering from DM. These results have been already discussed by other authors [8, 14].

The included in the analysis microvascular (nephropathy, retinopathy) and macrovascular diabetic complications can have different development stages, up to end organ stage – renal insufficiency, blindness and gangrene. The treatment costs vary according to the frequency, complications and lasting of the observed complications. The costs significantly increase with the presence of combined complications, especially if there are in an end organ stage. Macrovascular complications – heart attacks and stroke can be a direct death reason.

The developed model “decision tree” shows the possibility to predict future expenses within further periods of time. It could be multiply applied only after changing the input data parameters: disease, frequency of the observed complications, treatment costs. Moreover, the model allows a comparison among results obtained by other research projects or even comparison to real-life conclusions. Yet, there is no overall research project presented in the literature that summarizes the results from all resource inputs and the output net value of the treatment of women with previous GDM [8].

Gregory [3] presents an economic model for saving expenses by reducing the frequency of T2 DM DM via changing the lifestyle of women with GDM. He considers the progression frequency of T2 DM a constant value of 6.7% per year for a future ten-year period of time. The determined average annual DM treatment costs for the year is 2 834 USD with a discount of 5%. These expenses could be saved by changing the lifestyle in the following way: $29 for a dietologist consultation and $2,0 for annual blood glucose check [3].

Based on the presented economic model, Gregory considers that a prophylaxis strategy could reduce the T2 DM occurrence with frequency 10% per year and thus 231.8 million USD from the whole sum for treatment of women with previous GDM can be saved, which corresponds to 254. 8 USD per woman.
Women with DM have an expected life span by 9.1 years less. DALY with DM in correspondence to the indirect costs concerning the disease’s weight DALY varies according to the type and severity of diabetes and the presented complications. The corresponding expenses for treatment of end-stage diabetic complications can be obeyed only by early DM diagnosis.

REFERENCES

2. Веков, Т. Основи на управлението в България. Избрани лекции. 2008.
5. Основни резултати от изследването на здравното състояние на населението в България през месец март 2001 година и някои сравнения с данни от предходни изследвания. (http://www.nsi.bg/Census/).


Adress for correspondence:
Katya Todorova
High Risk Pregnancy Dep.
SHATOG “Maichin dom”
2 Zdrave Str.
1431 Sofia Bulgaria
+ 359 2 851 72 22
e-mail: toodorova_kate@yahoo.com
LASER-INDUCED AUTOFLUORESCENCE SPECTROSCOPY OF BASAL CELL CARCINOMA AND PAPILLOMA OF EYELIDS AND COMPARISON WITH THE RESULTS FROM THE HISTOLOGICAL INVESTIGATION

K. Koev\textsuperscript{1}, E. Borisova\textsuperscript{2} and L. Avramov\textsuperscript{2}

\textsuperscript{1}Alexandrovska University Hospital – Sofia
\textsuperscript{2}Institute of Electronics, Bulgarian Academy of Sciences – Sofia

Summary. Aim of the study was investigation and differentiation of normal eyelid skin and basal cell carcinoma and papilloma of eyelids with the method of laser-induced autofluorescence spectroscopy, and comparison with the results from the histological analysis of the tissues. 18 patients with basal cell carcinoma of eyelids and 12 patients with papilloma of eyelids were investigated. The method of laser-induced autofluorescence spectroscopy (LIAFS) was applied. Spectrometer S2000 produced by the company Ocean Optics was used. Nitrogenous laser with wavelength 337 nm was used for fluorescence excitation. Following the excision of the tumors, the materials were investigated histologically by standard methods. Two maximums of autofluorescence were observed from the normal eyelid tissue, respectively at 440 and 490 nm, due to the respective emission from the basic endogenous fluorophores in the skin: NADH and collagen. We ascertained identity between the clinical diagnoses of basal cell carcinoma and papilloma of the eyelid and the histological tests made after the extirpation. We registered increase of the intensity of the fluorescent signal in the sections affected by basal cell carcinoma and papilloma of the eyelid. In all cases of basal cell carcinoma of the eyelid, we established a new spectral component in the 400 nm range, and increase of the amplitude of fluorescence. There was a good correlation between the results from the histological analysis and the changes in the fluorescence spectra in cases of basal cell carcinoma and papilloma of eyelids. The potentials of fluorescence spectroscopy as a method for early diagnostic of tumor growths were demonstrated.

Key words: laser-induced autofluorescence spectroscopy, basal cell carcinoma and papilloma of eyelids
INTRODUCTION

Spectroscopic methods are used for determination of the functional condition of the examined tissue and for diagnosing various diseases at an early stage of their development [1]. Laser fluorescence spectroscopy can provide important diagnostic information about tissues. Tissues' own fluorescence is used or exogenous chromatophores are introduced [2]. As tumors are characterized by specific concentrations of certain substances, therefore they could be distinguished from healthy tissues by using the examined fluorescent spectra. So far, laser-induced autofluorescence spectroscopy has not been used in Bulgaria for the purposes of diagnosing eyelid tumors.

PURPOSE

Investigation and differentiation of normal eyelid skin and basal cell carcinoma and papilloma of eyelids with the method of laser-induced autofluorescence spectroscopy, and comparison with the results from the histological analysis of the tissues.

MATERIAL AND METHOD

18 patients with basal cell carcinoma of eyelids and 12 patients with papilloma of eyelids were investigated. The method of laser-induced autofluorescence spectroscopy (LIAFS) was applied. For this purpose, an integrated laser-induced autofluorescence diagnostic channel for eye tumors was constructed. The laser-induced auto fluorescence system was constructed on the basis of:
1. Nitrogenous laser generating emission with wavelength 337 nm;
2. Optical light guide for excitation emission;
3. Optical light guide for fluorescent response;
4. Small-sized optical fiber spectrometer consisting of a dispersing element - diffraction grating;
5. CCD-detector with ruler with 2048 elements;
6. A/D converter;
7. Operation software.

Spectrometer S2000 produced by the company Ocean Optics was used. The spectrometer is high sensitive in the UV-, the visible and the near infrared ranges of the optical spectrum. The system has a spectral resolution of 8.5 nm and a high sensitivity by intensity, and responds even to very slight signals, such as signals received from the eyelid skin and from the other eye structures.

Nitrogenous laser with wavelength 337 nm was used for fluorescence excitation. The monitor unit was made on a PC basis with the following characteristics:
All tumors were excised. Following the excision of the tumors, the materials were investigated histologically by standard methods.

RESULTS

Two maximums of autofluorescence were observed from the normal eyelid tissue, respectively at 440 and 490 nm, due to the respective emission from the basic endogenous fluorophores in the skin: NADH and collagen.

The obtained changes in the short-wave spectrum range and in the intensity of the fluorescent signal of normal eyelid skin, basal cell carcinoma and papilloma of eyelids – were used as a diagnostic criterion for determination of the condition of the tissue – correlation between the intensities of fluorescent signals: \( R_1 = \frac{1385}{1490}, \ R_2 = \frac{1400}{1490}, \ R_3 = \frac{1400}{1490} \).

We ascertained identity between the clinical diagnoses of basal cell carcinoma and papilloma of the eyelid and the histological tests made following the extirpation.

We registered increase of the intensity of the fluorescent signal in the sections affected by basal cell carcinoma and papilloma of the eyelid. In all cases of basal cell carcinoma of the eyelid we established a new spectral component in the 400 nm range, and increase of the amplitude of fluorescence. The same does not exist in the signal of a healthy skin.

We ascertained a new spectral component in the 500-520 nm range in all cases of papilloma of the eyelid, and increase of the amplitude of fluorescence. The same does not exist in the signal of a healthy skin either.

DISCUSSION

Some of the substances have their own fluorescence, and with excitation with appropriate light, their spectrum can be analyzed.

With laser-induced autofluorescence, fluorescent signal is received from the tissue without use of exogenous chromophores [3]. It is used for diagnosing tumors in various organs. The following endogenous fluorophores are used as sources of cellular fluorescence: tryptophan, reduced form of nicotinamid dinucleotide (NADH), the oxidized form (NAD) and oxidized forms of riboflavins.

For diagnostic purposes, some authors [4] apply laser-induced autofluorescence for the study of normal and neoplastic cells and tissues for determination of the spectral differences. Three endogenous fluorophores, sources of cell fluorescence, were used: tryptophan (Trp), reduced form of nicotinamid dinucleotide
(NADH), and oxidized forms of riboflavins. Eximer laser with wavelength 308 nm was used for excitation, respectively for Trp r and NADH, N2-laser with wavelength 337 – for excitation of NADH, and cumarin dyeing laser with wavelength 480 – for the flavin. In our investigation, in order to obtain laser-induced autofluorescence, we used nitric laser generating emission with wavelength 337 nm.

Some authors [5] investigate human skin on the basis of an autofluorescence signal received from NADH, pyridine nucleotides and flavoproteins, which are the most common fluorophores in the skin; by using the method of biphoton excitation in the UV spectrum range.

In contrast to the laser-induced autofluorescence of a healthy skin, we observed shift and increase of the autofluorescence amplitude in the 400 nm range in cases of basal cell carcinoma, and in the 500-520 nm range in cases of eyelid papilloma, proved with results from the histological analyses of the same.

**CONCLUSION**

There was a good correlation between the results from the histological analysis and the changes in the fluorescence spectra in cases of basal cell carcinoma and papilloma of eyelids. The potentials of fluorescence spectroscopy as a method for early diagnostic of tumor growths were demonstrated.

**REFERENCES**


**Address for correspondence:**
Dr. Krassimir Koev, PhD
Clinic of Ophthalmology
Aleksandrovska Hospital
1 Sv. G. Sofiiski str.
1431 Sofia
836-55-04
e-mail: sofia56@abv.bg
PHYSIOLOGICAL MECHANISMS CONTROLLING CARDIOVASCULAR RESPONSES TO MUSCULAR STATIC LOAD

R. Nikolova¹, E. Vodenitcharov² and N. Tzacheva³

¹National Center of Public Health Protection, Laboratory for Work Physiology and Psychology — Sofia
²Medical University, Faculty of Medicine, Department of Hygiene, — Sofia
³University Hospital “Tzaritza Joanna”, Faculty of Public Health, Department of Occupational Medicine — Sofia

Summary. A review synopsis of physiological mechanisms controlling cardiovascular responses to muscular static (isometric) load is presented. Muscular static load during work activity is associated with development of disorders of the musculoskeletal system known as repetitive strain injuries, cumulative trauma disorders or activity and work-related musculoskeletal disorders. One of the basic topics of occupational and physiological research is investigation of the mechanisms underlying induced cardiovascular responses to muscular static load. Static muscular load might affect most of the physiological cardiovascular responses, such as heart rate, cardiac cycle length, arterial pressure. Cardiovascular responses vary with the intensity of muscular exertion and contraction, and are part of processes that occur to adapt the circulation to the skeletal muscles’ need of blood. Reflex mechanisms that mediate circulatory changes during static muscular contraction, stimuli that initiate the reflex mechanism, and nerve structures which compose the reflex arc are indicated.

Key words: static load, isometric contraction, cardiovascular responses, reflex mechanisms, musculoskeletal disorders, health risk

Research studies indicate that human activity is associated with performance of muscular static work. Several main demands must be met: moving the body or its parts, transporting or moving other objects, and maintaining the body posture. Muscular loading during intensive work activity has been linked to the development of disorders of the musculoskeletal system known as repetitive strain injuries, cumulative trauma disorders or activity and work-related musculoskeletal disorders. Static muscular load is associated with muscle fatigue,
pain and myalgia. When exposed to demands of performing static muscular load, the human body responds with complex series of reactions, leading to muscular exercise. The muscle contraction is the end point of reactions taking place in the sensory organs, the brain, nervous system, heart, blood vessels, lungs, and musculoskeletal systems.

One of the basic topics of occupational and physiological research is investigating the mechanisms underlying induced cardiovascular responses to muscular static load. Activities that require static force development occur in lifting, pushing, and grasping. Static muscular load might affect most of the physiological responses, such as cardiovascular responses – heart rate, cardiac cycle length, arterial pressure. Heart rate, cardiac cycle length, and arterial pressure are cardiovascular indices frequently used for studying the response of cardiovascular function to static muscular exercise. Cardiovascular responses are controlled by neural, humoral, and biomechanical factors in order to adjust its function to the variable needs of the organism’s tissues. Among these, one of the most variable types of demands arises from the skeletal muscles – at isometric (static) muscular exercise. Cardiovascular responses vary with the intensity of isometric contraction and are among the processes developed to adapt the circulation to the muscles' need of blood.

A major part of the physiological literature concerning the phasic reaction of heart rate and arterial pressure describes results from studies where static contractions were performed [4, 5, 11, 15, 26, 30, 33, 36, 39]. One of the purposes of our studies was to demonstrate the relation between the changes in arterial pressure and pulse wave velocity in a study where the independent variable – the arterial pressure, is investigated at sustainment of muscular static effort performed at 25 % of Maximum Voluntary Contraction [2]. This model of increased arterial pressure revealed that the functional change of vascular wall (vasoconstriction) and the increased cardiac output induce decreasing of the Pulse Transit Time [1, 3].

Our studies in the filed of occupational medicine are associated with assessment of the risk of static workload and work-related musculoskeletal disorders at following occupations – medical doctors and nurses, lawyers and magistrates, video-display operators, teachers, social workers, employees, etc. (Hospital of Lung Diseases “Sveta Sofia”; Heatdistribution “Brunata”; Supreme Judicial Council; Ministry of Health; Sofia District Court of Justice; GSM Operator – Mobikom; Higher Transport School “Todor Kableskhoiv”; Children’s Social Medical Care Home “Sveta Paraskeva”; State Agency for Refugees, etc.).

Results of research investigations enable to be performed following conclusions about the pattern of cardiovascular responses at muscular static (isometric) load and contraction:
CIRCULATORY CHANGES TO ISOMETRIC CONTRACTIONS

At the onset of isometric contraction heart rate and arterial pressure both increase immediately \[11, 16, 21, 32, 36\]. The results of these studies reveal that at the maximal contraction of upper arm flexors for a period less than 1 sec in response to an acoustic signal the cardiac cycle following the one in which the contraction started was shortened in 95 % of cases. Research studies show also that a latency of about 550 msec exists between the onset of the contraction and the first detectable significant shortening in cardiac cycle length [21]. In subsequent study, there is concluded that anticipation or perception of the acoustic or visual signal might be responsible for the instantaneous rise in heart rate [6].

Following short-lasting (< 1 sec) maximal isometric contractions, a peak cycle length shortening was found at approximately 2 sec after the onset of contraction and the amount of cycle length shortening varied between individuals from 5 to 20 % [6, 21, 28]. With longer-lasting isometric contractions the increase in heart rate and arterial pressure depends on the intensity and duration of the muscular effort [23]. There is still no unanimity regarding the relation between the magnitude of the circulatory responses and the force of muscular contraction. Research studies reveal an independency of the cardiovascular responses to the amount of muscle mass involved at handgrip contractions, thigh muscle contractions or adduction of a single finger all performed at 20 % of their maximal effort [29]. Another result is that the effects of simultaneously contracting muscle groups was not additive – persisting and short-lasting (< 1 sec) bilateral and unilateral handgrip and ankle contractions were related to identical cardiovascular responses [6].

In contrast to the preceding results, recent studies show that the increase in heart rate and arterial pressure depends on the absolute force developed [33, 37]. Isometric finger contractions, handgrip contractions, knee extensions, and combined handgrip plus knee extensions all performed at 40% of Maximal Voluntary Contraction (MVC) resulted in increasing of the hemodynamic changes. A clear linear relation between the responses and the force developed is not found.

Summarized research studies investigate the cardiovascular responses to short-lasting isometric contractions. The extent of circulatory changes depends on the duration of the effort. With non-fatiguing contractions (less than 10-25 % MVC) the heart rate increases rapidly, reaches a plateau within the first minute and remains on this level throughout the duration of the contraction. With stronger contractions of long duration the heart rate and arterial pressure continue to rise during the contraction, reaching their peak values at the moment that fatigue occurs or when the contractions ends earlier at the moment of release. This implies that the sizes of the cardiovascular responses also depend on the type of muscles used, fatiguable (white musculature) or fatigue-resistant (red musculature). When a contraction is performed using a fatigue-resistant muscle at a given percentage of its maximal effort, the effect on heart rate and arterial pressure will be less than
the effect of contraction using a fatiguable muscle at the same percentage MVC and of equal duration.

**REFLEX MECHANISMS CONTROLLING CARDIOVASCULAR FUNCTION DURING MUSCULAR STATIC CONTRACTION**

**Reflex mechanism mediating contraction-induced cardiovascular responses**

At an investigation of reflex mechanism mediating the phasic changes in heart rate response at the onset of brief isometric handgrip contraction (0.5 sec lasting) (voluntary and electrically induced at 70% MVC), acceleration of heart rate response is observed [21]. The increase of duration extent of voluntary and electrically induced mm. quadriceps contractions at 20% MVC to 5 min is associated with identical responses in heart rate and arterial pressure [22]. Research analysis indicates that the reflex mechanism of central command or co-activation of the cardiovascular regulatory centers in the brainstem from impulses radiating from higher motor centers for motion control could not be excluded for the occurrence of circulatory changes during isometric contraction. Results of research studies reveal a reflex co-activated mechanism which co-ordinates cardiovascular control at the onset and during muscular contraction.

**Stimuli which initiate the reflex mechanism and nerve structures which compose the reflex arc**

*Stimuli which initiate the reflex mechanism*

The precise character of the stimulus necessary for the initiation of reflex mechanism mediating cardiovascular changes during isometric contraction is still debating. Research studies suggest the functional role of accumulation of some metabolite substances emanating from the contracting muscle, changes in pH, O2, and lactate, and the efflux of potassium for the changes in arterial pressure during isometric contraction [8, 9]. Results of these and other studies demonstrate the influence of intra-arterial injections of isotonic potassium solutions for stimulation of the activity of small myelinated (group III), and unmyelinated (group IV) muscle afferents [10, 15, 19]. This influence is related to increase in heart rate, arterial pressure, and contractility of the left ventricle.

Although potassium seems to be a likely stimulus for the mediation of the reflex responses to muscle contraction, the effect of other stimuli could not be excluded [16, 17, 25]. Intramuscular pressure has been shown to vary linearly with the force developed [38], and that the light pressure applied locally to the exposed belly of a muscle activates about 40% of myelinated muscle afferents [35]. Muscle stretch activates half of all group III afferents, and only 10% of group IV fibers [35]. 40% of group III muscle afferents are activated by tetanic muscle contractions in the range of 20-100% MVC, and about 30% of group IV fibers activate non-proportionally upon contraction. Thus the research studies assume that more than
one of the stimuli influence the reflex activation of the cardiovascular changes upon muscular contraction.

Nerve structures which compose the reflex arc

1. Muscle afferents involved in the reflex mechanism

There are research evidences showing that large myelinated fibers from muscle (group I and II) are not involved in the reflex mechanism mediating cardiovascular changes during isometric contraction. Research evidences reveal the functional role of autonomic activity in cardiovascular changes during isometric contraction. The fast vagally mediated cardiac acceleration at the onset of short-lasting muscle contractions might only be mediated by group III muscle afferents [21]. These results and the results presented in relation to the activation of muscle afferents by chemical and mechanical stimuli indicate the involvement of group III, and possibly of group IV afferents in the reflex mechanism [19, 36].

2. Central pathways and connections

Research studies examine the influence of the ascending pathways in the spinal cord that might mediate somato-cardiovascular reflexes [10, 12, 15, 39]. Kalia et al. (1981) [24] indicate that groups III and IV muscle afferents have significant role for the cardiovascular effects in muscular contraction. Researchers demonstrate, by using standard histological techniques, that some of those afferent fibers relay directly to the nucleus tractus solitarius in the brainstem. Fibers originating in this area are shown to have direct access to the nucleus ambiguus in the lower brainstem where cardiac vagal inhibitory fibers take their origin. Furthermore other fibers in the muscle nerve activated by muscular contraction are shown to terminate on ascending spino-thalamic tract neurons. Collaterals of these neurons may terminate in cardiovascular control center of the brainstem.

Inputs from group II and III somatic afferents crossing in the spinocerebellar tracts have been shown to elicit reflex responses in the inferior cardiac nerve. These afferents are known to project to the lateral reticularis nucleus in the brainstem. Electrical stimulation of this nucleus elicits arterial hypertension, tachycardia and increased activity in the inferior cardiac nerve through preganglionic sympathetic neurons emanating from this nucleus.

3. Efferent pathway of the reflex

The heart rate is controlled by the inhibitory effect of parasympathetic activity and the stimulating effect of sympathetic activity. Research topic of investigation is whether the increase of heart rate during isometric contraction is a result of withdrawal of vagal activity, enhancement of sympathetic activity or to a dual autonomic effect. The study of this research issue is significant to predict the time course of the cardiac acceleration upon the onset of muscular activity or alternatively following a change in the intensity of a sustained effort.

Investigations suggest contradictory results. Some researchers assume that the heart rate response to isometric contraction is vagally mediated while other indicates the significance of sympathetic activity [7, 26, 28, 34]. Hollander и Bouman
observed an inhibition of cardiac acceleration to short-lasting (< 1 sec) voluntary contractions after the injection of atropine.

In conclusion, it can be emphasized that the following three mechanisms control the response of heart rate during isometric contraction – immediately, i.e. within 0.5 sec after the onset of contraction heart rate increases as a result of the withdrawal of vagal restraint; after a delay of at least 2-5 sec following the onset of muscular contraction the effect of an increase of cardiac sympathetic activity may become apparent which also causes an acceleration of cardiac activity [20, 27]; predominantly during long-lasting contractions heart rate might be controlled by an increase in circulating catecholamines excreted by activation of the adrenal medulla.

4. Central command (cortical irradiation)

The efferent pathways are not activated only by a peripheral reflex mechanism but also by descending activity originating in higher motor structures in the brain passing over through the brainstem to its target – the spinal motorneurons. In passing by the circulatory brainstem centers it would radiate collateral impulses that activate those centers.

The mechanism of central command or co-activation of the cardiovascular centers by impulses irradiating from higher motor centers of motion control could not be excluded for the occurrence of circulatory changes during isometric contraction. This concept is sustained by the following research evidences:

Freyenschuss 1970 [14] compared the heart rate and arterial pressure responses to light handgrip contractions with the responses to intended contractions of the same muscles and the same intended force after local paralysis of the muscles and concluded that the cardiovascular changes during paralysis are elicited by central command.

Goodwin et al. (1972) [18] investigating the cardiovascular responses to isometric contractions vary the central command necessary to achieve a given force of contraction by means of tendon vibration. This vibration technique predominantly activates the primary afferents of muscle spindles. Activity in these afferents excites the spinal motoneurons of the homonymous and agonist muscles, and inhibits the activity in motoneurons of antagonist muscles. Consequently when during isometric contraction the tendon of the contracting muscle is vibrated, less central command is necessary to achieve a certain level of tension because the vibration-stimulated primary afferents promote to achieve this level by exciting homonymous motoneurons. When spindle afferents are activated in the antagonist of a contracting muscle, a greater central command is required to achieve a given level of force development. It was shown in these studies that when the effect of vibration promotes to build a given force in a contracting muscle, the heart rate and arterial pressure are less than without vibration, and conversely, when the effect of vibration counteracts the achievement of a given level of tension of an antagonist, the cardiovascular responses are more than in contractions at the same level of force development.
but without vibration. These observations suggest strongly that the cardiovascular responses are related to the required amount of central command.

Freund et al. (1979) [13] investigate the cardiovascular responses to a maximal effort of the quadriceps muscles during complete motor loss and lack of sensory information of the leg muscles during peridural anesthesia. No pressor responses are shown during the anesthesia but during the return of strength after anesthesia increasing pressor responses are observed at contractions of increasing force, the relation being linear.

The pressor responses are result of mechanism of central command. The existence of central command is indicated in other studies [12, 15, 18, 25, 31, 39, 40].

In conclusion, in this review article, evidences are indicated and analysed showing the existence of a reflex mechanism that controls the cardiovascular function from the onset of and throughout isometric contraction. The analysis of some results necessitates a second neural mechanism to be operative and inferential evidence in favour of central command is indicated. Both neural mechanisms might mediate cardiovascular responses during isometric contraction in normal circumstances. When one of the mechanisms is turned off the other will take over. This co-ordination necessitates convergence of neurons on cardiovascular brainstem centers. Responses of heart rate and arterial pressure vary with the intensity of isometric contraction during static load and are among the processes developed to adapt the circulation to the muscles' need of blood.

REFERENCES:

1. Данев, С., Р. Николова и Е. Дацов. Промени във времето на разпространение на пулсовата вълна при психо-физиологичен дискомфорт. – Хиг. и здравеоп., 1991, № 2, 30-36.
2. Драганова, Н. Електрофизиологично и биомеханично изучаване на статичната работа и умората. (Дисертация) София, Национален център по хигиена, медицинска екология и хранене, 1977.
3. Николова, Р. Апробация на метода за анализ на сърдечната вариативност при модели на нервно-сензорно професионално напрежение и неговото методично усъвършенстване. (Дисертация) София. Национален център по хигиена, медицинска екология и хранене, 1993.

Addresses for correspondence:
Rouja Nikolova, MD, PhD
National Center of Public Health Protection
Laboratory for Work Physiology and Psychology
15, Acad. Ivan Geshov Blvd.
1431 Sofia, Bulgaria
8056 207
Summary. Familial adenomatous polyposis (FAP) is a genetic disease, characterized by development of hundreds to thousands of intestinal polyps in the affected patients who are exposed nearly to 100% chance of developing colorectal cancer in their earlier ages. COX-2 selective inhibitors have been found to be effective in reduction of the number of adenomatous polyps in FAP-patients, as a secondary therapy to surgery, and additional endoscopic surveillance. The aim of this study was to assess the cost-effectiveness of the COX-2 inhibitor celecoxib in patients with FAP in Bulgaria. The non-selective non-steroidal anti-inflammatory medicines (NSAIDs) were selected as therapeutic alternative for celecoxib. Evidences for the final outcome in life years saved were derived from published studies after searching databases PubMed, Cochrane library, HTA, and NICE. There were selected 1 large-scale epidemiological study, 7 placebo-controlled randomized trials, and 5 pharmacoeconomic studies. The time horizon was for 1 year and point of view was for the health care system. It was considered the pharmacotherapy cost only. The total cost of therapy with celecoxib was calculated as 335 800 Bulgarian leva (BGN), while the lowest possible cost of therapy with non-steroidal anti-inflammatory drugs is 168 937 BGN. Data from the RCT showed, that 40 people more could be saved annually if they were treated with celecoxib instead of acetylsal, and the loss for the society is 10 times higher. Thus the cost per life year saved using celecoxib instead of acetylsal is 4172 BGN. Our results confirmed those from the international pharmacoeconomic studies, showing that celecoxib use is cost-effective also for Bulgaria because the cost per LYS is less than the yearly GDP per capita.

Key words: COX-2 inhibitors, celecoxib, cost-effectiveness, CRC, familial adenomatous polyposis
INTRODUCTION

Familial adenomatous polyposis (FAP) is a genetic disease, characterized by development of hundreds to thousands of intestinal polyps in the affected patients by the age of 30 – 40 years. FAP patients are exposed nearly to 100% chance of developing colorectal cancer usually after 10-15 years following the first symptoms appearance (at 30 – 40 years of patients age), but there are some cases even in 9 years old children. COX-2 selective inhibitors have been found to be effective in reduction of number of adenomatous polyps in familial adenomatous polyposis (FAP), as a secondary therapy to surgery, and additional endoscopic surveillance.

The aim of this study was to assess the cost-effectiveness of the COX-2 inhibitor celecoxib in patients with FAP in Bulgaria.

The point of view of the analysis is the health care system and time horizon for 3 years.

MATERIALS AND METHODS

Effectiveness and safety data analysis

There were searched databases publishing the medical and health economic studies as PudMed, NICE, Cochran library, and HTA databases. The search was performed with the key words celecoxib, familial adenomatous polyposis, safety, efficacy, cost-effectiveness. There were selected 5 RCT (2 long term), 2 safety, and 5 pharmacoeconomic studies. The studies were systematized according to their importance for the economic analysis (Table 1).

Cost calculations

The health care cost included pharmacotherapy cost, cost of surgical operation, and other cost of health care. The pharmaceutical products prices were taken from the official register of the Ministry of Health (MoH) (Table 2). The cost of pharmacotherapy was calculated for all available non-selective non-steroidal anti-inflammatory medicines. The cost of surgical operation and the costs for other healthcare resources were taken from the contracted by the National Health Insurance Fund (NHIF).

Cost-effectiveness analysis

As a measure of therapeutic result, there was selected the incidence of CRC development and life years saved (LYS) derived from the clinical studies. Two alternative therapies were considered in cost-effectiveness analysis (celecoxib and acetylsal). Acetylsal was chosen from all available non-selective non-steroidal anti-inflammatory medicines because of its lowest possible pharmacotherapy cost. The cost per life years saved was then calculated for both alternatives.
RESULTS

Analysis of the effectiveness and safety data

Rahme and al [9] compared the 3 months usage of celecoxib, rofecoxib, aspirin, NSAID with the incidence of CRC in case control study of 3477 patients 65 years of age, after a rectoscopy. Out of them 2568 were found healthy (74%), 730 (21%) with CR adenoma and 179 (5%) with CRC. The CRC incidence was lower in the group that was using celecoxib, while the CR adenoma incidence was lower in the group with NSAID. The odds ratio (OR) for CRC was 0,23 for celecoxib, 0,53 for rofecoxib, 0,87 for aspirin, 0,67 for NSIAD, 0,71 for acetaminophen. The respective figures for CR adenoma were 0,78 for celecoxib, 0,74 for rofecoxib, 0,85 for aspirin, 0,46 for NSIAD, 1,12 for acetaminophen. Steinbach et al [13] in a RCT, double blinded, compared placebo and different doses of celecoxib in 83 FAP patients, out of them 58 with colectomy and 25 without. Celecoxib 400 mg reduced the number of polyps on average by 28%, celecoxib 200 mg by 12% and 5% in placebo group. After 6 months usage number of polyps and their size decreased, as well as the polyps' area by 31% in patients with more than 5% affected area. The celecoxib 400 mg bid was tolerated well and ADR were found in 68% of placebo patients and 56-57% in celecoxib groups. The most frequent ADR reported were diarrhoea (11%), stomach pain (5%), and one allergic reaction. Similar is the study of Phillips et al. [8] (RCT, double blinded) comparing placebo and celecoxib 200 and 400 mg bid in 83 FAP patients with duodenal polyps. Celecoxib 400 mg bid after 6 months therapy decreased the affected areas by 14,5% more than placebo (1,4%).

The 2 long term studies evaluated the celecoxib effectiveness for the prevention of CR sporadic adenomatous polyposis [1, 3]. The first one lasted for 3 years and included 1250 patients. The cumulative incidence of detecting 1 or more adenomas after the 3rd year was 60,7% in placebo group, 43,3% in celecoxib 200 mg and 37,5% in celecoxib 400 mg. There was no statistically significant difference in ADR but celecoxib performed higher risk for cardiovascular events (RR celecoxib 200 mg bid = 2.6; RR celecoxib 400 mg bid = 3.4). Arber et al. [1] also evaluated the 3 years risk of adenomatous polyps appearance in 1561 individuals randomized on placebo and celecoxib 400 mg. The cumulative risk of appearance of polyps was 49,3% in the placebo group and 33,6% in celecoxib 400 mg group.

CLASS study [11] belongs to the group of safety studies evaluating the gastrointestinal toxicity of celecoxib, and ibuprofen or diclophenac. The incidence was found to be 0,76% vs 1,45%, respectively. The second safety study summarizes the risks and benefits of celecoxib usage for the prevention of recidives of adenomatous polyps [4]. The Preventive Task Force analysis concludes that low doses of aspirin result in 3 per 1000 serious GI events. In advanced adenomas, celecoxib possesses an advantage (1,6 CRC less in celecoxib group vs 1,2 in aspirin). Solomon et al. [12] analysed all possible serious CV events in 2035 patients with colorectal neoplasms, treated with celecoxib 200 mg and 400 mg for 2,8 – 3,1 years. In 7 out of 679 patients, a fatal incidence was reported in the placebo group, 16 out of 685 in the celecoxib...
200 mg and 23 in 671 patients in celecoxib 400 mg groups. The authors concluded that celecoxib is related to dose dependent risk of CV mortality.

Additional information on the important economic results of the therapy was collected from 5 pharmacoeconomic studies. Chin et al. [5] created a model for a cohort of 50 healthy men that were using 325 mg aspirin daily or celecoxib 400 mg bid for a 10-year period. They found that the aspirin therapy costs $23000 per QALY and results in 0.03 more QALY’s. The Health Service Technology assessment text model compared the colonoscopy every 3 or 5 years with celecoxib 200 mg per day, or non treatment of the risk for CR adenomas [6]. The costs for colonoscopy were found to be 514$, 658$ for colonoscopy and polypectomy and $100 000 per CRC health care. Colonoscopy vs non treatment saves 0.01995 life years for patients with colonoscopy, that costs $27 970 for additional life years saved. Celecoxib vs non treatment saves 0.00579 more and costs $407 498 per additional life year saved. Sanga S. et al. [10] conclude that NSAID’s are more useful for secondary prophylactics. For primary prevention of the CRC and its complication, it is necessary to treat 471 962 and 1250 people respectively. The primary prophylactics requires 10 or more years, but the toxicity of aspirin decreases its benefits because it will be necessary to treat 100 more GI hemorrhages, 300-800 more for bigger GI hemorrhages and 800 more for hemorrhagic insult. Ladabaum, U. [7] modelled the potential cost-effectiveness of COX-2 inhibitors for chemoprevention of CRC, or as supplementary therapy to colonoscopy every 10 years, for every 5 years for people with first line relatives with CRC. The incremental cost for a life year saved with COX-2 inhibitors is $233 300 for patients with an average risk, and $56,700 for patients with two relatives with CRC. Arguedas el al. [2] compare the colonoscopy with the risk of CRC. The non treatment alternative costs $1014 per patient, colonoscopy is $1571 per patient, and celecoxib $11 503. After 10 years patients with lesions are 15%, 13% and 6% respectively in the 3 compared groups.

The most important clinical and safety results that might have an impact on the economic results are summarized in Table 1.

Table 1. Effectiveness and safety data in the selected studies

<table>
<thead>
<tr>
<th>Alternative/Result</th>
<th>Celecoxib 200 mg BID</th>
<th>Celecoxib 400 mg BID</th>
<th>Placebo NSIADs</th>
<th>Acetysal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence CRC (OR) 9</td>
<td></td>
<td>0.23</td>
<td>0.67</td>
<td>0.87</td>
</tr>
<tr>
<td>Incidence colorectal adenoma (OR) 9</td>
<td></td>
<td>0.78</td>
<td>0.46</td>
<td>0.85</td>
</tr>
<tr>
<td>Number of polyps in the affected area13</td>
<td>11.9% decrease</td>
<td>28% decrease</td>
<td>5% decrease</td>
<td></td>
</tr>
<tr>
<td>Relative risk of advanced adenoma (RR) 4</td>
<td></td>
<td>1.6 less</td>
<td>1.2 less</td>
<td></td>
</tr>
<tr>
<td>Incidence colorectal adenoma in 3 years 8</td>
<td>43.3%</td>
<td>37.5%</td>
<td>60.7%</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal adverse events – annual incidence¹</td>
<td></td>
<td>0.76%</td>
<td>1.45%</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular events (RR)²</td>
<td>2.6</td>
<td>3.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death– 3 years</td>
<td>16 out of 685 (2.3%)</td>
<td>23 out of 671 (3.4%)</td>
<td>7 out of 679 (1.03%)</td>
<td></td>
</tr>
</tbody>
</table>
Cost analysis

Based on the officially registered manufacturing prices and dosage regimes used in the studies, the annual cost of competing medicines is calculated and presented in Table 2. Amongst the alternatives used as control group in the reviewed clinical trials, acetysal is with the lowest annual cost, followed by other NSAIDs and both forms of celecoxib. If all expected patients are treated with celecoxib, based on the manufacture prices, the costs of pharmacotherapy will vary among 11.8 mill. BGN for 200 mg and 23.5 mill. BGN for 400 mg dosage regime.

The cost of one surgical operation as agreed by the National Health Insurance Fund and physicians is 1189 BGN. The additional cost of annual care after the operation, calculated on the basis of the lowest country income per month is 3000 BGN per patient (12 months per 250 BGN).

Table 2. Pharmacotherapy costs with competitive pharmaceutical products

<table>
<thead>
<tr>
<th>INN</th>
<th>Manufacture price (BGN)</th>
<th>Dose regimen</th>
<th>Annual costs (BGN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen 400 mg</td>
<td>0.088</td>
<td>1 x 400 mg</td>
<td>32.12</td>
</tr>
<tr>
<td>Diclophenac 50 mg</td>
<td>0.082</td>
<td>1 x 50 mg</td>
<td>29.93</td>
</tr>
<tr>
<td>Acetysal 300 mg</td>
<td>0.034</td>
<td>1 x 300 mg</td>
<td>12.41</td>
</tr>
<tr>
<td>Celecoxib 200 mg</td>
<td>1.46</td>
<td>2 x 200 mg</td>
<td>1679</td>
</tr>
<tr>
<td>Celecoxib 400 mg</td>
<td>2.92</td>
<td>2 x 400 mg</td>
<td>3358</td>
</tr>
</tbody>
</table>

Results of cost-effectiveness analysis

Based on the first therapeutic result on table 1 – OR for CRC development, we can calculate the number of patients needed to treat (NNT) to avoid 1 CRC. The incremental ratio is 40, which means that 40 people more should be treated with acetysal to avoid 1 CRC. The comparison between celecoxib and NSIADs showed that 17 people more should be treated with NSIADs in order to prevent one case of CRC, respectively 6 people more to avoid one colorectal adenoma.

The annual cost of therapy for a cohort of 100 patients treated with celecoxib 400 mg bid is 335 800 BGN and for acetysal is 1241. Thus the additional cost per one CRC avoided using celecoxib instead of acetysal is 8364 BGN per patient, including only the medicines therapy.

It is hard to estimate the economical importance of the other positive therapeutic results, but is possible to calculate the loss of society due to a higher mortality. In the case of celecoxib 200 mg and average expectation of remaining life of 10 years, the figures would be the following:

3 years use of celecoxib 200 mg is associated with 2.3 deaths/100 people compared to 1.03 in placebo group. The difference is 1.27.

The mortality rate for 10 years period would be \((1.27 \times 3) + 0.42) = 4.23\) people more.
The potential losses, associated with these deaths for the next 10 years are estimated 211 500 BGN based on the yearly GDP (5000 BGN yearly per capita). On the other hand, the avoided CRC cases are significantly more due to the mortality caused by the adverse drug reactions.

**CONCLUSION**

As found in the clinical trials, celecoxib appears to be more effective in treatment of FAP-patients in comparison with other competitive pharmaceutical products. The lowest cost alternative is acetylsal treatment, although it is related with higher frequency of CRC cases.

We assume that the results confirmed by international pharmacoeconomic studies, showing that celecoxib use is cost-effective in case of $50000/per LY saved could be considered relevant for Bulgaria.

However due to a higher risk of cardiovascular death associated with celecoxib, the treatment should be justified individually according to the risk.

Although the adequate therapy of rare diseases is priority set in the national healthcare programs, the realization is often prevented by the lack of interest from the industry. Therefore, every available pharmaceutical product which has a chance to decrease the burden of a severe disease should be carefully assessed.

**REFERENCES**


Address for correspondence:
Manoela Manova
Faculty of Pharmacy
Department of Social Pharmacy
Medical University – Sofia
2 Dunav St.
1000 Sofia
Bulgaria
e-mail: manoela_manova@yahoo.com
FOOD SUPPLEMENTS IN CENTRAL AND EASTERN EUROPEAN COUNTRIES

A. Stoimenova

Faculty of Pharmacy, Department of Social Pharmacy, Medical University – Sofia

Summary. The consumption of food supplements, functional foods and beverages is constantly increasing. The increase of the different segments of the market varies from 5 to 15%. Worldwide, the most dynamic food supplement markets are the ones in United States, European Union (EU), China, India and Japan. In recent years, the economics of Central and Eastern European countries (Russia, Poland, Ukraine, Bulgaria, Romania, Czech Republic, Slovakia, Slovenia and Croatia) have shown significant development which also reflects the food supplement market. The article outlines the main tendencies in the development of food supplement markets in Central and Eastern European countries as one of the most dynamic segments of the EU food supplements market. Market drivers, business trends in the industry and market prospects are discussed. The food supplement market in Eastern European countries is dominated by the multivitamin market and mineral supplement. Other food supplements with significant consumption are various combination products, vitamin C, vitamin B, tonics and child-specific preparations. Plant-based food supplement are less used. The common interest for development of regulated and stable markets of food supplements with the efforts of regulators, manufacturers, distributors, medical specialists and consumers would further develop food supplements markets for the benefit of the consumers. Consumer and medical specialists’ education is needed in order to balance the safety of food supplements with the free market concept.

Key words: food supplement, dietary supplement, vitamins, market, Eastern Europe, Bulgaria

INTRODUCTION

From Europe to Latin America the consumption of food supplements, functional foods and beverages is constantly increasing. The increase of the different segments of the market varies from 5 to 15%. Worldwide, the most dynamic food supplements markets are the ones in United States, European Union (EU), China, India and Japan [9].
In recent years, the economics of Central and Eastern European countries (Russia, Poland, Ukraine, Bulgaria, Romania, Czech Republic, Slovakia, Slovenia and Croatia) have shown significant development. The economical situation, increasing incomes and the change in life style and taking a bigger responsibility for own health resulted in increase of food supplements and over-the-counter medicinal product sales [10].

In general, in the studied countries the over-the-counter medicinal products are distributed via pharmacies only. In Hungary approximately 390 OTC medicinal products are sold in regular shops as well. Food supplements are sold not only in pharmacies but also via Internet, through multilevel marketing companies and direct marketing. At the same time, many pharmaceutical companies started to produce and market food supplements [10]. According to many specialists, the potential of food supplements market is similar to the one of pharmaceutical products. One of the best sold food supplements worldwide are chondroprotectors, cardioprotectors, probiotics, vitamins and minerals, some herbal food supplements (ginseng, ginkgo biloba, green tea etc.) etc. [9, 10].

AIM

The aim of the current article is to outline the main tendencies in the development of food supplements markets in Central and Eastern European countries as one of the most dynamic segments of the EU food supplements market.

MATERIALS AND METHODS

Sources of information for this article were publications on food supplements; sales reports, published by marketing companies; publications on food supplements found in Scopus database and product brochures and catalogues.

RESULTS

In general, the experts consider that the liberal legislation on food supplements (compared with over-the-counter (OTC) pharmaceuticals) leads to fast market growth and more often pharmaceutical companies switch to development and production of food supplements product lines [3]. The main food supplements market drivers are the legislation (liberal legislation increases the market size), aging, media publicity [5], dissatisfaction with western healthcare [1, 11] and the increasing knowledge about diet-disease relationship. People in the developed countries are informed about alternatives to synthetic medications and seek an alternative. Rising healthcare costs also stimulates the process of consumption of food supplements.

Eastern Europe has the second highest share of population which is over 60 years of age (after Western Europe). People in Europe live longer and pay more and more attention to the quality of their life.
Worldwide, according to the Euromonitor International [8] food supplements market is very dynamic, but still below pharmaceutical market by volume and value (Figure 1). As shown on the Figure 1, both OTC segment and food supplements segment show a positive trend [8].

![Fig. 1. Global overview of food supplements and OTC market](image)

The good performance of vitamins and food supplements can be seen as a result of the drivers affecting the industry. These drivers can be grouped in 3 categories: regulation [6], product innovations [6-8] and consumer knowledge and needs [4, 12]. Overall regulation is probably the most impactful of all factors. In order to protect consumers, different regulations are often put in place. These can vary from market to market. Overall vitamins and food supplements benefit from a less strict regulation in comparison to OTC medicinal products. Regulation generally affects which products can be sold on the market and how products can be sold, governing the product advertising, packaging and distribution. Figure 2 presents the distribution channels for food supplements [8].

Supply drivers are very important and they are determined by the legislation [9]. These factors are controlled by the manufacturers. Product innovation is key as consumers taste and preferences can change very quickly in this market. Fashionable products can appear very quickly following a positive review published in the press. One such example is resveratrol grape extract following studies showing this ingredient benefit on extending life of mice. Similarly quickly products can disappear from the market – for example sales of Vitamin E were impacted by negative studies published in the media. Generics are mainly a case for single vitamins, as consumers are more comfortable comparing those [8].
On the other hand, market restraints are exaggerated health claims, lack of consumers’ knowledge on food supplements, limited brand loyalty etc. [2].

The differences in legislative regimens of the two types of markets (OTC pharmaceutical products and food supplements) influence their distribution. Vitamins distributed as OTC pharmaceuticals have limited distribution channels mainly through pharmacies. Vitamins offered as food supplements are also supplied via pharmacies mainly but have more distribution channels which reflect the consumption. The main market drivers are product innovations, multilevel marketing and consumer education.

The development of the food supplements market in Eastern Europe is dominated by the dynamic markets of Lithuania, Hungary, Czech Republic, Estonia and Latvia. These are the leading countries within the Eastern Europe in terms of spenders in food supplements per capita. Fastest growing markets within the studied region are Russia and Ukraine, while in Southeastern Europe the biggest markets are Romania, Bulgaria and Croatia (Figure 3) [8].
The biggest sales in Eastern Europe recorded multivitamin food supplements, followed by combinations, minerals, probiotic supplements, calcium supplements, child-specific vitamins and minerals (Figure 4) [8].

![Eastern European sales](image)

**Fig. 4. Eastern European sales**

In the studied countries, the share of multivitamins is dominating (Fig. 5), and is most significant in Romania and Bulgaria. Of monopreparations most sold in Bulgaria are vitamin B, vitamin C and vitamin A. Only in Macedonia and Croatia, vitamin D is amongst the best sold food supplements. Vitamin A is best sold in Slovakia, and vitamin E – in Macedonia, Slovenia, Bosna and Herzegovina. Vitamin C is the most popular monocomponent vitamin, a fact that could be explained with the existence of both food supplements and OTC drug forms.[8]

13% of the sales of food supplements in Bulgaria are due to beauty and wellness products (estimated as 3% for Romania and 10% for Hungary). Within this group, most popular are suntan products such as beta-carotene, vitamin E, vitamin C, zinc, selenium, fatty acids, hair-loss products etc. The market specialists foresee significant growth in multivitamins, tonics, probiotics, eye health products, fish oil, coenzyme Q10 [8].
DISCUSSION

The food supplements market in Eastern European countries is dominated by the market of multivitamins and mineral supplements. Other food supplements with significant consumption are various combination products, vitamin C, vitamin B, tonics and child-specific preparations. Plant-based food supplements are less used.

Currently, there is no knowledge on inclusion of food supplements in different prophylaxis programs. There is necessity of independent monitoring by non-governmental associations and consumer associations on the quality of distributed food supplements and correctness of the health claims and promotions. Thus one of the factors which hinder the development of food supplements market is the reluctance of significant part of medical specialists to include the alternative in their advice to patients. The exaggerated health claims on the packages of many food supplements on the other hand make the consumers suspicious to these products.

There should be a common interest for development of regulated and stable markets of food supplements with the efforts of regulators, manufacturers, distributors, medical specialists and consumers.

Consumer and medical specialists’ education is therefore to play even a bigger role for the development of food supplements market in the future balancing the safety of food supplements with the free market concept.

REFERENCES


Address for correspondence:
Assena Stoimenova, M.Sc.Pharm., Ph.D.
Department of social pharmacy
Faculty of pharmacy
Medical University – Sofia
2 Dunav, Str.
1000 Sofia
e-mail: assena_stoimenova@mail.bg
QUALITY OF LIFE AND AGE AT ONSET IN PATIENTS WITH PARKINSON’S DISEASE

A. Todorova
University Hospital for Neurology and Psychiatry “Sv. Naum” – Sofia, Bulgaria

Summary. The impact of Parkinson’s disease (PD) on the lives of young patients differs significantly from the impact the disease has on the lives of older patients. In this study, we investigated 35 patients with early onset of PD and 81 with late onset. For assessing the severity of PD we used Hoehn and Yahr scale and for clinical evaluation – Unified Parkinson’s Disease Rating Scale (UPDRS). Beck Depression Inventory (BDI) was used for assessing the presence and severity of depression. For measuring quality of life, the three disease-specific quality of life questionnaires – PDQ-39, PDQL and PIMS, were used. The patients with early onset of PD had worse results for the summary index score PDQ-39Bg-Si. Still, among some of the subscales of the questionnaire – “mobility”, “daily activities”, and “social support”, there was a statistically significant difference between the two groups, and the patients with early onset reported worse quality of life. Young onset patients had also worse results on the stigma subscale and were more frequently depressed. Moderate to severe depression, defined as such by BDI scores above 20, was present in a significantly high percentage of the patients within the group with early onset of the disease (43%) in comparison to those with late onset (34%). In conclusion, the impact of PD on the life of the patients is more expressed when the disease starts at a younger age which could partially be due to the differences in the Parkinsonian symptoms or the more frequent occurrence of levodopa related dyskinesias.

Key words: Parkinson’s disease, quality of life, young onset, late onset, depression

INTRODUCTION

Parkinson’s disease (PD) is a common progressive neurodegenerative disorder, which is the leading cause of neurological disability in individuals more than 60 years old.
Parkinson’s symptoms typically begin after the age of 50, with the age onset peak occurring in the sixth decade. However a substantial minority of patients develop PD at a younger age. The clinical features of the early onset are generally similar to those of the classic, older onset PD. Still, the beginning of the disorder at a younger age produces some differences in disease characteristics. In their daily life the young, 30-40 years old people, have problems that are entirely different from the problems encountered by people in their sixties or seventies and for this reason the impact of PD on patients with early onset is probably very different from the impact on patients with late onset of the disease. Some studies by Schrag et al. [15, 16, 17] highlighted the fact that patients with early onset PD are more likely to become unemployed or have to take early retirement because of their disability. They also experience more family and marital problems than patients with late onset of the disease.

The occurrence of depression is found to be more common in young onset Parkinson’s patients than it is in late onset patients despite similar disease severity and disease duration. Physical impairment may induce greater stigmatization in this group of patients, which can lead to reduced overall wellbeing.

There are different results about the influence of age of onset over the quality of life of parkinsonian patients. Some studies did not find a significant relationship between the age of onset and the scores of quality of life in PD, and one study reported worse quality of life scores in patients with late onset of the disease [11]. However, there are other studies that demonstrate worse scores in most dimensions of quality of life in patients with early onset of PD compared to patients with late onset [15, 16, 17].

**Our aim in this study** was to investigate the influence of PD on various areas of lives of patients with onset before 50 years of age in comparison to those with older onset of the disease, measuring quality of life, assessing depression and clinical state of the patients.

**PATIENTS AND METHODS**

The current study took place in the Neurology Department of University Hospital “Sv. Naum”, Sofia. Through prospective recruitment of patients who attended the movement disorder clinic, we randomized 116 patients with idiopathic PD. They were divided into two groups according to the onset of PD to patients with onset of PD before the age 50 years (young onset) and patients with onset at an older age (late onset). This threshold was based on previous studies which suggested that a substantial number of patients (10%) develop the disease symptoms prior to the age of 50 [8, 16].

After obtaining their informed consent, all the patients were examined thoroughly and their detailed clinical history was recorded. Their cognitive functioning was assessed by Mini Mental State examination (MMSE) and they all had results
above 24. For assessing the severity of PD, we used Hoehn and Yahr scale (HYS) [12]. For clinical evaluation of the present status of the patients – activities of daily living and motor functioning – we used Unified Parkinson’s Disease Rating Scale (UPDRS) [7]. Beck Depression Inventory (BDI) [4] was used for assessing the presence and severity of depression.

For measuring quality of life we used the three disease-specific quality of life questionnaires – PDQ-39, PDQL and PIMS. Parkinson’s disease Questionnaire (PDQ-39) [13] is designed specifically for PD impact assessment. It consists of 39 questions, organised in 8 subscales: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily discomfort. Each of the items is scored on a 5-point Likert-type scale, ranging from 0 (“never”) to 4 (“always”). One summary index score can be calculated from the PDQ-39 with higher scores indicating worse quality of life. Parkinson’s Disease Quality of Life Questionnaire (PDQL) [6] consists of 37 questions, combined in 4 subscales: Parkinsonian symptoms, systemic symptoms, social functioning, and emotional functioning. Each question has 5 different answer options – all of the time, most of the time, some of the time, a little of the time, never. Higher results of this questionnaire mean better quality of life. Parkinson’s Impact Scale (PIMS) [5] is a short assessment scale that consists of 10 items, each one inquiring into an area of patient’s lives: Self, Feelings, Family, Community, Work, Travel, Leisure, Safety, Financial security and Sexuality. Each item was scored from 0 to 4, with 0 indicating no change and 4 the most severe. Higher scores reflect lower quality of life. Before being used, the three instruments were translated into Bulgarian and were given the following names – PIMS-Bg [19], PDQL-Bg [2] and PDQ-39Bg [1]. Afterwards they were validated for the Bulgarian population and all showed good reliability, validity and reproducibility, and are now used in many research studies [1, 2, 19].

We analyzed the accumulated data using SPSS version 12.0 for Windows. Comparisons between the scores from the questionnaires in the different groups were performed using ANOVA, while the correlations between the clinical methods such as UPDRS, Hoehn &Yahr scale and BDI and the questionnaires were analyzed using Pearson and Spearman correlation coefficients. A p value less or equal to 0.05 was considered to indicate statistical significance.

**RESULTS**

Out of 116 patients whose quality of life was investigated, 35 were with early onset of PD (younger than 50 years old) and 81 were with late onset (above 50 years old). Their demographic and clinical characteristics are presented in Table 1. In accordance with the way the patients were divided, those with early onset of the disease were significantly younger at onset (p<0.001), and at the time of the study (p<0.001). The patients in both groups also differed significantly in the duration of the disease (p<0.01).
There was no significant difference between both groups with regard to sex, Hoehn and Yahr stage of PD and predominant symptom – tremor or rigidity. In addition, the number of patients, suffering from “on-off” periods was the same in both groups, while more patients with early onset of PD reported levodopa-related involuntarily movements than did those with late onset (40 vs. 16%, respectively; p<0.05).

The mean results of BDI were similar in both groups (Table 1). There was no statistically significant difference established between them (p>0.05). Yet the moderate to severe depression, defined as such by BDI scores above 20, was present in a significantly high percentage of the patients within the group with early onset of the disease (43%) in comparison to those with late onset (34%) (Figure 1).

**Table 1.** Demographic and clinical characteristics of patients with early and late onset of Parkinson’s disease

<table>
<thead>
<tr>
<th></th>
<th>Patients with early onset</th>
<th>Patients with late onset</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Mean value (SD)</td>
<td>Number</td>
</tr>
<tr>
<td>Sex ( M : F )</td>
<td>22:13</td>
<td>52:29</td>
<td>0,89</td>
</tr>
<tr>
<td>Disease onset (years)</td>
<td>35</td>
<td>42,5 (6,1)</td>
<td>81</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35</td>
<td>51,4 (8,2)</td>
<td>81</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>35</td>
<td>8,9 (5,5)</td>
<td>81</td>
</tr>
<tr>
<td>Disease stage according to Hoehn &amp; Yahr</td>
<td>35</td>
<td>2,3 (0,7)</td>
<td>81</td>
</tr>
<tr>
<td>BDI</td>
<td>35</td>
<td>19,0 (11,8)</td>
<td>81</td>
</tr>
<tr>
<td>UPDRS II</td>
<td>35</td>
<td>22,3 (14,6)</td>
<td>81</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>35</td>
<td>23,7 (13,0)</td>
<td>81</td>
</tr>
<tr>
<td>Dyskinesia (%)</td>
<td>14 (40)</td>
<td>13 (16)</td>
<td>0,01*</td>
</tr>
<tr>
<td>“On-off” periods (%)</td>
<td>9 (26)</td>
<td>22 (27)</td>
<td>0,10</td>
</tr>
<tr>
<td>Tremor (%)</td>
<td>3 (9)</td>
<td>25 (31)</td>
<td>0,01*</td>
</tr>
<tr>
<td>Rigidity (%)</td>
<td>9 (25)</td>
<td>21 (26)</td>
<td>0,10</td>
</tr>
</tbody>
</table>

* p < 0,05, ** p < 0,01
The patients with early onset of PD had worse results for the summary index score PDQ-39Bg-Si (Table 2). Still, among some of the subscales of the questionnaire – “mobility”, “daily activities”, and “social support”, there was a statistically significant difference between the two groups (p<0.05), and the patients with early onset reported worse quality of life. There was also a difference, which could be considered significant (p=0.05) in the subscale “stigma”. In the remaining PDQ-39Bg subscales, there was no significant difference between the patients in both groups (p>0.1) but in all of them patients with early onset had higher results and correspondingly lower quality of life than the patients with late onset.

Considering the health status and the quality of life of patients, determined by PIMS-Bg and PDQL-Bg, there were no substantial differences between the two groups (Table 2). But still, according to these questionnaires, the quality of life of patients with early onset was worsened as compared to those with late onset (Table 2). In subscale “Parkinsonian symptoms” of PDQL-Bg, there was a significant difference between the two groups (p=0.05), and this confirms the assertion that when the disease appears earlier its symptoms are more severe and disabling for the patients in the physical and psychological aspects.
Table 2. Quality of life of patients with early and late onset of Parkinson’s disease assessed with PDQ-39Bg, PDQL-Bg, PIMS-Bg

<table>
<thead>
<tr>
<th>Quality of life questionaries</th>
<th>Early onset patients</th>
<th>Late onset patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Mean value (SD)</td>
<td>Number</td>
</tr>
<tr>
<td>PDQ-39Bg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>35</td>
<td>48,2 (25,3)</td>
<td>81</td>
</tr>
<tr>
<td>Daily activities</td>
<td>35</td>
<td>52,5 (20,5)</td>
<td>81</td>
</tr>
<tr>
<td>Emotional wellbeing</td>
<td>35</td>
<td>49,4 (18,9)</td>
<td>81</td>
</tr>
<tr>
<td>Stigma</td>
<td>35</td>
<td>54,3 (26,8)</td>
<td>81</td>
</tr>
<tr>
<td>Social support</td>
<td>35</td>
<td>13,3 (18,8)</td>
<td>81</td>
</tr>
<tr>
<td>Cognition</td>
<td>35</td>
<td>28,6 (21,5)</td>
<td>81</td>
</tr>
<tr>
<td>Communication</td>
<td>35</td>
<td>27,1 (21,8)</td>
<td>81</td>
</tr>
<tr>
<td>Bodily discomfort</td>
<td>35</td>
<td>45,7 (23,4)</td>
<td>81</td>
</tr>
<tr>
<td>PDQ-39Bg-SI</td>
<td>35</td>
<td>39,7 (15,9)</td>
<td>81</td>
</tr>
<tr>
<td>PDQL-Bg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonian symptoms</td>
<td>35</td>
<td>43,4 (10,2)</td>
<td>81</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>35</td>
<td>22,3 (5,2)</td>
<td>81</td>
</tr>
<tr>
<td>Social functioning</td>
<td>35</td>
<td>21,7 (6,2)</td>
<td>81</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>35</td>
<td>28,0 (6,6)</td>
<td>81</td>
</tr>
<tr>
<td>PDQL-Bg-Total</td>
<td>35</td>
<td>115,5 (24,6)</td>
<td>81</td>
</tr>
<tr>
<td>PIMS-Bg</td>
<td>35</td>
<td>25,5 (15,5)</td>
<td>81</td>
</tr>
</tbody>
</table>

* p < 0,05

The clinical investigation of the patients with the scale for assessment of PD – UPDRS showed significantly lower results and worse health status for the patients with early onset (p<0,05) when using part II of UPDRS “Daily activities” (Table 1). Motor functioning of the patients according to the objective UPDRS assessment was not as disturbed as presented by the patients themselves. There was no difference between the two groups when investigated with part III of UPDRS (p>0,5) and also there was no correlation between the disease onset and this motor section of the scale.
DISCUSSION

Our results showed that PD has stronger negative impact on patients’ lives if it starts at an early age. The quality of life measured with the summary index score PDQ-39Bg-SI was substantially worse for patients with early onset, especially regarding motor functioning and psychosocial wellbeing. Thus, despite the fact that severity of the disease and the disability did not differ substantially among the patients in both groups, it became clear that patients with early onset experience much stronger impact of PD on their lives.

This difference partially can be explained by the different clinical symptoms. Some authors [3, 9, 10, 14] considered certain clinical characteristics as typical for patients with early onset while other clinical symptoms correspond to patients with late onset. In 1988 Gibb and Lees [9] in a comparative study for the clinical symptoms of patients with early and late onset found that for 43% of the patients with early onset, the disease started with rigidity while the patients with late onset reported gait disturbances as their initial complaint. In other studies [3, 14], it has been proven that in more than half of the cases of patients with early onset the akinetic-rigid form of PD prevails. Unlike them though, Giovannini et al found no dependence between the clinical symptoms and the age of patients at disease onset [10]. In relation to rigidity this was confirmed by the current study. Regarding the tremor, our results showed that it occurs more often for patients with late onset of the disease. This finding was confirmed by Hoehn and Yahr in whose study for more than 70% of the patients with mean age of above 50 years the tremor was the most typical initial symptom [12].

In the current study, “Mobility” and “Activities of daily living” as dimensions of quality of life were influenced to a bigger extent by dyskinesias, which are complications of the disease therapy, than by the rigidity as an early symptom. As it was known from previous studies [3, 9, 14, 17, 20] as well as it was established here, the dyskinesias were more frequent and more severe for the patients with early onset of the disease. Besides the fact that the dyskinesias hamper patients daily activities, these unusual and strange movements could make the patients feel different, unattractive and abandoned.

It was quite probable that other, unrelated to the disease aspects, could as well determine the negative impact PD has on the younger patients. According to the current study “stigma” from the disease and “Social support” were the most affected psychological aspects of quality of life. Probably the most important period in the life of these patients is the adaptation of their family life, career, finances and emotions to the various situations of stress from this potentially disabling state. The disease impacts the work and daily life of these people, their family relationships, friendships, pleasure of life, sometimes to the extreme, and this is quite different from the impact on older patients, usually pensioners with no need to take care of families and small children. Besides, the older patients find the symptoms of PD and disability as more “normal” and more acceptable for them while the younger
patients are more susceptible to the stigma of the disease and consider themselves as untimely aged with the loss of their natural everyday role [16]. There is also a more negative impact of PD on the social activities of patients with an early onset. Because of the disturbed movement function substantial part of young patients are unemployed or retire early. The necessity to abandon their jobs and the following financial difficulties are the major concern for these patients. We also found that a big part of the younger patients reported sexual problems as compared to the older ones. The sexual satisfaction was reduced in both groups of patients with PD but still patients with early onset complained more about this problem.

Moderate to severe depression was common for a big percentage (43%) of the patients with early onset in the current study, which was consistent with previous studies [18, 20]. Our findings that depression is more frequent for patients with an early onset PD also correspond to previous results that the depression is more common in young-onset patients despite the similar duration and severity of the disease. Since the etiology of PD related depression is still a controversial question, it is not clear if the disease itself or other factors, independent of disease pathophysiology, play role in the development of depression in young patients with PD.

In conclusion, the impact of PD on the life of patients is more expressed when it starts at a younger age. The difference in the quality of life with respect to the physical activities and the psychosocial wellbeing between the patients with early and late onset could partially be due to the differences in the Parkinsonian symptoms or the more frequent occurrence of levodopa related dyskinesias. However, the differences in the impact of PD on the social factors like work, stigma and sexuality could also worsen the psychological state of the patients with early onset and lead them to depression.

REFERENCES


Address for correspondence:
Antoniya Todorova, MD
University hospital for Neurology and Psychiatry “Sv. Naum”
1 Lyuben Russev Str.
1113 Sofia, Bulgaria
02 9702 204; 0888 977405
e-mail: an.todorova@gmail.com
A COMPARISON OF REMISSION IN BIPOLAR AND RECURRENT DEPRESSIVE DISORDERS: CLINICAL AND SOCIO-DEMOGRAPHIC CHARACTERISTICS

V. Stoyanova¹, S. Krastev¹, R. Vladimirova¹, G. Genchev² and V. Milanova¹

¹Psychiatric Clinic – University Hospital “Alexandrovska”
²Department of Medical Information and Biostatistics, Medical University – Sofia

Summary. Even in periods of remission, affective disorders are illnesses with hidden morbidity and serious implications on both the family and society. During the last years, the problem of recurrence has been emerging as the leading in diagnosis, treatment and prognosis of these conditions. The aim of this study was to evaluate some important socio-demographic and clinical characteristics during the period of remission in patients with uni- and bipolar course of the affective disorders. The design of the study was naturalistic, the data processing used the statistical software package SPSS 17.0.1 and the study sample comprised 37 patients with bipolar affective disorder (BAD) and 28 patients with recurrent depressive disorder (RDD). The mean illness duration for the patients with BAD significantly exceeded that for the patients with RDD (p=0.003), as the number of episodes and the number of hospitalizations were also higher for the patients with BAD (p<0.001). The presence of psychotic symptoms during an episode was mainly characteristic for the patients with BAD (p=0.003), while more residual depressive symptoms during a remission were observed in the patients with RDD (p=0.023). The number of individuals with high educational status was significantly higher for the patients with BAD (p<0.001). Social dysfunctions were manifested to a greater degree in the patients with RDD, reaching, however, the cut-off value of significance (p=0.097). Conclusions: The period of remission is a part of the illness history, as some important characteristics, such as educational status, residual symptoms and functioning, may serve as predictors for the remission stability and course of the disease.

Key words: recurrent depressive disorder, bipolar affective disorder, clinical characteristics, quality of remission
A comparison of remission in bipolar...
hand, it depends on the regular anti-recurrence treatment and quality of remission. Therefore, the period of remission is something dynamic, occurring both as a result and a precondition of correct treatment, attitude and prevention of recurrence. This makes the remission a period of extreme importance for clinical observations, evaluations and interventions.

There are relatively few studies on the quality of remission and the comparison of this period in unipolar and bipolar patients.

The objective of this study was to compare some important clinical and socio-demographic characteristics of patients with unipolar and bipolar affective disorders, followed-up catamnestically and during their period of remission.

**MATERIAL AND METHODS**

The present study had a naturalistic design and covered a follow-up period of 3 months (September – December 2008), during which, all regular, but randomly chosen outpatients were included in the study in case they had met the following criteria:

- Availability of strictly actuated medical documentation, in order to enable correct catamnestic following-up of the clinical picture and some important socio-demographic characteristics;
- Patients with an established diagnosis of RDD, with at least two depressive episodes, and BAD, currently in remission;
- The diagnosis has been established in conformity with the ICD-10 Diagnostic Criteria and has been verified by at least two psychiatrists;
- The remission has been, in clinical point of view, a relatively stable condition, with duration of at least 6 months, during which the maintenance therapy has been stable and remained unchanged. The remission has been identified by an experienced specialist, following a clinical evaluation and psychometrically objectified (MADRS ≤ 10; YMRS ≤ 6);
- For evaluating of psychopathology during the remission, the study team has used well-known evaluating instruments – the Montgomery-Asberg Depression Rating Scale (MADRS) [29] and the Young Mania Rating Scale (YMRS) [44];
- For evaluating the quality of functioning during a remission, the self-rating Sheehan Disability Scale (SDS) [38] and the global assessment of functioning (GAF according to DSM – IV) scale [5] have been used.

Data were processed with SPSS, version 17.0.1. The following statistical methods were applied: descriptive analysis, variation analysis, one-sample Kolmogorov – Smirnov and Shapiro – Wilk test to check the type of distributions of continuous variables; \( \chi^2 \) test and Fischer’s exact test for testing the correlation between the categorical variables; alternative analysis for comparing the relative proportions of dichotomous signs; the non-parametric Mann-Whitney test and the Student’s t-test for hypothesis testing for difference between two independent samples. A p-value < 0.05 was considered significant.
RESULTS
The study sample involved 65 patients, 15 (23.1%) males and 50 (76.9%) females, mainly urban inhabitants, meeting the criteria for inclusion into the study. The mean age of the study subjects was 48.72 ± 15.46, in the range from 22 to 78 years. The patients with diagnosed BAD were 37 (56.9%) and those with diagnosed RDD were 28 (43.1%). The obscuring variables, gender and age, were statistically equalized for both groups.

The more important socio-demographic and clinical characteristics, analyzed in the study have been presented in Table 1.

Table 1. Comparative analysis of BAD and RDD patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BAD</th>
<th>RDD</th>
<th>p</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases (%)</td>
<td>37 (56.9)</td>
<td>28 (43.1)</td>
<td>&gt;0.05</td>
<td>Alternative analysis</td>
</tr>
<tr>
<td>Mean age ± SD (years)</td>
<td>49.05 ± 15.85</td>
<td>48.28 ± 15.20</td>
<td>0.931</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>Gender – number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>9 (60.0)</td>
<td>6 (40.0)</td>
<td>0.512</td>
<td>Fischer's exact test</td>
</tr>
<tr>
<td>Females</td>
<td>28 (56.0)</td>
<td>22 (44.0)</td>
<td></td>
<td>test</td>
</tr>
<tr>
<td>Mean age of illness onset ± SD (years)</td>
<td>31.30 ± 13.10</td>
<td>37.04 ± 13.43</td>
<td>0.051</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>Duration of illness ± SD (years)</td>
<td>17.76 ± 10.76</td>
<td>11.25 ± 10.20</td>
<td>0.003</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>Presence of psychotic symptoms – number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (37.1)</td>
<td>22 (62.9)</td>
<td>0.001</td>
<td>Fischer's exact test</td>
</tr>
<tr>
<td>Yes</td>
<td>24 (60.0)</td>
<td>6 (20.0)</td>
<td></td>
<td>test</td>
</tr>
<tr>
<td>Number of hospitalizations X ± SD</td>
<td>4.00 ± 3.58</td>
<td>2.07 ± 2.00</td>
<td>0.003</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>Number of phases X ± SD</td>
<td>6.92 ± 4.23</td>
<td>3.64 ± 1.79</td>
<td>&lt;0.001</td>
<td>test</td>
</tr>
<tr>
<td>Number of phases per year illness X ± SD</td>
<td>0.46 ± 0.29</td>
<td>0.48 ± 0.26</td>
<td>0.582</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>Number of hospitalizations per number of phases X ± SD</td>
<td>0.56 ± 0.29</td>
<td>0.54 ± 0.37</td>
<td>0.828</td>
<td>T-criterion</td>
</tr>
<tr>
<td>Number of hospitalizations per years illness X ± SD</td>
<td>0.25 ± 0.21</td>
<td>0.24 ± 0.22</td>
<td>0.858</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>MADRAS X ± SD</td>
<td>2.08 ± 1.86</td>
<td>3.86 ± 3.08</td>
<td>0.023</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>YMRS X ± SD</td>
<td>1.78 ± 2.16</td>
<td>1.14 ± 1.41</td>
<td>0.265</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>GAF X ± SD</td>
<td>89.92 ± 5.02</td>
<td>87.07 ± 8.15</td>
<td>0.252</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>SDS X ± SD</td>
<td>3.22 ± 2.99</td>
<td>4.75 ± 3.93</td>
<td>0.097</td>
<td>Mann-Whitney</td>
</tr>
<tr>
<td>Family history – number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16 (55.2)</td>
<td>13 (44.8)</td>
<td>0.498</td>
<td>Fischer's exact test</td>
</tr>
<tr>
<td>Yes</td>
<td>21 (58.3)</td>
<td>15 (41.7)</td>
<td></td>
<td>test</td>
</tr>
<tr>
<td>Marital status – number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>21 (63.6)</td>
<td>12 (36.4)</td>
<td>0.195</td>
<td>Fischer's exact test</td>
</tr>
<tr>
<td>Married</td>
<td>16 (50.0)</td>
<td>16 (50.0)</td>
<td></td>
<td>test</td>
</tr>
<tr>
<td>Educational status – number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to secondary education</td>
<td>11 (52.4)</td>
<td>10 (47.6)</td>
<td>&lt;0.001</td>
<td>Fischer's exact test</td>
</tr>
<tr>
<td>Above secondary education</td>
<td>26 (59.1)</td>
<td>18 (40.9)</td>
<td></td>
<td>test</td>
</tr>
<tr>
<td>Social status – number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-students, non-employed, persons on a disablement pension</td>
<td>6 (50.0)</td>
<td>6 (50.0)</td>
<td>0.488</td>
<td>χ²</td>
</tr>
<tr>
<td>Employees</td>
<td>23 (54.8)</td>
<td>19 (45.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons on an old age pension</td>
<td>8 (72.7)</td>
<td>3 (27.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The comparison of the described variables in both groups revealed that the age of illness onset was earlier for the patients with BAD, $31.30 \pm 13.10$ years, than for the patients with RDD, $37.04 \pm 13.43$ years, as this difference has reached the cut-off value of statistical significance ($p=0.051$). The mean duration of illness for the patients with BAD was $17.76 (\pm 10.76)$ years and exceeded with a statistical significance that for the patients with RDD, $11.25 (\pm 10.20)$ years, respectively ($p=0.003$).

The patients with bipolar course had approximately two more affective episodes for the period of their illness, $6.92 \pm 4.23$, than those with unipolar course, $3.64 \pm 1.79$, respectively, as this difference has reached a high statistical significance ($p<0.001$). In parallel with this, the patients with BAD had almost two times more hospitalizations than those with RDD, as the difference was also statistically significant ($p=0.003$). The performed analysis has revealed that hospitalization was required in almost every second phase of the illness and every 4 years. The two diagnostic groups did not differ significantly on these variables.

The greater part of the patients with psychotic symptoms, 24 (80%), belonged to the BAD group, while those with RDD were 6 (20%). The level of statistical significance for this variable was also high ($p=0.003$).

The two diagnostic groups did not differ significantly on the variables of marital status, social status and family history. There was, however, a highly reliable, statistically significant difference between the groups in the educational status. In both groups the patients, whose educational status exceeded the secondary educational level prevailed, as those individuals were significantly more among the patients with BAD ($p<0.001$).

The performed analyses have revealed that the presence of depressive symptoms during a remission was more commonly observed among the patients with RDD, as the mean value of the MADRS for the patients with unipolar course was $3.86 \pm 3.08$ scores versus $2.08 \pm 1.86$ scores for the patients with BAD ($p=0.023$). The mean value of the mania symptoms, assessed by the YMRS was higher for the patients with BAD, but the difference was not statistically reliable.

The general functioning during a remission, assessed using the GAF, did not show significant differences between the two diagnostic groups. The application of Sheehan self-rating scale, however, demonstrated that the patients with RDD had a higher level of disturbed functioning, than those with BAD, though this difference reached only a cut-off value of significance ($p=0.097$).

**DISCUSSION**

Affective disorders are many-sided, as their most definitive clinical characteristic remains the recurrence, even after successfully performed treatment and prophylaxis [40, 41]. As previously mentioned, the period of remission is of extreme importance not only for evaluating the performed acute treatment, but also
for predicting the subsequent course and outcome of the affective disorder. In this sense, the period of remission appears, in certain aspects, more important than the period of illness, from both clinical and therapeutic point of view. The number of studies, comparing the period of remission in BAD and RDD, or in other words, trying to establish whether there is a difference between clinically healthy patients with bipolar and unipolar course of the illness, is relatively small. In this study, we have observed that for a 3-month period, covering the autumn season, 37 patients with BAD and 28 patients with RDD visited our outpatient department. They were diagnosed in conformity with the ICD-10 diagnostic criteria, although multiple literature data have revealed that the establishment of a diagnosis of RDD is rather disputable and frequently incorrect [40]. For example, according to many authors, the initial diagnosis of depression was changed, during the follow-up period, to BAD in 40% to 60% of the patients [32, 33]. As mentioned above, there is no exact definition of the term “remission” [45]. Most of the studies define the period of remission as a period with duration of at least 3 months [9], combining the lack of symptoms and the absence of disturbed functioning [45] or scores according to the MADRS ≤ 10 (points) and scores according to the YMRS ≤ 6 (points). Based on our clinical experience, we decided, however, to accept the 6-month period, recommended by other authors [42], in order to ascertain the presence of a remission. The study subjects were regularly followed-up patients on maintenance therapy. The number of the patients with BAD was higher, but this might be explained with the higher frequency of the ambulatory visits they were recommended to perform, in comparison with the patients with RDD. Of course, the increasing “incidence” of BAD should not be underestimated [6], as well as the probability of the fact, that the patients with a mild course of recurrent depression are less likely to search for regular psychiatric help. In general, the two groups did not differ quantitatively on gender and age, which made it possible to ignore the impact of these variables on the subsequent statistical analyses. The age of illness onset was earlier for the patients with BAD, than for the patients with RDD and although this difference has reached the cut-off value of statistical significance, it is a fact, established by many other researchers [3, 27]. Logically, this results in longer duration of the illness in the patients with BAD, than in these with RDD, an observation supported by the results of our study.

Of course, the recurrence, i.e. the number of affective deteriorations and the respective number of required hospitalizations, and not simply the absolute value in years of the illness, is of essential importance. The patients with BAD in the study sample had almost two times more phases and hospitalizations, than the patients with RDD, as the difference was statistically significant. Other authors have reported similar results [13], thus confirming the conclusion that bipolar disorders differ from the unipolar ones not only with their bipolarity, but also with the higher frequency of recurrence. The course is progressive and generally the following episodes are more severe [7, 35], which imposes more regular and thorough following-up of
these outpatients, in order to prevent subsequent deterioration and/or hospitalizations. It is interesting that the ratio number of phases/number of hospitalizations did not show a difference between the two diagnostic groups. This might be a result of the poor diagnostic homogeneity of the patients with RDD (a real problem of the current diagnostic classifications). Possibly, the patients with more frequent and severely manifested clinical episodes, as well as the patients with “hidden bipolarity” have influenced the results in this diagnostic group. In connection to this, another important indicator associated with the diagnostic consideration, is the presence of psychotic symptoms. They are a sign of a greater degree of severity of the affective disorder and of a stronger affiliation to the bipolar spectrum [3]. In our study, only 20% of the patients with similar symptoms during their phases had the diagnosis of RDD. It is important to mention here, that such patients need special attention, as they are with unipolar course of the illness “for the present” and are always at risk of revising and changing of their diagnosis.

In contrast to the literature data, indicating that the patients with BAD have more serious, long-standing disturbances in social and professional aspects than the patients with RDD [10, 15], our study has not confirmed this fact. It should be taken into account, of course, that the adequate family and social functioning should be considered not necessarily a function of the illness, but rather a protective factor against frequent recurrence [28]. The difference in the educational status of the study sample is a fact of interest. In both diagnostic groups the patients, whose educational status exceeded the secondary educational level prevailed, as these individuals were significantly more among the patients with BAD. Most probably, the reasons for such a result should be sought in the status of residence of the patients, visiting this ambulatory room, as well as in the fact that the patients with a higher educational status have a higher potential for psycho-education [23] and adherence to the administered treatment [37]; respectively, such patients are likely to be in remission.

The presence of sub-syndromes during a remission is an extremely important indicator for the quality of the acute and maintenance treatment, as well as for the prognosis of the clinical course of ADs. It is commonly accepted that the presence of residual symptoms during a remission is rather a rule than an exception [7, 41], and that the residual symptoms are observed in almost every second patient in remission [30]. On the other hand, the presence of similar symptoms deteriorates the quality of remission and results in a higher frequency of recurrence [7]. Therefore, it should be considered that the patients with more symptoms during a remission have more phases and a more unfavorable course, regardless of the polarity of the course [26, 34]. It seems, however, that the presence of similar complaints, especially these with depressive characteristics, has a different impact on the two types, unipolar and bipolar, of the affective disorder. It is established that in RDD, the disturbances in functioning of patients with sub-threshold depressions, are comparable with these during a real depressive episode [24] and in this case,
probably, a more aggressive treatment approach is advisable [20]. The comparison data in literature are contradictory. According to some studies, the residual depressive symptoms are more frequently met in the BAD II type, than in RDD and BAD I type, while according to other studies, the remission in both diagnostic categories cannot be differentiated with regard to the sub-syndrome depressive symptoms [7]. In our study, the patients with RDD had significantly more sub-depressive complaints during a remission, than the patients with BAD. Similar results have been reported by other authors, who have indicated that the patients with unipolar and bipolar depressions in remission demonstrate more depressive complaints than the healthy controls, as these complaints are more in RDD, than in BAD, mainly on account of anxiety and somatic complaints [30, 42]. It should be noted that the significant disturbances in BAD are mainly associated with the sub-syndrome depressive conditions, while the presence of hypomanic symptoms does not affect or even enhances functioning [18].

There was no difference between the two groups with regard to overall functioning, assessed via the GAF. Several authors have recommended the application of the self-rating Sheehan scale as a suitable, rapid and valid enough instrument for the evaluation of functioning during a remission [39]. The method of evaluation, based on a visual-analogue scale, is easily applied under ambulatory conditions and is sufficiently reliable. Here, the patients with RDD have also manifested more disturbances in their everyday functioning, but the difference was at the limit of statistical reliability. Several studies have established a sufficiently high level of concordance between the presence of residual depressive symptoms and the decrease in functioning of patients with RDD [17, 45]. This was also observed in our study, as the presence of higher MADRS scores probably correlated with higher SDS scores. It is here the place to draw the attention to the fact that recurrent depression ranks fourth among the diseases in relation to severity and disability in all ages [31] and ranks first in the age-range between 15 and 44 years, compared with BAD, which ranks ninth and fifth, respectively [43]. This is explained with the high incidence – up to 20% of the population has suffered from this illness at least once in a life [21], as well as with long-standing presence of the depressive symptoms – in up to 60% of the time of a continuous follow-up [16]. According to the literature data, BAD is also related with a functional deficit, even during a period of stable remission [11]. Patients with BAD have significantly lower self-rating of the social functioning than healthy controls [2, 8]. We may conclude, however, that the leading factor for complete recovery and functioning is not the diagnosis itself, but the quality of remission, respectively, the asymptomatic stabilization.

**Conclusion:** ADs are complex, cerebral and behavioral disorders, caused by the dynamic interrelations between a great number of genetic and non-genetic, including environmental factors [1, 40]. The modern diagnostic criteria are rather large-scaled and based on the phenotype expression. Thus, the diagnostic confusion is a part of the clinical reality. The most important and indisputable sign of
these disorders (independently of their polarity) is recurrence. In this sense, the period of remission, especially in the early stage of the illness, is of key importance. In many aspects, it is of essential importance for the diagnosis, as well as for the treatment and prognosis. The fulfillment and duration of this period determine not only the diagnosis, but also the prognostic and outcome expectations. It appears that in ambulatory conditions, the patients with BAD, having a higher educational status and more favorable course of the illness, and the patients with RDD, having a lower educational status and more sub-depressive symptoms during the remission period, are the most frequently followed-up.

REFERENCES:
1. Миланова, В. Афективни разстройства: взаимодействие на генетични и психосоциални фактори. – Психосом. Мед., 14, 2006, 137-158.
A comparison of remission in bipolar...

Address for correspondence:
Vessela Stoyanova
Psychiatric Clinic
University Hospital “Aleksandrovska”
1 Sv. G. Sofiiský str.
1431 Sofia
9230 979
e-mail: vestoyan@yahoo.com
## CONTENTS

M. Panchovska, E. Firkova, H. Georgiev, A. Gosmanov and R. Makuleva.  
Periarticular calcifications in normocalcemic primary hyperparathyroidism ........................................3

A. Loukova and J. Radenkova-Saeva. Deanxit self-poisoning in a patient  
with facioscapulohumeral muscular dystrophy – a case report ..............................................................9

H. Blagoeva, Ch. Balabanov and D. Petrov. Pseudoexfoliation syndrome and glaucoma .................12

K. Koev, E. Borisova and L. Avramov. He-Ne low level laser therapeutic  
applications for treatment of acute iridocyclitis .................................................................................22

Pregnancy outcomes in normoglycemic women  
with hyperinsulinemia treated with metformin before and during pregnancy  
– a case-control study  
biguanid in pregnancy of hyperinsulinemic women ...........................................................................30

K. Todorova-Ananieva. Pharmacoeconomic analysis for the future treatment  
of diabetes mellitus after gestational diabetes .....................................................................................39

K. Koev, E. Borisova and L. Avramov. Laser-induced autofluorescence  
spectroscopy of basal cell carcinoma and papilloma of eyelids and comparison  
with the results from the histological investigation .............................................................................51

R. Nikolova, E. Vodenitcharov and N. Tzacheva. Physiological mechanisms  
controlling cardiovascular responses to muscular static load ..................................................................55

G. Petrova, A. Stoimenova and M. Manova. Cost-effectiveness of celecoxib  
in patients with familial adenomatous polyposis: a Bulgarian scenario .............................................64

A. Stoimenova. Food supplements in Central and Eastern European countries .................................71

A. Todorova. Quality of life and age at onset in patients with Parkinson’s disease .............................78

V. Stoyanova, S. Krastev, R. Vladimirova, G. Genchev and V. Milanova. A comparison  
of remission in bipolar and recurrent depressive disorders: clinical  
and socio-demographic characteristics .................................................................................................87

---

**ACTA MEDICA BULGARICA 1/2009**

Editor in Chief: Prof. V. Mitev, MD, Ph. D., DSc  
Scientific editor: Prof. W. Bossnev, MD, Ph. D., DSc  
Editor of the English text: B. Stancheva, MD  
Art editor and computer design: D. Alexandrova  
Organizing secretary: M. Dimitrova  
Publisher’s sheets: 7.3  
Printer’s sheets: 5.5  
Format: 70 x 100/16  
Issued by the Central Medical Library