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ORIGINAL ARTICLE

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Feet deformities in patients with hip osteoarthritis

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ABSTRACT

Background: The lower limb constitutes a complex motor system consisting of interdependent components. Any feet disorder may cause disturbances in the biomechanics of the entire lower limb and in consequence can lead to joint degeneration and affect gait.

Methods: Participants were divided into two groups. The research group consisted of n = 60 patients with hip osteoarthritis, aged 52–84 and the control group consisted of n = 32 individuals without hip osteoarthritis, aged 50–74. A dynamic pedobarographic analysis was conducted using a RSScan® International Footscan system — a two-meter-long plantar pressure platform with an interface box. Upon completion of the measurement, results were printed and foot deformity was assessed using: Wejsflog index, Clarke's angle, hallux Valgus ALFA angle, pronation-supination index.

Results: The research group had a significantly lower mean Wejsflog index compared to the control group (2.32 *vs* 2.59). Results showed also that Hallux Valgus ALFA angle was significantly higher and Clarke's angle significantly lower in the research group when compared to the control group.

Conclusions: Foot deformities are significantly more common among patients with hip osteoarthritis. Fallen medial longitudinal arch, fallen transverse arch and hallux valgus are factors to consider in prevention and treatment of hip osteoarthritis.

Key words: hip osteoarthritis, feet deformities, pedobarography

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Introduction

Coxarthrosis is one of the most common diseases of the locomotor system affecting the middle-aged and the elderly with the onset most often occurring in the fifth and sixth decade of life [1, 2]. Factors affecting the course and the development of osteoarthritis (OA) can be categorised into the following groups: mechanical, genetic, metabolic, inflammatory and immunologic [3, 4]. Chondrocyte activity depends significantly on mechanical stress [5]. Hip dysplasia is a primary example of mechanically induced osteoarthritis. Yet, Perthes disease, slipped capital femoral epiphysis, acetabular protrusion or femoral head avascular necrosis also share the mechanical origin of OA [6]. It should be stressed that physical activity significantly contributes to the pathogenesis of OA when it is of high intensity. It leads to increased catabolism in the cartilage and thus its degeneration, i.e., collagen network weakening, loss of proteoglycans and decrease in cartilage rigidity and flexibility [7].

The lower limb constitutes a complex motor system consisting of interdependent components, among which the feet are of paramount importance, having evolved in the course of phylogenesis to carry significant weight. Any feet disorder may cause disturbances in the biomechanics of the entire lower limb. The gait becomes anomalous and the joints operate in unsuitable conditions. The resulting compensatory mechanisms and suboptimal biomechanics accelerate the degenerative changes. Hence, it may be hypothesised that a significantly higher incidence of feet deformities is to be found in patients with hip osteoarthritis.

Table 1. Group characteristics

	Control Group			Research Group			
	N		SD	N		SD	p < 0.05
Age	32.00	60.56	6.65	60.00	67.57	7.86	0.00254*
Weight [kg]	32.00	71.80	12.31	60.00	77.79	12.07	0.01956*
Height [cm]	32.00	164.75	8.29	60.00	164.20	7.17	0.34462
BMI [kg/m^2]	32.00	26.42	3.97	60.00	28.80	4.22	0.00062*

Subject, materials and methods

The research was conducted in 2014–2015 in the Physical Effort and Sports Genetics Laboratory at Gdansk University of Physical Education and Sport. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Participants were divided into two groups. The research group consisted of n = 60 patients with hip osteoarthritis, aged 52–84 (mean 67,57, SD 7,86) and the control group consisted of n = 32 individuals without hip osteoarthritis, aged 50–74(mean 60,56, SD 6,65). Table 1 presents sample characteristics.

A dynamic pedobarographic analysis was conducted using a RSScan® International Footscan system — a two-meter-long plantar pressure platform with an interface box. The system consists of 16,384 sensors and has a scanning rate of 500Hz. The participants were asked to walk barefoot across the platform. Owing to a runway attached to the platform, the participants were not aware of the exact moment of measurement. The measurement was considered valid when both feet were placed on the platform and their scan appeared on the screen.

Patients selection procedure

Patients were chosen after clinical examination and hip X-Ray conducted by the main doctor. Subsequently, they were selected by inclusion and exclusion criteria. All patients also signed an informed consent form. Research inclusion criteria involved: diagnosed unilateral hip osteoarthritis, age 50–85 and consent for research. Research exclusion criteria were: diagnosed bilateral hip osteoarthritis, rheumatoid arthritis, osteoarthritic changes in the joints of the knee, ankle or foot, any pain reported in the joint of the knee, ankle or foot, past joint replacement or other surgical interventions in the lower limb, changed anatomy of the lower limb (i.e.varus and valgus knee deformities), mobility aid, deep vein thrombosis, acute radiculopathy and lower limb length discrepancy > 1 cm.

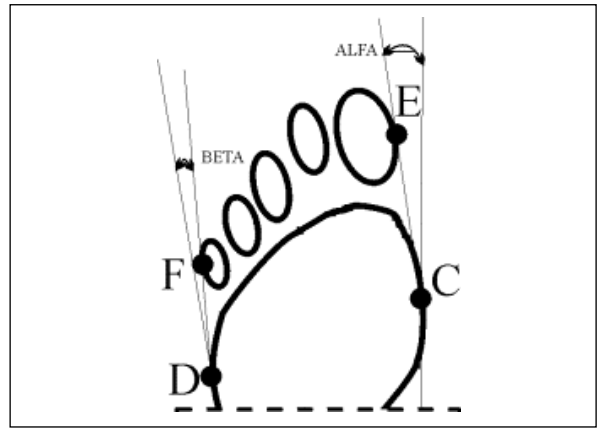

Figure 1. Definition of Wejsflog Index [22]

Determination of used angles

Upon completion of the measurement, results were printed and foot deformity was assessed using:

1. Wejsflog index,
2. Clarke's angle,
3. Hallux Valgus ALFA angle,
4. Pronation-supination index (calculated by the software).

The parameters were calculated for both feet only for the control group. The research group was recording the side affected by hip OA.

To calculate Wejsflog index, the length (the AB line) and width of the foot (the CD line) were measured, as shown in Figure 1. Subsequently, the length-to-width ratio (normally, 3:1) was calculated [8, 9].

The cut-off value for a normal foot arch was defined as ≥ 2.56. A Wejsflog index ≤ 2.55 indicates a fallen arch.

Clarke's angle is defined at the intersecting tangents to points CS and qQ, as shown in Figure 2.

Based on the angle value, the following categories were defined:

1. ≤ 30° — pes planus
2. 31–41° — low arch
3. 42–54° — normal arch
4. ≥ 55° — high arch [10].

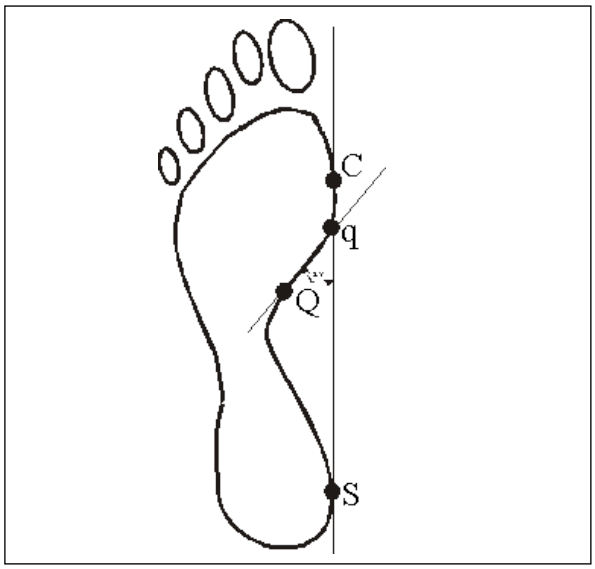

Figure 2. Definition of Clarke's Angle [22]

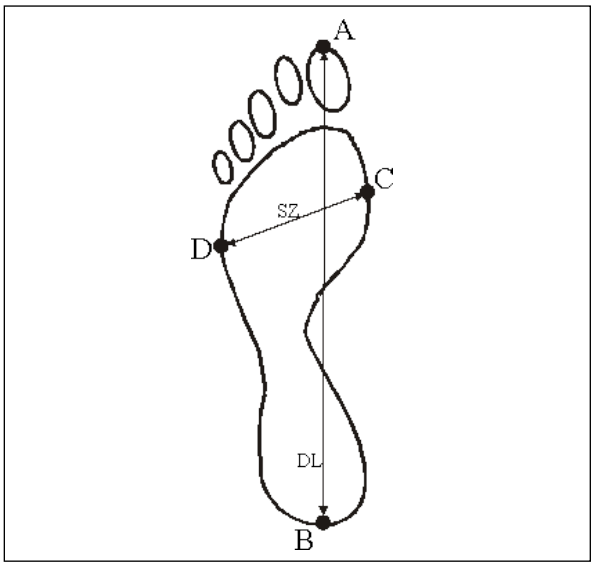

Figure 3. Definition of Hallux Valgus ALFA Angle [22]

To assess hallux valgus, the angle between intersecting tangent to the medial foot outline and the tangent running through points C (the medial end of the foot width) and E (medial toe outline) was measured, as shown in Figure 3. It was assumed that the 0–9° angle indicates a normal position.

External rotation angle for the stance phase was also calculated.

Statistical analysis

Shapiro-Wilk test was used for data distribution, and non-parametric U-Mann Whitney test was used for comparing means in independent samples.

In order to increase reliability, the median and quartile deviation Q were calculated. In this way, extreme values that could bias the results were eliminated. Quartile deviation is one-half the difference between the first and the third quartiles, that is 25% and 75% of results sorted in the ascending order [11].

Significance level (accepted probability level of making a type I error) was set at $\alpha = 0{,}05$.

Results

U-Mann Whitney test has shown a statistically significant difference between the research group and the control group for Wejsflog index, Clarke's angle and Hallux Valgus ALFA angle.

The research group had a significantly lower mean Wejsflog index compared to the control group (2.32 vs. 2.59). The index was falling together with the fall of the transverse arch of the foot.

Hallux Valgus ALFA angle was significantly higher in the research group (mean at 13.87°) when compared to the control group (mean at 8.85°). Significant differences between groups were found in the Clarke's angle, which is used to assess the longitudinal arch. The control group had a mean angle of 52°, which falls into the normal range. The research group, in turn, had a mean angle of 39° indicative of low longitudinal arch.

External rotation (eversion) angle during the stance phase was also significantly different between the two groups. The research group had an eversion mean of 19.49° compared to half that angle (10.16°) in the control group. The results are shown in Table 2.

Table 2. Comparison of Wejsflog Index, Clarke's Angle, Hallux Valgus ALFA Angle and External Rotation Range between control and research groups

	Control Group			Research Group			
			Q			Q	p < 0.05
Wejsflog Index	2.59	2.6	0.20	2.32	2.30	0.16	0.0000*
Clarke Angle [°]	52.23	52.00	6.375	39.00	35.00	11.00	0.0000*
Hallux Valgus ALFA Angle [°]	8.85	7.50	7.50	13.87	10.00	7.50	0.0306*
External Rotation Range [°]	10.16	11.46	3.8325	19.49	18.375	5.8	0.0000*

Discussion

Data collected in multiple studies show that as many as 80% of the adult population may suffer from foot disorders, which are often diagnosed already in childhood. Foot or toes disorder erodes the lower limb activity and function. Abnormalities in the structure or biomechanics trigger changes of function up to the kinetic chain of the lower limb and the axial skeleton. Shifts in the stance pattern changed the centre of gravity and deviated gait pattern leads to OA changes that are secondary to such non-physiological wear and tear process [12].

Pes planus is one of the most common postural deformities affecting the motor system often with positive feedback that leads to further anatomic changes in the foot, i.e. pes valgus, excessive foot pronation and abduction of the forefoot. Pathomorphological changes, such as pathology of connective tissue or Achilles tendon shortening may also occur [13, 14].

According to Dziak, pathologies of the knee and the hip may stem from changes of the foot that occurred in childhood and went unnoticed [15].

A noteworthy contribution to the subject was the research conducted by Rongies et al. investigating the incidence of pes planus in relation to coxarthrosis and gonarthrosis. A total of 76 patients were divided into 3 groups: A — patients with gonarthrosis, B — patients with coxarthrosis and the control group. Based on the results, it was found that pes planus and low longitudinal arch were significantly more common in participants with coxarthrosis and gonarthrosis when compared to the control group. Mean Clarke's angle in group B was 32° [16]. These findings correspond with our results since the Clarke's angle in our research group was 39°. Both values fall into the category of low foot arch (between 31° and 41°) [16].

Rzaniak et al. conducted research that lays the further ground for the coexistence of a fallen longitudinal arch with OA of the knee or the hip. The authors compared 27 patients with coxarthrosis with 27 healthy controls. Clarke's angle was measured for all participants. The study concluded that patients with coxarthrosis had a significantly lower Clarke's angle compared to the control group [17], which is in line with our findings.

Lorkowski points out that primary coxarthrosis must be a result of some specific mechanical factors. He points that a fallen longitudinal arch causes increased the contact area between the foot and the ground, which affects the distribution of loading forces in the joints above. Thus, according to Lorkowski, such altered mechanics in the transfer of weight from the proximal joints, via the feet, towards the ground, may lead to arthrosis [18].

Similarly, von Grabowski found that accelerated wear of the knee joint stems from inborn or acquired lower limb axis deviation [19].

Research also confirms observations made by Cavanagh who believes changes in the height of the foot arch determine the posture, which may contribute to the development of locomotor pathology. Cavanagh argues that normal foot anatomy is indispensable for proper locomotion. Therefore, neglecting fallen arches in childhood results in the development of deformities in adulthood. Cavanagh stresses that even the smallest deformity may trigger changes in the locomotor system, while abnormalities in the longitudinal arch have the most far-reaching consequences in the biomechanics chain of the leg. This, in turn, may cause abnormalities of the stance, gait, development of arthrosis and pain, even in distant joints such as the vertebral column [12].

Evidence for the extended impact of a foot fallen arch on the locomotor system has been provided by Skura et al. in their study consisting of 370 women and 514 men sampled randomly. The results have shown that a fallen arch coincides not only with coxarthrosis and gonarthrosis but also with disorders of the ankle joints, sacroiliac joints and the lumbar spine [20].

In our study, we have used Wejsflog index to assess the degree of the transverse arch of the foot for both groups. Statistical analysis has shown a significant difference in Wejsflog index between the research group (2.32) and the control group (2.59).

Wantabe et al. stress that fallen arch is a complex of deformities such as low longitudinal arch, pes valgus and abduction of the forefoot. Authors also note that tibialis posterior dysfunction is a common cause of acquired pes planus, which remains flexible up to stage II of dysfunction when the deformity is passively correctable. Such findings have been widely discussed in the literature in the past 20 years [21].

A fallen transverse arch may often be associated with hallux valgus. In this study, we have observed a significant difference in the mean Hallux Valgus ALFA angle between the research group (13.87°) and the control group (8.85°).

Conclusions

1. Foot deformities are significantly more common among patients with hip osteoarthritis.
2. Fallen medial longitudinal arch, fallen transverse arch and hallux valgus are factors to consider in prevention and treatment of hip osteoarthritis.

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Conflict of interest

The authors of this paper have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) our work.

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ORIGINAL ARTICLE

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Losartan effects on liver cytochromes CYP3A, CYP2C and CYP2E1 functioning at metabolic syndrome in young and adult rats

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ABSTRACT

CYP450-dependent interactions and toxicological consequences of hypoglycemic and antihypertensive drugs used in treatment of children with metabolic syndrome (MS) remained unclear. Our aim was to carry out a complex estimation of metabolic syndrome and losartan mediated changes in CYP3A, CYP2C, CYP2E1 mRNA expression, corresponding marker enzymes activities, liver antioxidant system and lipid peroxidation parameters of adult and pubertal rats. Wistar albino male rats of two age categories (young animals of 21 days age (50–70 g) and adults (160–180 g) were divided into 6 groups (6 animals in each): 1 – Control 1 (intact young rats); 2 – Control 2 (intact adult rats); 3 –young rats with MS; 4 – adult rats with MS; 5 – young rats with MS+losartan; 6 – adult rats with MS+ losartan. The metabolic syndrome model was induced by full replacement of drinking water with 20% fructose solution (200 g/l). After 60 days of MS modeling, investigation of rat liver CYP3A, CYP2C, CYP2E1 mRNA expression, their marker enzymes activities, lipid peroxidation parameters were carried out. Losartan administration caused increase of CYP3A, CYP2C and CYP2E1 mRNA expression rates in both age groups. Marker enzymes, glutathione transferase and reductase rates were normalized only in adult rats. In group of pubertal animals losartan administration led to CYP3A and CYP2C marker enzymes activities normalization. Liver reduced glutathione contents remained decreased in both age groups. Thus, losartan demonstrates some age-dependent effectiveness towards normalization of CYP450 isoforms expression rates, p-nitrophenol hydroxylase, erythromycin-N-demethylase and diclofenac hydroxylase activities, but not glutathione system and lipid peroxidation rates.

Key words: metabolic syndrome, losartan, CYP450, pubertal, rats

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Introduction

Metabolic syndrome (MS) belongs to pathological states that could affect CYP450 activity. It is modern medicine's actual problem caused by an unhealthy lifestyle. Last decades MS is increasingly spreading among children and adolescents [1]. An emerging epidemic of pediatric hypertension is paralleled an increasing prevalence of childhood obesity. Elevated blood pressure during childhood and adolescence is associated with end-organ damage [1].

Already available clinical data highlight that pediatric drug dosing, safety and efficacy cannot simply be extrapolated from adult clinical trials [1]. Particularly interesting is the study of the joint effect of metabolic syndrome and drugs designed to correct its symptoms. In this case, it is possible to identify possible additional modifying factors for drugs biotransformation with this pathology. Unfortunately, the information dedicated to this issue is extremely limited [2, 3]. There are no data on CYP450-dependent interactions of hypoglycemic and antihypertensive drugs used in the treatment of MS in children and adolescents and no detailed analysis of their use toxicological consequences. Our preliminary results indicate the presence of certain dependencies of CYP3A, CYP2C and CYP2E1 levels on age at MS [4].

Losartan was the first among angiotensin receptor blockers approved for pediatric hypertension by the United States FDA in 2004 following completion of the required clinical trials [1]. According to data obtained in vitro losartan is metabolized mainly via CYP3A and CYP2C isoforms of CYP450 [5, 6]. But there are no

data on its effects on CYP450 isoforms in children and adolescents with MS.

The aim of this work was to study the joint effects of MS and losartan on hepatic *CYP3A, CYP2C, CYP2E1* mRNA expression, their marker enzymes, liver antioxidant system and lipid peroxidation of adult and pubertal rats with MS.

Materials and methods

A total of 36 Wistar albino male rats of two age categories (young animals of 21 days age (50-70g) and adults (160–180g)) were used in the study. They were kept under a controlled temperature (from 22 °C to 24 °C), relative humidity of 40 % to 70 %, lighting (12 h light-dark cycle), and on a standard pellet feed diet ("Phoenix" Ltd., Ukraine). The study was performed in accordance with the recommendations of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes and approved by the Institutional Animal Care and Use Committee. The model of metabolic syndrome was reproduced according to the protocol of Abdulla et al. [7]. Young and adult animals were divided into 6 groups (6 animals in each group): 1 — Control 1 (intact young rats), 2 — Control 2 (intact adults), 3 — MS3 (young rats with MS), 4 — MS4 (adult rats with MS), 5 — MS3+losartan (young rats with MS and losartan (4,43 mg/kg of body weight, *per os*, 60 days)), 6 — MS4+ losartan (adult rats with MS and losartan treatment). MS was induced by full replacement of drinking water with 20% fructose solution (200g/l).

Crystalline D-fructose > 99% (Khimlaborreactiv, Ukraine, series 072000897834, batch XW 130105) was used in experiments. 20% fructose was prepared daily and given every day for two months *ad libitum*. In our experiments, losartan (potassium losartan, manufactured by LLC "KUSUM PHARM", Sumy, Ukraine) was used.

After 60 days of 20%, fructose solution consumption and losartan treatment rats were sacrificed under mild ether anaesthesia by decapitation.

Post mitochondrial and microsomal fractions of livers were obtained by the method of Kamath et al. [8], and aliquots were kept frozen at -70°C until needed.

We investigated changes of rat orthologs of human cytochromes P-450: CYP2E1, CYP3A2 instead of CYP3A4 [9] and CYP2C23 instead of CYP2C9 and CYP2C19 [10]. *p*-Nitrophenol (PNP) hydroxylase activity (a selective enzyme marker for CYP2E1) was determined in a microsomal fraction of liver according to the method of Koop et al. [11]. Erythromycin N-demethylase activity (a selective enzyme marker for CYP3A) was determined in liver microsomal fraction according to the method of Wang et al. [12], diclofenac hydroxylase activity (a selective enzyme marker for CYP2C) — according to the method of Necrasova et al. [13]. Glutathione-S-transferase activity was determined in liver post mitochondrial fraction according to the method of Habig et al. [14], glutathione reductase activity - in microsomes in accordance with „Current Protocols in Toxicology" [15], reduced glutathione and proteins SH-groups contents — in liver homogenates by method of Sedlak with Ellman's reagent [16]. Protein contents were determined with Total Protein Kit, Micro Lowry, Onishi & Barr Modification (Sigma-Aldrich, Ink., USA).

The rats' livers were used for investigation of cytochrome P-450 isoforms mRNA expression rates by method of reversed transcriptase polymerase chain reaction (rPCR). Isolation of total mRNA was carried out with TRI-Reagent (Sigma, USA). Synthesis of cDNA was carried out with reagents and protocol of Fermentas (Germany). rPCR reaction mixture contents, specific primers for *CYP2E1* gene amplification (forward 5'-CTTCGGGCCAGTGTTCAC-3' and reverse 5'- CCCATATCTCAGAGTTGTGC-3'), as well as amplification protocol were chosen according to Lankford et al. [17]. rPCR reaction mixture, amplification protocol and following specific primers – forward 5'-TACTACAAGGGCTTAGGGAG-3' and reverse 5'- CTTGCCTGTCTCCGCCTCTT-3' were used for *CYP3A2* gene amplification according to Jager et al. [9]. rPCR reaction mixture, amplification protocol and following specific primers — forward 5'-GATGCTGTCTTCCGTCATGC-3' and reverse 5'- GTAATAGGCTTGATGTCAAG-3' were used for *CYP2C23* gene amplification according to Imaoka et al. [10]. rPCR with primers of β-actin (sense 5'–GCTCGTCGTCGACAACGGCTC–3' and antisense 5'–CAAACATGAT CTGGGTCATCTTCT–3') was carried out for internal control. All primers were synthesized by «Metabion» (Germany). Thermocycler MyCycler (BioRaD, USA) was used for amplification. Electrophoresis of PCR products (CYP2E1-744 b.p., *CYP2C23*-252 b.p., *CYP3A2* — 349 b.p. and β-actin-353 b.p.) was carried out in 2% agarose gels (80 V; 1.5 h). After electrophoresis gels were stained with ethidium bromide and visualized under a UV transilluminator (BIORAD, USA). Electrophoresis data analysis was carried out with Quantity One Software (USA).

The levels of lipid peroxidation (LPO) in liver microsomes were investigated as the rates of NADPH-dependent thiobarbituric acid reactive substances (TBARS) formation [18].

Results

CYP2E1 mRNA expression comparative study in the livers of pubertal and adult rats with MS and losartan administration demonstrated pronounced changes at both age groups of rats (Fig. 1).

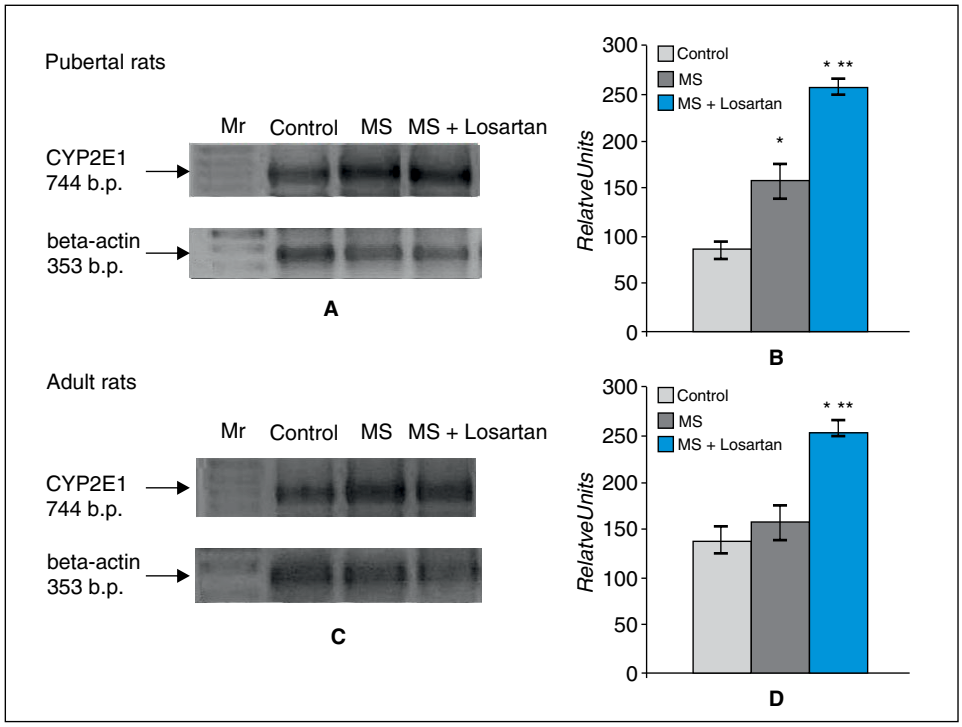

Figure 1. *CYP2E1* mRNA content in the liver of pubertal and adult rats with MS and losartan administration: **A**, **C** — representative electrophoregrams of *CYP2E1* (744 b.p) and reference-gene β-actin (353 b.p.) RT-PCR products; **B**, **D** — average rate of *CYP2E1* mRNA expression in the liver (n = 6, Mr - DNA marker, signal intensity of β-actin was taken as 100%); *P < 0.05 in comparison with control; **P < 0.05 in comparison with MS

CYP2E1 mRNA expression was increased at a group of pubertal animals with MS (1.8 folds compared with the control) and the group of pubertal animals with MS and losartan administration (more than 2.0 folds compared with the control). Losartan, administered to adult animals with MS, resulted in 2–2.5 folds increase in expression of the *CYP2E1* gene.

MS caused statistically significant growth of *CYP3A2* mRNA expression at a group of pubertal animals (Fig. 2). Changes of *CYP3A2* gene expression in adult animals with MS were not significantly different from control. Results on CYP3A2 mRNA expression investigation in the livers of pubertal and adult rats with MS and losartan administration demonstrated more pronounced changes at groups of young rats. Losartan, administered to pubertal animals with MS, increased the level of CYP3A2 mRNA expression. In adult animals, losartan did not cause statistically significant changes in the level of CYP3A2 mRNA expression.

In the case of CYP2C23, we detected a reduction of mRNA expression levels in livers of both age groups with MS as compared with controls: pubertal animals -1.4 folds, adults — 1.6 folds (Fig. 3). Losartan administration allowed normalizing *CYP2C23* mRNA expression rates only in the group of pubertal animals. In the group of adult animals, such losartan effect was absent.

We investigated the activity of PNP-hydroxylase in liver microsomes of adult and pubertal rats with MS and losartan administration. Statistically significant growth of PNP- hydroxylase activity with MS was detected both at pubertal (1.6 fold) and adult (1.38 fold) animals groups (Tab. 1).

Study of pubertal rats' microsomal PNP-hydroxylase activity with MS and losartan administration also generally matched data on CYP2E1 gene expression. In this group rate of PNP-hydroxylase activity was increased by 1.7 fold as compared with the control. Changes in PNP-hydroxylase activity in the liver microsomal fraction of adult animals with MS and losartal administration were opposite: normalization to the control levels.

The investigation of erythromycin-N-demethylase activity showed MS opposite (by nature) effects in groups of pubertal (3 fold reduction) and adult animals (46% increase). But losartan administration caused normalization of erythromycin-N-demethylase activities with MS irrespective of age.

Investigation of diclofenac-hydroxylase activity rates (Tab. 1) demonstrated its reduction with MS in rats of both age groups (more pronounced in adults). As in the case of erythromycin-N-demethylase losartan administration led to normalization of diclofenac-hydroxylase activity rate in both age groups.

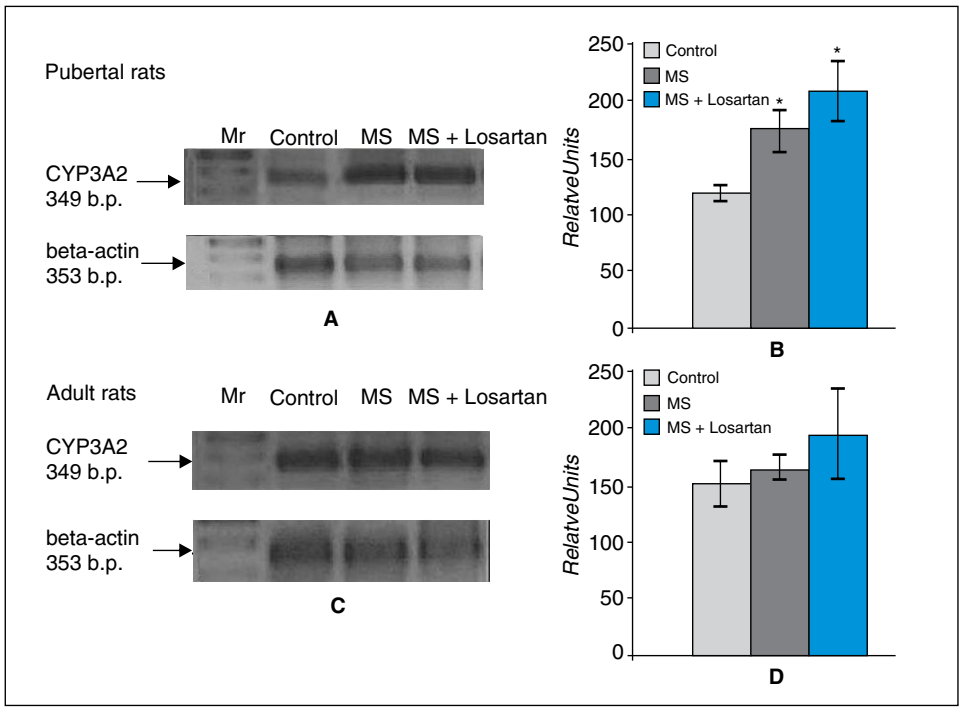

Figure 2. *CYP3A2* mRNA content in the liver of pubertal and adult rats with MS and losartan administration: **A**, **C** — representative electrophoregrams of *CYP3A2* (349 b.p) and reference-gene β-actin (353 b.p.) RT-PCR products; **B**, **D** — average rate of *CYP3A2* mRNA expression in liver (n = 6, Mr — DNA marker, signal intensity of β-actin was taken as 100%) *P < 0.05 in comparison with control

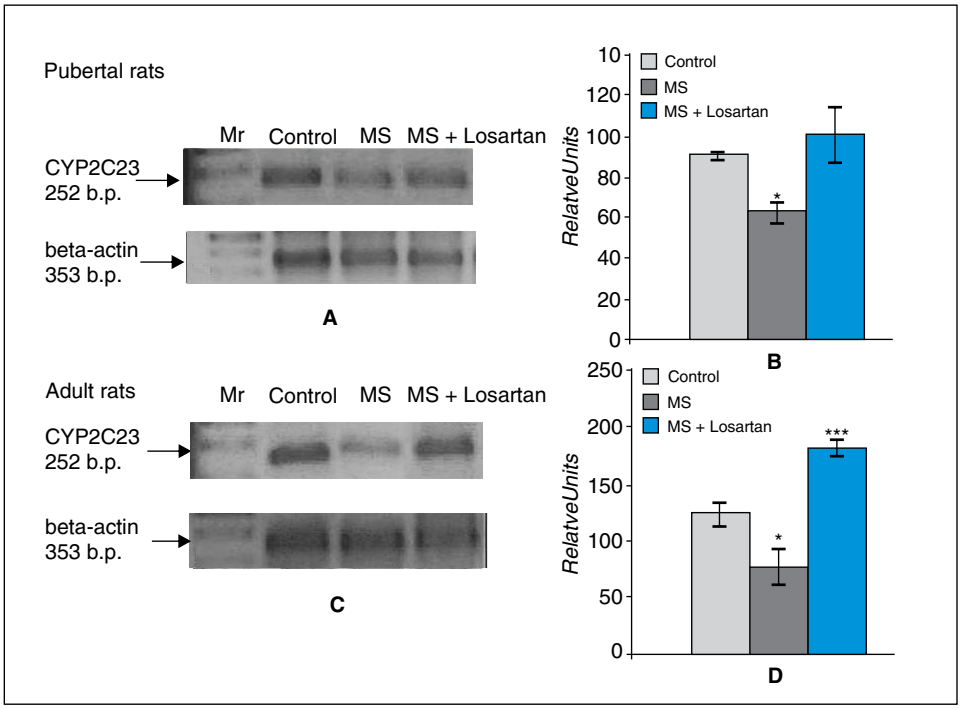

Figure 3. *CYP2C23* mRNA content in the liver of pubertal and adult rats with MS and losartan administration: **A**, **C** — representative electrophoregrams of *CYP2C23* (252 b.p) and reference-gene b-actin (353 b.p.) RT-PCR products; **B**, **D** — average rate of *CYP2C23* mRNA expression in liver (n = 6, Mr — DNA marker, signal intensity of β-actin was taken as 100%); *P < 0.05 in comparison with control; **P < 0.05 in comparison with MS

Table 1. Activities of PNP-hydroxylase, erythromycin-N-demethylase and diclofenac hydroxylase in liver microsomal fraction of pubertal and adult rats (M ± SEM, n = 6)

Groups	Activity of PNP- hydroxylase, nmoles×min^{-1} × mg of protein^{-1}	Activity of erythromycin-N-demethylase, nmoles×min^{-1} × mg of protein^{-1}	Activity of diclofenac hydroxylase, nmoles×min^{-1} × mg of protein^{-1}
Control 1	0.46 ± 0.021	0.96 ± 0.17	552.0 ± 19.1
MS3	0.74± 0.051*	0.32 ± 0.09*	380.2 ± 13.8*
MS3 + losartan	0,77 ± 0,065 *	1,04 ± 0,38	568,8 ± 161,0
Control 2	0.45 ± 0.018	0.22 ± 0.02	403.6 ± 14.8
MS4	0.62 ± 0.055**	0.32 ± 0.03**	140.8 ± 14.3**
MS4 + losartan	0,44 ± 0,040	0,20 ± 0,02	576,7 ± 93,5$^{\#}$

*P < 0.05 in comparison with control 1; **P < 0.05 in comparison with control 2; $^{\#}$ P < 0.05 in comparison with MS4

Table 2. Contents of reduced glutathione and glutathione transferase and reductase activities in liver of pubertal and adult rats with MS (M ± SEM, n = 6)

Groups	Activity of glutathione reductase, nmoles×min^{-1} × mg of protein^{-1}	Activity of glutathione transferase, μmoles×min^{-1} × mg of protein^{-1}	Contents of glutathione, μmoles×g of tissue^{-1}
Control 1	109.8 ± 4.6	1.35 ± 0.09	2.28 ± 0.33
MS3	89.4 ± 5.9 *	1.08 ± 0.05 *	1.30 ± 0.15*
MS3 + losartan	88,6 ± 6,4 *	1,04 ± 0,080 *	1,25 ± 0,11*
Control 2	115.0 ± 5.5	1.25 ± 0.09	2.58 ± 0.27
MS4	114.0 ± 5.0	1.12 ± 0.06	1.48 ± 0.18**
MS4 + losartan	110,8 ± 4,2	1,04 ± 0,059	1,80 ± 0,18**

*P < 0.05 in comparison with control 1; **P < 0.05 in comparison with control 2

In our experiments, glutathione-S-reductase (-18.5%), glutathione transferase (-20%) activities and reduced glutathione contents (-43%) were significantly decreased in pubertal rats with MS (Tab. 2). Losartan administration also caused a profound decrease in levels of glutathione-S-reductase, glutathione transferase and glutathione contents. In adults losartan administration with MS led only to glutathione contents decrease.

Simultaneously with changes in glutathione metabolism, LPO processes in rats liver cells were intensified (Tab. 3). This was indicated by the increased rates of NADPH-dependent thiobarbituric acid reactive substances production both in groups with MS and losartan administration with MS irrespective of age.

Discussion

It is absolutely obvious that to increase therapy's efficiency and safety it is necessary to have accurate CYP450 isoforms profile information in each individual case. It allows to establish the potential interaction of drugs, including competition for specific isoforms, the individual variability associated with high polymorphism of these isoforms, and different isoenzymes possible induction. Some of the pathologies including MS, obesity and diabetes could additionally modify profiles of CYP450 isoforms thus changing drugs effects. Unfortunately, such data are limited to several studies in adults, and specifics of metabolic processes in children and adolescents are generally not taken into account by researchers and clinicians [2, 3]. In view of the above, we have identified expression profiles of three isozyme CYP450 in the liver of pubertal rats and adult animals with MS and losartan administration.

Our results on the enhancement of CYP2E1 gene expression with MS are in agreement with other authors data, which showed an increase in CYP2E1 activity in laboratory animals with obesity, which is one of the main constituents of MS [19, 20]. Administration of losartan to pubertal and adult rats with MS did not lead to normalization of the CYP2E1 expression level in the liver. Regarding the p-nitrophenol hydroxylase (CYP2E1 marker enzyme), its activity increased in the group of pubertal rats both with MS and losartan administration with MS. This is consistent with the above findings of the CYP2E1 gene expression study. However, we have not registered changes in the p-nitrophenol

Table 3. NADPH-dependent LPO in rat liver microsomal fractions with MS and losartan administration (M ± SEM; n = 6;)

Groups	NADPH-dependent LPO, nmoles×min^{-1} × mg of protein^{-1}	
	Pubertal rats	Adult rats
Control	0,078 ± 0,007	0,105 ± 0,02
Metabolic syndrome	0,170 ± 0,04*	0,167 ± 0,02*
Metabolic syndrome +losartan	0,133 ± 0,016*	0,164 ± 0,015*

*P < 0.05 in comparison with control

hydroxylase activity in the microsomal fraction of adult rat liver. In this case, CYP2E1 expression intensification was not accompanied by the stimulation of the corresponding enzyme activity, as noted by other researchers in relation to various isoforms of CYP450 [21, 22]. Such age-dependent differences in losartan effects with MS might be due to changes in number, affinity, density, and/or subtypes of angiotensin I and II receptors [23–25].

The metabolism of losartan in the liver of rats also involves CYP2C and CYP3A isoforms [26–28]. The MS greatly affects the expression of the *CYP3A2* gene (*CYP3A4* orthologue) in the liver of pubertal rats, increasing its level by 30% compared with the control group. Regarding the erythromycin-N-demethylase (CYP3A2 marker enzyme), its activity decreased in the group of pubertal rats with MS. Interestingly, other authors also showed a decrease in the clearance of CYP3A4 cytochrome substrates in obese patients compared to normal [21]. It could be evidence of this isoenzyme's activity decrease with this pathology. In our opinion, synchronous loss of CYP3A4 activity and its gene expression increasing might be in this case due to post-translational glycosylation. This process includes, besides the modification of enzyme's activity, changes of its localization in certain cellular compartments and start of proteasomal degradation processes [29]. Our assumption is confirmed by the data of enzymatic kinetics study of non-glycosylated and glycosylated isomyforms of CYP450 aromatase [30].

Losartan increased the expression level of *CYP3A2* mRNA in pubertal rats, but the erythromycin-N-demethylase activity remained at the control level. This, obviously, could be explained by the complex interrelations of this drug simultaneous actions as a substrate and an inducer on the erythromycin-N-demethylase [31, 32]. Losartan affinity to CYP3A2 could be also changed with MS [33]. In adult rats with MS, administration of losartan resulted in the maintenance of both *CYP3A2* expression and enzymatic activity at the control levels.

We demonstrated the reduced expression of *CYP2C23* mRNA (ortholog *CYP2C9* and *CYP2C19*) in the liver of pubertal rats with MS compared to controls. This can be entirely expected taking into account the particular sensitivity of *CYP1A2, CYP2C19*, and *CYP3A4* isoforms expression regulatory systems with liver pathological changes [34]. Although it should be noted that their activity may vary selectively, depending on the type of pathology [34]. Losartan administration under these conditions led to the normalization of this indicator: expression of the *CYP2C23* gene in the liver of pubertal rats was at the same level as in the control group. The activity of diclofenac hydroxylase (CYP2C23 marker enzyme) also remained at the control level. Losartan, administered to adult rats, revealed increased both the level of *CYP2C* mRNA expression and the activity of diclofenac hydroxylase.

It should be noted (summarizing the results of CYP450 isoforms expression study), that significant variability in the expression rates of *CYP3A* and *CYP2C* genes is present in pubertal rats compared with adults with MS. Also, must be stressed the fact that losartan, administered to adult and pubertal rats, has different effects on *CYP3A* and *CYP2C* mRNA expressions regulation. While this drug did not correct CYP2C expression rate in the liver of adult rats with MS, it provided this indicator normalization in pubertal rats. Similarly, with respect to CYP3A, losartan had a much stronger effect on gene expression in pubertal rats.

Among profound changes in CYP450 isoforms expression rates, treated pathological processes, additionally, could significantly change rates of other biotransformation processes, which play the important role on drugs effects realization [19]. During the drugs biotransformation, not only biologically active and inactive metabolites are produced, but also cytotoxic reactive intermediates may appear [19]. The reactive metabolites formed as a result of the metabolism in the first phase of detoxification can be neutralized through reactions of the second phase, most a significant of which is the conjugation with the glutathione with the participation of S-transferase. In previous experiments, we showed that with metabolic syndrome at the same time as changes in certain cytochrome P-450 isoforms expression levels, deviations in the functioning of the glutathione system occur [4]. They differed significantly depending on the age of the experimental animals and were more profound in pubertal rats with MS.

Modulations of CYP450 system caused by MS and losartan administration are accompanied by the reduc-

tion of antioxidant protection, which creates conditions for oxidative stress development. Our previous investigations of MS age-dependent effects showed more profound changes in reduced glutathione contents, as well as glutathione-S-transferase and reductase activities at pubertal animals, while at adults — only glutathione contents decreased [4]. Losartan administration didn't cause any normalizing effects on glutathione-system at both age groups. But in groups of pubertal animals negative effects of MS and losartan administration on glutathione-S-transferase and glutathione reductase were more pronounced. Our data on glutathione system changes are in accordance with other authors' results obtained in experiments *in vivo* [35–37].

The analysis of our own data and other authors' results allows suggesting that the antioxidant and anti-inflammatory effect of losartan in liver tissues [37] obviously is realized by the cytokine-mediated mechanism without involving glutathione system.

MS (according to our previous data) caused oxidative stress and stimulated lipid peroxidation [4]. These processes play important roles in MS development [38]. Losartan administration weakly suppresses levels of MS-induced lipid peroxidation. More pronounced this effect was in a group of pubertal animals. Our results are consistent with other researchers data [39]. These results could be an additional confirmation of our above-mentioned suppositions on mechanisms of losartan antioxidant and anti-inflammatory effects in liver tissues.

Conclusion

Thus, losartan effectiveness towards normalization of CYP450 isoforms expression rates, p-nitrophenol hydroxylase, erythromycin-N-demethylase and diclofenac hydroxylase activities (but not glutathione system and lipid peroxidation rates) depends on the age of experimental animals. The lack of information on the age characteristics of losartan effects on the CYP450 and glutathione systems states with MS makes this data particularly important. The obtained results are another confirmation of the need to optimize and individualize MS therapy, taking into account the age of the patient.

Conflict of interest

There is no financial or other relationships that might lead to a conflict of interest

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VIA MEDICA

ORIGINAL ARTICLE

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Assessment of risk factors and its fetal outcome of preterm birth: in rural tertiary care hospital, Karad, Maharashtra

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ABSTRACT

Background: Preterm birth is an alarming cause of complication in pregnancy that leads to an immense burden for imitation of children to their householders and health care providers. The present study was to find out the functional relationship of preterm birth (PTB) and its study parameters at the Krishna Hospital and Medical Research Centre Karad, Maharashtra from 2016–17. In SPSS (20.0), IBM, INDIA, multiple regression method was used to analyze the results.

Methods: This was cross-sectional study done at rural tertiary care hospital, Karad. The examination was done in the ob-gyn. ward and various details were collected in the form of the questionnaire at present that ward with support of oral discussion of that patient.

Results: Age and many more demographic variables were significantly associated with its fetal outcome of preterm birth. Also, it seems that pregnancy-induced hypertension, placenta diameter; numbers of meals, delivery mode, and those reasons were effective measures of risk factors of assessment of preterm birth.

Conclusions: All the variables analyzed in this study were the part of the determinants of PTB needs to check time to time during the period of pregnancy. Heath care providers still need to take efforts for pregnancy-induced hypertension, placenta diameter.

Key words: fetal outcome, preterm delivery, preterm risk, PTB.

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Introduction

PTB is the theory of gestational weeks. The early interruption of the course of pregnancy can lead to structural and anatomic changes of the central nervous system. It is more likely measured into various determinants like mortality and morbidity of neonates: mild, very pre-term and extremely childhood disability and remains one of the most serious problems in obstetrics [1–3] Approximately in developing countries have > 90% of the world's PTBs, of which 60% are in South Asian and African countries, and 12.3% of PTBs are from sub-Saharan African countries [4]. 1.2 million PTBs occur per year in developed countries, and among these more than half a million deliveries take place in the US [5].

PTB is the second-leading cause of mortality in children aged < 5 years, after pneumonia. Complications of PTBs are the largest cause of neonatal deaths. Globally, more than 3.1 million neonatal deaths occur every year, and about 35% of deaths are due to prematurity of newborns [6]. in developing countries, about 99% of immature babies death within the early days of life [7]. Moreover, more than 3 million annual neonatal deaths are directly related to stillbirth and PTB. In addition to this mortality, PTB is also associated with long term disabilities in surviving neonates [8].

Since, the last twenty years despite major preventive efforts, the incidence of PTB has remained constant at about 5–10% of live births in most countries [9–11]. Approximately 12.7% of births are preterm and 2% are less than 32 weeks. It is estimated that 70 to 80% of PTBs occur spontaneously. The remaining 20 to 30% of PTBs are due to intervention for maternal or fetal problems [12, 13].

Aim and objectives

— To assess the risk factors of preterm singleton birth
— To assess the fetal outcome of preterm singleton birth

Material and methods

Methodology of research indicates the general pattern for organizing the procedure for the empirical study of obtaining valid and reliable data for the problem under investigation.

Sources of data: Mothers who are delivered (before 37 weeks of gestation) at maternity wards of Krishna Hospital, Karad.

Research Approach: In view of the nature of the statement of a problem for the study, the descriptive approach will be appropriate for the study.

Research design: The cross-sectional study design was used for the present study.

Variables of the study: In this study, the variables were a risk factor of preterm birth. Such as Age, socioeconomic category, type of diet, previous history of preterm delivery, height, weight before delivery, the pre-pregnancy weight of the mother, Body mass index, no of antenatal checkup visit, Drug used during pregnancy, Antenatal morbidity, Gestational age etc.

Research setting: The study was conducted at the maternity ward of Krishna Hospital, Karad District Satara.

Population: Population was the entire aggregation of cases in which a researcher is interested. In the present study, the population comprises mothers who are delivered before 37 weeks of gestation in maternity wards of Krishna Hospital, Karad.

Sample: A sample was a portion of the entire population that represents a subset of the entire population elements. For present study samples were mothers delivered before 37 weeks of gestation in maternity wards of Krishna Hospital, Karad available at the time of data collection.

Sample size: According to antenatal check-ups observed in preterm and term deliveries

$$n = \frac{(SD_1^2 + SD_2^2)\ (Z_{1-} \bullet /2 + Z_1^{-}\beta)^2}{(X_{1-} X_2)^2}$$

$$= \frac{(4.12^2 + 3.89^2)\ (1.96 + 0.84)^2}{(6.9\text{-}8.5)^2} = 99$$

So, here I considered 100 preterm deliveries were included in the present study.

Inclusion criteria:
— The mothers delivered before 37 weeks of gestations and admitted in the maternity ward of Krishna Hospital, Karad.
— Those who were willing to participate during the period of data collection.

Exclusion criteria:
— Mothers admitted for other obstetrical conditions except for delivery.
— Mothers who were in critical condition (developed complications) after delivery.

Methods of data collection

Sampling Technique: Randomization sampling technique was used for the present study.

Tools for Data Collection: Structured interview schedule for assessing risk factors of preterm births was used for the collection of data. The Structured interview schedule will be developed in 2 sections.

Section I: Demographic variables.

Section II: a Risk factor of preterm birth.

Ethical Clearance/Permissions for Collection of Data: The researcher was obtaining ethical clearance from Institutional Ethical Committee of KIMSDU and permission taken by Medical Director of Krishna Hospital, head of the department of Obstetrics and Gynecology, Dean KINS, Director of Nursing Services and from the ward supervisor.

The steps used for data collection as follows:
— Investigator finds out related subjects and notifies about objectives and steps of study and takes informed consent.
— Data was collected by using the interview method and referring the case record of each mother.
— Data was analyzed and interpreted by using descriptive and inferential statistics.

Statistical/Data analysis

— The analyzed data was presented in the form of tables, diagrams, and graphs based on findings. For comparing study variables with demographic variables chi-square analysis was used also comparison was done by using the unpaired t-test. SPSS 20.0, IBM, INDIA, Software was used for analyzing data. If $p < 0.05$ then there was statistical significance.

Results and discussion

In this study, it was revealed that the classification of various demographic variables and birth outcomes. Here we assess age, religion, education, socio-economic status, type of family, habits, residency, type of diet, employed during pregnancy, PTD, no. of abortions etc. We found that there was statistical significance ($p < 0.05$) of fetal outcome among the demographic variables like age, religion, socio-economic status, type of family, habits, residency, & PTD. Also, we not able to found a significant association between education, type of diet, employed during pregnancy, parity, previous abortions and its fetal outcome (Tab. 1).

Table 1. Association between demographic variables and fetal outcome

Demographic variables	No. of mothers	LBW	NBW	Chi-square χ^2	P-value
Age (in yrs.)					
20–22	34	29	5	19.704	< 0.0001*
23–25	41	30	11		
26–28	25	8	17		
Religion					
Hindu	57	47	10	23.205	< 0.0001*
Muslim	27	17	10		
Christian	16	3	13		
Education					
Illiterate	8	7	1	3.37	0.338
Primary	3	1	2		
Secondary	62	40	22		
Graduate & Above	27	19	8		
Socio-economic status					
≥ 32,050	28	10	18	17.749	0.0005*
12,020–16,019	52	40	12		
8,010–12,019	19	16	3		
≤ 4,810–8,009	1	1	0		
Type of family					
Nuclear	34	28	6	12.168	0.0023*
Joint	51	26	25		
Extended	15	13	2		
Habits					
Alcoholism	10	9	1	15.956	0.0012*
Tobacco Chewing	30	27	3		
Smoking	4	2	2		
Other	56	29	27		
Residency					
Rural	50	39	11	5.473	0.0193*
Urban	50	28	22		
Type of diet					
Pure Veg.	15	11	4	0.3201	0.8521
Mixed Diet	85	56	29		
Employed during pregnancy					
Yes	18	13	5	0.2708	0.6028
No	82	54	28		
Parity					
Nulliparous	84	56	28	0.02638	0.871
Multiparous	16	11	5		
PTD					
Yes	98	67	31	4.143	0.0418*
No	2	0	2		
No. of previous abortion					
Yes	86	57	29	0.1444	0.7039
No	14	10	4		

*Significant when $p < 0.05$ LBW — Lower Birth Weight; PTD — Preterm Delivery; NBW — Normal Birth Weight

Table 2. Association between study variables and fetal outcome

Study variables	No. of mothers	LBW (%)	NBW (%)	Chi-square χ^2	P-value	Odds ratio (C. I)
Placenta diameter						
< 18 cm	47(47)	40(40)	7(7)	11.64	0.0006	0.1817 (0.069–0.47)
≥ 18 cm	53(53)	27(27)	26(26)			
Total	100(100)	67(67)	33(33)			
Body Mass Index						
≤ 25	43	35(35)	8(8)	5.974	0.0145	0.2926 (0.1155–0.7412)
> 25	57	32(32)	25(25)			
Total	100	67(67)	33(33)			
No. of meals (in one day)						
≤ 2	33(33)	29(29)	4(4)	17.327	<0.0001	0.099 (0.03126–0.3137)
≥ 3	67(67)	37(37)	29(29)			
Total	100(100)	67(67)	33(33)			
Pregnancy-induced hypertension						
Yes	52(52)	41(41)	11(11)	5.805	0.016	0.3171 (0.1322-0.7606)
No	48(48)	26(26)	22(22)			
Total	100(100)	67(67)	33(33)			
Gestational diabetes mellitus						
Yes	68(68)	44(44)	24(24)	0.2335	0.6289	1.394 (0.5570–3.489)
No	32(32)	23(23)	9(9)			
Total	100(100)	67(67)	33(33)			

Table 3. Relationship between mode of delivery and fetal outcome

Mode of delivery	No. of mothers	LBW	NBW	Chi-Square	P-value
Spontaneous vaginal delivery	26(26)	20(20)	6(6)	8.256	0.041
assisted vaginal delivery	26(26)	19(19)	7(7)		
elective LSCS	22(22)	9(9)	13(13)		
emergency LSCS	26(26)	18(18)	8(8)		
Total	100(100)	67(67)	33(33)		

Also some of the variables which were previously found as risk factors of the preterm birth. Here I had considered placenta diameter, body mass index, no. of meals (in a day), pregnancy-induced hypertension and gestational diabetes mellitus. It was observed that meal numbers, placenta diameter, pregnancy-induced hypertension were significantly associated with PTB. But, there was no such role of body mass index. Also by odds ratio, we had stated that there was a definite role of these parameters to overcome the risk of PTB (Tab. 2)

We had to assess the role of mode of delivery in PTB and it was observed significant association ($p < 0.05$) between mode of delivery and fetal outcome (Tab. 3).

Discussion

There were lots of studies was done in this same concept previously, but this study focused on apart from various parameters identified those determinants which influenced to identified risk factors of PTB. In various studies, pregnancy-induced hypertension was found to be significantly associated with PTB outcome variables [14–16]. In the current study, we observed a similar scenario in which pregnancy-induced hypertension was significantly associated with all categories of preterm delivery also it seems the majority of study variables were significantly associated with PTB except BMI. This

study revealed the same situation as any maternal age. It is, therefore, possible to consider advanced maternal age as a direct link or a risk marker through its association with age-dependent confounders for PTD. The present study was shown that PTB was significantly associated with age, religion, socio-economic status, type of family, habits, residency, and PTD delivered in the study period. Also, here we found that placenta diameter, pregnancy-induced hypertension were negatively correlated with birth outcome. So many studies were done in the same situation but in this environment very rare studies done on this topic so it was needed to take review on the same situation which really helps for the community.

Conclusion

This study dataset revealed that PTB remains high in India and findings suggest the same situation in many more developing countries. This study results revealed that there are both modifiable and non-modifiable factors that furnish as PTB in the study group of individuals. As reliable on this study data and also the same type of studies was done in related study area I advise that maximum pregnancies are interpret as a huge risk by the health care providers in Western Maharashtra. It is needed to work on before birth care in order to substantially minimize unfavourable birth conclusion such as PTB. It is too essential to establish in the early period of pregnancy, a follow-up target system between health service providers, private practitioners, ASHA sevika, PHC's and family support for specialist doctors/hospitals to ensure that each and every woman gets quality prenatal as well as antenatal care.

Implication

Nursing practice, education, administration and research

The midwives have a vital role in providing safe and effective nursing care and education to prevent preterm birth. Such would be done by motivating the nurse midwives to (a) have in-depth knowledge about risk factors of PTB and known to prevent that by giving the education to antenatal women. Nurse educator needs to provide health education to women in pregnancy which will reduce the risk of preterm birth. Educate the students about the various risk factor of preterm birth. Practical sessions also provided to give comprehensive care for the intro natal mothers. Encourage the students for effective utilization of research-based practice. Nurse Manager can plan for antenatal classes as well as video-assisted programs on OPD basis in order to prevent preterm birth.

Nursing Managers and administrators need to facilitate the utilization of research-based nursing care aspects in day-to-day practices to formulate policies and make necessary changes in the healthcare delivery system in the hospitals.

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VIA MEDICA

ORIGINAL ARTICLE

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The effect of initial sonication on disinfectant efficacy against *Listeria monocytogenes* biofilm

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ABSTRACT

Background: *Listeria monocytogenes* is a Gram-positive, foodborne pathogen. Biofilms formed by this bacterium are a serious problem in the food industry. Bacteria in biofilms are much more resistant to cleaning and disinfection agents posing a risk of food recontamination. The aim of this study was the assessment of the influence of initial sonication on disinfectant efficacy, based on QAC, against *L. monocytogenes* biofilm on the stainless steel.

Methods: The biofilm formed on the stainless steel by the reference strain *L. monocytogenes* ATCC 19111 was sonicated for 1 and 5 minutes (500W/ 20kHz/ 100% amplitude). Then disinfection with quaternary ammonium compounds (0.5% working solution) was applied for 1 and 5 minutes and the number of bacteria recovered from the biofilm was assessed.

Results: It was found that disinfection was more efficient than sonication ($p \leq 0.05$). However, the combination of sonication and disinfection significantly improved biofilm eradication compared to the use of one of these methods separately ($p \leq 0.05$). The greatest reduction of bacteria number was achieved after 5 minutes of sonication combined with 5 minutes of disinfection (6.42 log CFU $\times$ cm^{-2}), whereas the lowest reduction was observed after 1 minute-sonication (2.03 log CFU $\times$ cm^{-2}).

Conclusions: Combination of sonication and disinfection based on quaternary ammonium compounds is an effective method allowing biofilm eradication from the food production surfaces.

Key words: *Listeria monocytogenes*, biofilm, sonication, disinfectants, quaternary ammonium compounds

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Introduction

Listeria monocytogenes is a cause of human listeriosis, dangerous especially for pregnant women and an elderly [1]. Since the pathogen is widespread in the environment and food plants it may easily contaminate food. The bacterium was isolated from the variety of food products, including vegetables, fish, meat and dairy products [2].

An important problem in the food industry is recontamination and cross-contamination of food due to biofilm formation ability by *L. monocytogenes* [2]. The pathogen is able to colonize both abiotic and biotic surfaces [3]. In biofilm, *L. monocytogenes* is more resistant to disinfectants, UV light, mechanical cleaning and disinfection [1, 5]. The biofilm structure was shown to be affected by the type of the surface. The biofilms formed on the stainless steel were easier to eradicate compared to biofilms on the polyethene [4]. Effective disinfection is a key factor allowing biofilm eradication and food safety. Quaternary ammonium compounds (QAC) are cationic agents that act by cell membrane disruption. QAC are widely used in hospitals, household and food industry [6]. A serious problem determining bacteria resistance in the biofilm structure is the synthesis of EPS (Extracellular Polymeric Substances) [1, 5]. This structure limits disinfectants penetration so eventually they work in a subinhibitory concentration and may generate disinfectant resistance [7]. The disinfection effectiveness through biofilm disintegration might be increased by an application of enzymatic methods or ultrasounds in a range 20–100 Hz [7, 8]. Ultrasound waves of this frequency, in the liquid environment, contribute to cavitation and change of pressure [8].

Cavitation may destruct biofilm architecture releasing single bacterial cells that are more susceptible to chemical disinfection [1].

The aim of this study was the assessment of the influence of initial sonication on disinfectant efficacy, based on QAC, against *L. monocytogenes* biofilm on the stainless steel.

Materials and methods

Materials

The study was conducted on the reference strain *L. monocytogenes* ATCC 19111. Stainless steel AISI 304 coupons of 1 cm × 2 cm and disinfectant based on QAC were used. Coupons were washed in detergent, soaked in 70% ethanol (POCH), washed with sterile water, dried and autoclaved.

The experiment was carried out in three replications.

Biofilm formation by L. monocytogenes strain

In a tube of bacterial suspension in Brain Heart Infusion (BHI, Becton Dickinson) (0.5 McFarland scale) a sterile stainless steel coupon was placed and was incubated for 72 hours at 37°C. The negative control were coupons placed in sterile BHI. Every 24 hours coupons were rinsed with sterile PBS and medium was changed into a fresh BHI. Then coupons were shaken in PBS at 400 rpm for 30 min., 10-fold serial dilutions were made and plated onto Columbia Agar with 5% of sheep blood (Becton Dickinson). After 24-hour incubation at 37°C, the number of bacteria per cm^2 was calculated.

Sonication of *L. monocytogenes* biofilm on stainless steel coupons

Coupons with biofilm were placed in a beaker containing 500 ml of sterile PBS. The height of the liquid layer above coupons was 6 cm. The sonicator probe (Sonicator VCX500, Sonics) of 19 mm diameter was placed in the beaker and the samples were sonicated for 1 and 5 minutes (500W/20kHz/100% amplitude).

Assessment of the effectiveness of disinfection based on QAC

Coupons after sonication were exposed to 0.5% QAC disinfectant for 1 and 5 minutes. Subsequently, coupons were neutralized for 2 min in a solution of Tween 80 (Sigma Aldrich) –10 g; lecithin (Sigma Aldrich) — 1 g; histidine-L (Sigma Aldrich). Finally, coupons were rinsed with a sterile PBS, shaken at 400 rpm for 30 min and serial 10-fold dilutions were made and plated onto Columbia Agar with 5% of sheep blood. After 24-hour incubation at 37°C, the number of bacteria per cm^2 was calculated. The control variant were coupons with formed biofilm, immersed in PBS for 1 and 5 min, treated with QAC, but not sonicated.

Statistical analysis

Statistical analysis was made using STATISTICA 12 PL software (StatSoft). For each variant mean of 3 replicates was calculated. The statistical differences between the tested variants were evaluated using Tukey post-hoc test at the significance level $\alpha = 0.05$.

Results

The number of bacteria reisolated from biofilm was 7.11 log CFU × cm^{-2}. Both sonication and disinfection significantly reduced the number of bacteria, regardless of exposition time. The most efficient biofilm eradication was noted for the combination of sonication and disinfection (Fig. 1). The extension of sonication and disinfection time significantly increased the efficacy of both methods ($p \leq 0.05$). The greatest reduction of bacteria number was noted after 5-minute sonication, followed by 5-minute disinfection (6.42 log CFU × cm^{-2}). In turn, the lowest reduction was observed after 1 minute of sonication (2.03 log CFU × cm^{-2}). It was found that disinfection is more effective than sonication ($p \leq 0.05$). The reduction of bacteria number after 5-minute sonication and 5-minute disinfection was 2.99 log CFU × cm^{-2} and4.67 log CFU × cm^{-2}, respectively.

Discussion

The key element ensuring food safety of the consumer is control of cleaning and disinfection in the food-processing plants. An important problem in the food industry, hindering effective cleaning and disinfection, is a biofilm formation. This structure prevents bacteria from adverse environmental factors, e.g. disinfectants and UV light [1, 9]. In the present study sonication and disinfectant based on QAC were used to disrupt *L. monocytogenes* biofilm. It was shown that the combination of 5-minute sonication and QAC exposure resulted in the greatest reduction of the bacteria number (6.42 log CFU × cm^{-2}). Bauman et al. (2009) [10] using sonication for 60s (20 kHz/ 100% amplitude/ 120 W) observed reduction of 3.8 log CFU/ml. In turn, other researchers [11–13] applying lower power of ultrasounds found the only minimal effect of sonication on biofilm

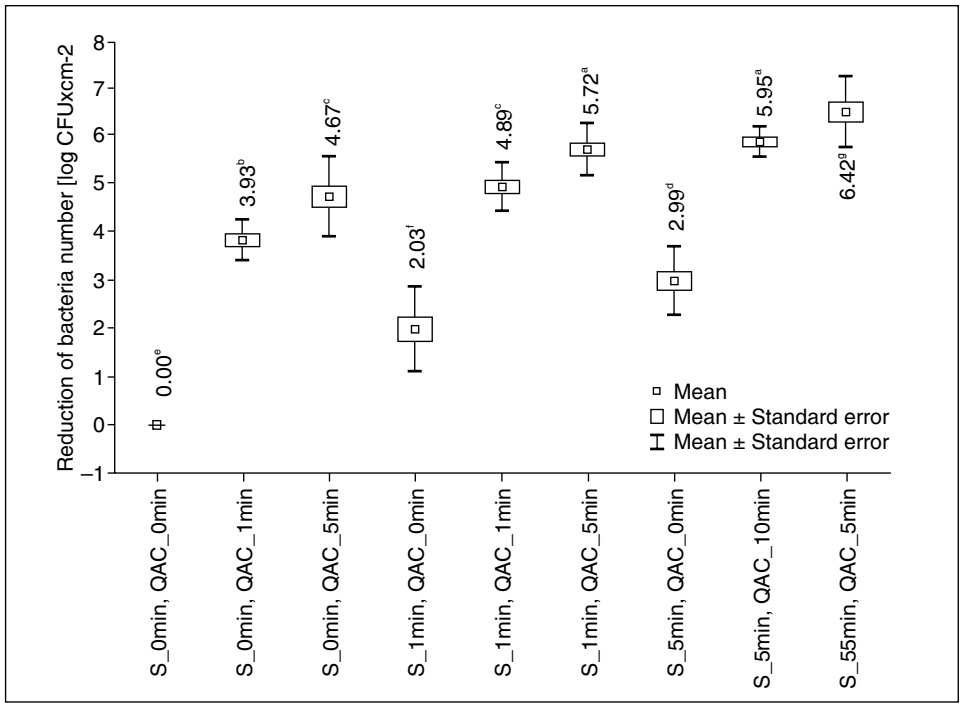

Figure 1. The reduction of bacteria number reisolated from biofilm exposed to sonication and QAC [a, b, c, … — variables with different letters are statistically different ($p \leq 0.05$)]

eradication on the prosthesis surface. The frequency of ultrasounds also has an impact on biofilm elimination. In our study 20kHz was applied. Application of ultrasound of this frequency for 30 seconds was found to decrease bacteria number 10 times [1]. Bauman et al. (2009) [10] and Qian et al. (1996) [12] noticed that ultrasounds of 70kHz frequency better eliminate biofilm than the application of high frequency (500 kHz) ultrasounds. An important aspect is also the efficacy of the disinfectant. We showed that QAC was more effective in biofilm disruption than sonication. Torlak and Sort (2013) [14] using QAC found only 27% reduction of bacteria number on the plastic surface. However, Romanova et al. (2007) [15] stated that efficient disinfection with QAC requires at least 30 minutes.

In the present stud, the greatest effectiveness in biofilm eradication was noted for the combination of sonication and QAC disinfection. This is in agreement with a study of Torlak and Sert (2013) [14] who demonstrated that regardless of time exposure the best eradication was achieved for the combination of sonication and benzalkonium chloride disinfection. Also, Berrang et al. (2008) [1] contended that sonication might improve disinfectants efficacy against bacterial biofilms. The results of mathematical modelling and conducted experiments revealed that the application of low-frequency ultrasounds boosts biomass transport through biofilm [16–18]. Therefore, it can be assumed that an increase of biomass transport facilitates the transport of disinfectant compound to the biofilm structure [14].

Conclusions

We have demonstrated that the combination of sonication and disinfection based on QAC the most effectively eliminate biofilm from the stainless steel. Application of sonication might be an easy and cheap method to improve disinfection efficacy leading to *L. monocytogenes* biofilm eradication and food safety.

Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

ORIGINAL ARTICLE

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Evaluation factors affecting the maternal mortality among pregnant women during 2001–2011 in Ardabil Province, Iran

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ABSTRACT

Background: considering health indicators, analyzing pregnant women population is an important subject and mortality degree among this population is disastrous. According to the World Health Organization, annually 600,000 women die due to side-effects of pregnancy and delivery; it means that 1600 women die daily and one woman dies in each minute because of progeny side-effects. The average of MMR is 200 in developing countries and it is 20 out of 1000 in developed countries. This study was done aimed to determine the rate of maternal mortality among pregnant women and the factors affecting it in the Ardabil province so that identified dominant effective factors and presented Executive Solutions for reducing maternal mortality.

Methods: This study was conducted as a cross-sectional and descriptive-analysis study by using existing data in the health centre network system of Ardabil province during 2001–2011. According to the information of all maternal deaths (50 cases) in the health care system, the causes of death were extracted by study and evaluation of the documents and questionnaires about and the control group information have been collected randomly in the ratio of 1 to 4 (N = 200). Data was analyzed by using the Statistical tests as Chi-square, t2test and regression with the SPSS.20 software.

Results: findings showed that the proportion of maternal deaths is 20 per 100,000 live births in Ardabil province. 70% of maternal death was direct because of pregnancy's side-effects.68% of deaths occurred in the postpartum period. The common causes of death were respectively, the bleeding (28%), preeclampsia, eclampsia and its side-effects (16%) were thromboembolic disorders (16%) and infection (8%). The maximum number of deaths were in the years 2003 and 2011 (18%) and the minimum number of these were 2008 (zero). 72% of maternal deaths were in the age range of 18 to 35 years. 33% of mothers were illiterate and less educated (the primary school). 62% of died mothers, lived urban residents. In this study, the relationship between cares before pregnancy, suffering from different diseases during pregnancy and distance between two pregnancy times were evaluated by Logistic regression test which was significant.

Conclusions: The most effective factors to reduce the maternal deaths in the province were increased coverage of pre-pregnancy, pregnancy and postpartum cares and improving its quality.

Key words: mortality, delivery, pregnant mothers, hemorrhage

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Introduction

Research background & statement of problem

Maternal death during pregnancy or during delivery and up to 42 days after the termination of pregnancy for any reason other than accidents is considered maternal mortality resulting from side-effects of pregnancy and delivery [1, 2]. Measurement of maternal mortality is done by an index called maternal mortality ratio or briefly MMR which shows a number of maternal deaths due to pregnancy and delivery side-effects per 100,000 live births [2]. Average MMR in developing countries and developed countries respectively was 200 and 20% of thousand live births. Comparison of these numbers showed a significant difference in the health status of mothers in developed and developing countries. Proportions of maternal deaths because of the pregnancy and delivery side-effects are the most

effective indicators that represent the development of countries. The reason for choosing this index as the profile development is its potential for evaluating the impact of various social and economic factors on increasing or decreasing of the variable. This index is affected by the women's educational state, rural roads network, accessing to obstetric emergencies, the cost of health care, telecommunications, communication networks, family income and etc. [3].

According to the World Health Organization (WHO), 600/000 women die annually as a result of pregnancy and delivery side-effects. Daily in the world, 1600 women lose their lives due to pregnancy and delivery side-effects. More than 99 percent of these deaths occur in developing countries. 60 to 80 % of maternal deaths are because of hemorrhage, hard delivery, high blood pressure, infections and side-effects of unsanitary abortions that a significant percentage of them (61 %) occur after in the delivery and 78 % of them happen in 24–48 hours after delivery (5). According to the *UN Millennium Development Goals*, the rates of maternal mortality should be decreased to 75 % by 2015 compared to baseline (1990). According to the fifth developmental plan, the maternal deaths statistics should be decreased to 15 per 100 thousand people that are about 22.5 percent now [4]. Maternal deaths are evitable because many causes of death in the world are preventable today, and necessary facilities are available to preventing and a safe pregnancy in currently. The causes of maternal deaths have not been changed to the 21st century. Bleeding, blood pressure and maternal sepsis form mortal triangle. HIV infection and AIDS is considered as the leading causes of deaths in South Africa and Sub-Saharan of Africa today [4]. Some common causes of death are preventable, including septic abortion, uterine rupture, eclampsia, postpartum hemorrhage, puerperal sepsis [6]. Also, amniotic fluid embolism is very controversial today [9]. The new statistics show that the thousands of women die during delivery every day thatmost of them live in sub-Saharan of Africa and South Asia. The maternal mortality rate has dropped by one-third between 1990 and 2008, while 600 thousand mothers lose their lives in the world annually as a result of pregnancy and side-effects related to delivery time. Iran has achieved the huge results in the reduction of maternal mortality in the past few years and also maternal mortality reduction programs of Iran is known as a global activity, so 80% of maternal mortality is reduced during the past 10 years [10]. So checking the causes of maternal mortality during the different years and comparison of reducing or increasing in the number of deaths and its causes, causes to achieve the predisposing or preventive factors and could enhance the health of mothers. Regarding any background about the present research in Ardabil province, this study is done aimed to determine the mortality rate of pregnant women and the effective factors in Ardabil province to identify the effective factors and most executive solutions for reducing the mortality rate of pregnant women.

Materials and methods

The present research is a descriptive-analytic and cross-sectional study to investigate the causes and factors affected women's deaths in Ardabil province, which was done during the years 2001–2011. The research population is including the pregnant mothers who were died in 2001–2011 in Ardabil and research sample also includes the live mothers after pregnancy that visit the health centres to be taken care of them. Given that the number of deaths of pregnant women (study group) was about 50 in the province of Ardabil in 2001–2011, so all the eleven-year deaths were studied in order to increase the precision of the investigations in the study. And then, because the impact of impressive maternal and environmental factors to be measured we selected 200 people as the treatment group randomly from the live mothers after pregnancy that visited the health centers to be taken care of them (in a ratio of 1 to 4). According to this that mother's death system is running in the health system and all of the data is available in the form of a survey questionnaire, collected data from questionnaires related to the maternal death system which exists in the Vice President of health and treatment Department of Ardabil University of medical sciences and then the data of the treatment group also was collected from Health Centers affiliated to the province of Ardabil. Descriptive data and demographic data of women took place based on the research sample for data analysis, then was used of Chi-2 or t-test for independent groups for reviews of the relationship between the independent variables with the death of a pregnant mother and for control of confounding factors also was used of the logistic regression model. After data analysis, the related variables to pregnant women mortality in a significant level of 0.1 were inserted in the logistics model. To estimate the risk of each variable, the odds ratios with 95% confidence interval has been used. In this study, the p-value of less than 0.05 was considered statistically significant.

Research findings

According to research findings, the average of pregnant maternal mortality is 20 per cent out of 1000 live births. Also, findings indicated that maternal mortality was 50 cases in and also all births during 2001–2011 were 241783. The changes during 11 years

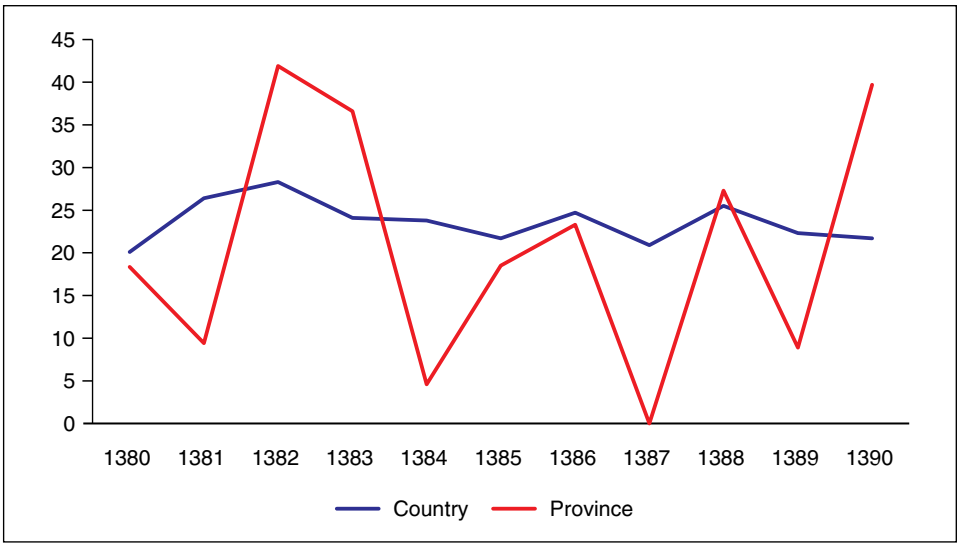

Figure 1. Frequency of mother's mortality in Ardabil province during 2001–2011

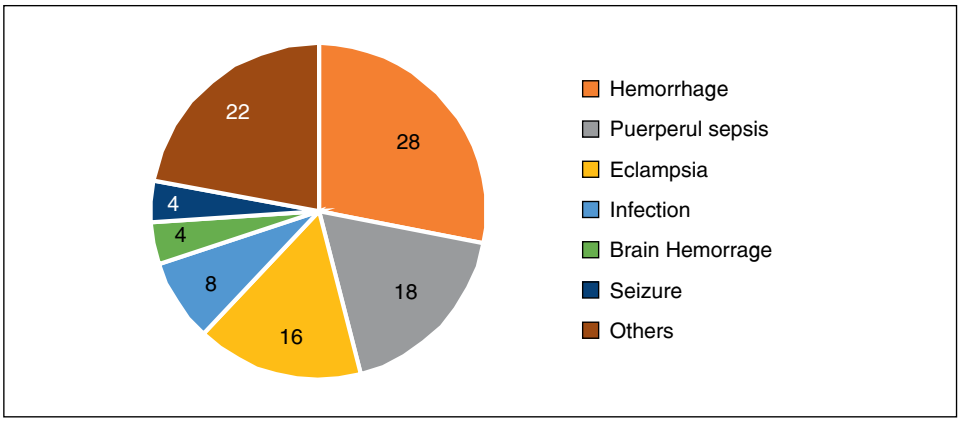

Figure 2. Relative frequency of pregnant women deaths in Ardabil province during 2001–2011

by considering the death because of pregnancy side effects in Ardabil were very frequent and the maximum and a minimum number of maternal deaths were in 2003, 2011 (9 cases) and in 2008 (zero) respectively (Fig. 1).

In 50 pregnant women who died, 70% of maternal deaths were due to pregnancy and 68% of deaths occurred in the period after delivery. In terms of access to health services, there was a 48% delay in family deciding for help, 42% delayed for referring to the hospital and 48% delayed in starting treatments in hospitals (Fig. 2).

Discussion & conclusion

The most important conclusion in the present research is the mortality rate among pregnant women in Ardabil which obtained as 20% of per thousand of live births among them 62% were resident in the city and 38% were in rural areas. This finding is in agreement with the findings of Bagheri Lankarani [11] and the reported results by health population office, family and schools [10] that dead mothers percentage are 61/2% between 2006–2010. Maternal mortality rates did not follow a specific pattern in Ardabil province and different cities of the province like Bileh Savar, germs, Meshginshahr, Nir were not desirable to evaluate the ratio of births and death (Tab. 1–3).

The most important causes of pregnancy mothers deaths in during 11 years (2001–2011) were hemorrhage which agreed with findings of Akhlaghi [7], Hejazi [1], Bagheri Lankarani [3], Gholami Taramsary [9], Abdollahipour [6], World Health Organization report [10]. In the study by autopsy, Khan and coworkers [3] showed that 80/5% of pregnancy mother deaths were due to pregnancy. Direct and indirect causes formed 64% and 36% of mother deaths respectively in Ilam

Table 1. Descriptive statistics

Variable	Deaths group	Number	Percentage
Types of mother death	Direct in pregnancy	35	70
	indirect	15	30
Time of mother death	pregnancy	16	32
	During delivery	0	0
	After delivery	34	68
Location of mother deaths	house	5	10
	In the way of hospital	6	12
	hospital	39	78
The date of mother deaths	1380–1385	27	54
	1386–1390	23	46
The age of the pregnancy	First trimester	4	8
	Second trimester	5	10
	Third trimester	7	14
	After the delivery	34	68
Delay in decision making	yes	24	48
Delay in refer	yes	21	42
Delay in time	yes	24	48

province in the study of abdollahipour and coworkers [11] that agreed with our study with means 70% for direct causes and 30% for indirect causes (Tab. 1–3).

According to the performance and country's military achievements of maternal death care by the health Bureau of Population, Family and Schools in 2010, the percentage of death women in pregnancy, during delivery and postpartum were 4/24%, 4/3% and 2/72 respectively. In the study of abdollahipour and coworkers [4], the greatest period of pregnant mother deaths occurred after the delivery (68%).

In the study by Gholami Taramsari, 68%, 18% and 14% of mothers, died in hospital, house and in the way of hospital respectively. According to the population health office, the percentage of deaths mothers were 84% in the hospital that matched with results of our study (78% in hospital, 12% in the way of the hospital and 10% in the house) [5].

In the study by Hejazi [10], the gestational age of death mothers was between 15–42 weeks and the most mortality occurred in the third quarter of pregnant that agreed with our study and 14% of mortality occurred in the third quarter in the pregnant death.

According to report of performance and achievement of the country's military maternal mortality by the population health office, family and schools, 24/2% of delay in family decision to get help, 16% of delay in the mother refers from out of hospital into hospital and 39/6% of delay in the start treatment in hospitals were reported that matched with our study (Tab. 1–3).

In this study, there was a significant relationship between lack of care before pregnancy with the mother death ($p = 0.01$).

In our study, the maximum percentage of people in two groups for death mothers and lived mothers were 72% and 86% in the age range 18 to 35 year respectively that agreed with the findings of Gelian Tehrani [4] study and Azimi and Jalilvand [6].

Arshinchi [8] found that the progeny age has not been affected the literacy for mother deaths that agreed with our study. According to the test results of regression logistic in our study are the significant statically difference between the mother pregnant and mother death ($p = 0/01$). In the study of Bagheri Lankaran [10], 76/3% of mothers with high risks and 85/7% mothers with of low risk had distance 24 months with the previous pregnancy and in the study of abdollahipour [11], the interval between pregnancies announced 23% less than 3 years (Tab. 1–3).

In our study, according to regression logistic, there is the significant difference between getting the underlying disease and maternal death ($p < 0/001$) that agreed with study of Abdollahipour [11] and Gholam Taramsari [10]. The results showed that raising the awareness of families about pregnancy and delivery side-effects and appropriate approach meeting with it, attention

Table 2. The frequency of dependent and independent variables (personal, social) in control and treatment groups in Ardabil province dyeing 2001–2011 years

Variable		Treatment group		Lived group		Odds ratio	Confidence interval 95%	P
		Number	Percentage	Number	Percentage			
Residence	City	31	62	136	68	7/0	7/1 – 4/0	8/0
	Village	19	38	64	32			
Husband Job	Employee	7	14	58	29	9/0	2/1 – 6/0	5/0
	Working	9	18	10	5			
	Self-employment	32	64	107	5/53			
	Unemployed	2	4	25	5/12			
Type of pregnancy	Programmed	44	88	170	85	2/1	1/3 – 7/0	1/0
	Mistime	0	0	8	4			
	Undesirable	6	12	22	11			
Mother job	Housewife	47	94	185	5/92	1/1	2/2 – 1/0	5/0
	Practitioner	3	6	15	5/7			
Distance with previous delivery	Less than 36 months	10	8/20	20	10	2/2	5/2 – 7/0	01/0
	More than 36 month	22	8/45	81	5/40			
	First birthday	16	3/33	99	5/49			
Mother age	Under 18 year	3	6	12	6	1	3/1 – 3/0	7/0
	Between 18–35 year	36	72	172	86			
	Olders than 35 year	11	22	16	8			
Mother's education level	Illiterate	33	3/67	55	6/27	5/2	7/6 – 2	06/0
	Upper than primary school	13	5/26	107	8/53			
	University education	3	1/6	37	6/18			
Spouse's education level	Illiterate	33	3/67	55	6/27	87/0	53/1 – 493/0	4/0
	Upper than primary school	13	5/26	107	8/53			
	University education	3	1/6	37	6/18			
Number of pregnancy	3 ≥	37	74	181	5/90	4/2	41/7 – 118/0	
	4 ≤	13	26	19	5/9			

The findings of the regression logistic test showed that there is a significant relationship between pre-pregnancy care, the distance between the two pregnancies, underlying the disease in mother and the child status in both control and treatment groups

to equipment and provision of hospitals to drugs and requirements which are necessary for Midwifery and delivery emergencies.

Increased coverage of care pre-pregnancy and pregnancy and after the delivery, timely identifying and avoiding from delay in the decision making and referring the high risk cases, non- delay in providing health care to mothers in hospitals and labour centres, preventing from undue cesarean and providing the professional services and based on the evidence will be the most important effective measures in reducing maternal mortality (Tab. 1–3).

Table 3. The frequency of dependent and independent variables (personal, social) in treatment and control groups

Variable	Treatment group	Lived group	Confidence interval 95%		Chance ratio	P value
	Number (percentage)	Number (percentage)				
Pre-pregnancy care	(92) 46	(95) 190	.384	6.163	2/3	.027
The interval between pregnancies	(8/20) 10	(10) 20	.784	2.593	2/2	.013
Underlying disease	(32) 16	(5/2) 5	.364	3.41	5/2	.000
Baby status	(50) 25	(5/99) 199	.015	.195	77/0	.000
Pregnancy care	(76) 38	(5/88) 177	.188	.674	47/0	.999
Appropriateness of care	(76) 38	(5/85) 171	.297	1.889	2/1	.999
Birth place	(56) 28	(100) 200	.502	1.510	1	.357
Type of delivery	(38) 19	(5/50) 101	.368	1.766	1/1	.325
Economic status	(1/27) 214	(4/15) 90	.431	1.765	4/1	.278

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REVIEW ARTICLE

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Diagnostic and therapeutic procedures in gout

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ABSTRACT

Gout, a rheumatic disease caused by crystals (crystal arthropathy), is a form of inflammatory arthritis caused by monosodium urate depositing in the synovial fluid and as time goes by outside the joints as well (in other tissues and organs).Gout attacks are sudden and often result from a dietary mistake. In 2015 the European and American Rheumatological Associations (EULAR and ACR) published joint classification criteria for gout. The criteria involve gout-specific clinical symptoms, irregular results of laboratory tests and lesions visible in imaging tests. The "golden standard" of diagnostics still remains the presence of uric acid crystals in a sample of synovial fluid, the contents of the bursa and of the gouty tophus. The course of treatment for patients with gout depends on the stage of the disease, but it comes down to implementing various forms of preventing hyperuricemia by modifying the patient's lifestyle and diet, reducing risk factors (such as overweight and obesity) and pharmacological treatment, both in-between and during attacks.

Key words: gout, arthritis, crystal arthropathy, hyperuricemia, flares of joint inflammation, tophaceous gout, gouty tophi, Colchicine

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Introduction

Gout, a rheumatic disease caused by crystals (crystal arthropathy), is a form of inflammatory arthritis caused by monosodium urate depositing in the synovial fluid and as time goes by outside the joints as well (in other tissues and organs).

Gout is believed to be the most common type of inflammatory arthropathy in men after 40. It is 3 times more common in man than in women and the rate of incidence increases with age. It is also more common in developed countries, due to unhealthy lifestyle.

The course of the disease

Clinical symptoms of the disease are a result of hyperuricemia, which is an elevated level of uric acid. This happens due to a lack of balance between its supplied and excreted amount. Uric acid is the end product of the metabolic breakdown of purines, which may originate from food or internal metabolic processes. The overall amount of uric acid in the human body is estimated at approx. 1200mg, which translates into a blood serum concentration of 5.2mg/dl (310μmol/L) in males, 4.0mg/dl (240μmol/L) in pre-menopause females, and 4.7mg/dl (280μmol/L) in post-menopause females. The daily renal excretion rate is 700–800mg. [1]

The natural course of the disease can be characterized by four stages:

1. Asymptomatic hyperuricemia
2. Flares of joint inflammation (acute attacks of gout)
3. Interparoxysmal periods
4. Chronic gout (tophaceous gout) with symptoms of multi-joint inflammation and the formation of so-called gouty tophi.

The most recent modification of the course of gout classifies it into the following stages:

1. A great risk of gout — corresponds to the hyperuricemia stage, both without clinical symptoms and without typical irregularities in imaging tests or the presence of uric acid crystals in microscopic tests.
2. Asymptomatic hyperuricemia — a phase which is characterized by a lack of symptoms with the presence of monosodium urate in imaging and microscopic tests.
3. Gout attacks
4. Tophaceous gout — chronic arthritis with inflammation visible in imaging tests in the form of joint destruction and bone erosions.

The course of treatment for patients with gout depends on the stage of the disease, but it comes down

to implementing various forms of preventing hyperuricemia by modifying the patient's lifestyle and diet, reducing risk factors (such as overweight and obesity) and pharmacological treatment, both in-between and during attacks. [2]

Clinical symptoms

Gout attacks are sudden and often result from a dietary mistake (too many purines and fructose, excessive portions, alcohol intake), substantive physical strain, fever, dehydration, effects of medication, an injury, or surgery.

The symptoms of an attack have all the characteristics of acute arthritis: intense pain, haphalgesia, articular hydrops, and anasarca. The skin around the joint is red, warm and tense. The first attack of gout usually affects the first metatarsophalangeal joint (podagra) and consecutive attacks may also affects this area. The inflammation may also affect other regions: ankle joints, knee joints, and rarely the joints in the upper extremities. The attacks usually affect a single joint, multi-joint inflammation is rarer.

Laboratory tests show an accelerated ESR, elevated CRP levels and neutrocytosis. The level of uric acid in the blood serum increases significantly, but sometimes it can be surprisingly normal. Proteinuria and microscopic haematuria can be observed in urinalysis. An examination of the synovial fluid confirms inflammation and a microscopic evaluation in polarized light shows monosodium urate crystals. An ultrasound of the joints shows a double contour specific for gout, which is a result of deposits on the surface of the cartilage.

Diagnosing an attack of gout based on a thorough history, a physical examination and basic laboratory test result is usually not difficult. Implementing the right treatment significantly shortens the time-span of attacks, which can last several to a dozen days if untreated.

During a differential diagnosis of a gout attack in the form of acute inflammation of a single or multiple peripheral joints the following should be considered:

— infectious, that is septic, arthritis
— reactive arthritis
— peripheral joints affected by AS
— psoriatic arthritis
— other crystal arthropathies, such as calcium pyrophosphate dihydrate deposition disease (CPPD)
— an exacerbation of osteoarthritis.

Diagnosis

In 2015 the European and American Rheumatological Associations (EULAR and ACR) published joint classification criteria for gout. [3] They apply to patients who had at least 1 episode of peripheral arthritis or bursitis (oedema, pain, or tenderness). The criteria involve gout-specific clinical symptoms, irregular results of laboratory tests and lesions visible in imaging tests [X-ray, ultrasound and dual-energy CT (dual energy computed tomography — DECT)].

The "golden standard" of diagnostics still remains the presence of uric acid crystals in a sample of synovial fluid, the contents of the bursa and of the gouty tophus. If crystals are found, there is no need to apply the remaining criteria. If however, for various reasons, the examination of the synovial fluid is not possible, 2015 ACR-EULAR gout classification criteria need to be followed.

2015 ACR-EULAR Gout Classification Criteria [3, 4]

Preliminary condition: 1 episode of peripheral arthritis or bursitis (oedema, pain, or tenderness).

The presence of uric acid crystals in the synovial fluid is sufficient to diagnose gout (if this condition is met, the patient can be diagnosed with gout without applying the criteria below)

The maximum score is 23 points. A score of ≥ 8 point allows to diagnose the patient with gout. The Full ACR-EULAR Gout Classification Criteria are presented in Table 1.

Treatment of gout

The essence of gout treatment is to lower the level of uric acid to < 6mg/dl by modifying the patient's lifestyle, implementing a proper diet and prescribing adequate treatment. Hyperuricemia prophylaxis, the difference between treating gout attacks, treating the disease in interparoxysmal (intercritical) periods and treating chronic gout should be considered.

Lifestyle and diet

— reducing body mass in overweight and obese patients
— a diet low in purines
— increasing the frequency of physical activity
— fighting addictions — reducing alcohol consumption, especially beer consumption, and nicotine intake
— primary and secondary prophylaxis of cardiovascular diseases, such as ischemic heart disease and circulatory failure, hypertension, peripheral artery disease, stroke, chronic kidney disease, and diabetes.

Table 1. The full ACR-EULAR Gout Classification Criteria table with values for each item's score from web page: http://goutclassificationcalculator.auckland.ac.nz/. The following website contains an algorithm of diagnostic procedures in accordance with the criteria and a calculator

Entry Criterion → *(Only apply criteria below to those meeting this entry criterion)*	At least one episode of swelling, pain, or tenderness in a peripheral joint or bursa	Yes No
Sufficient Criterion → *(If met, can classify as gout without applying criteria below)*	Presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus	Yes No
Criteria (to be used if Sufficient Criterion not met) *Score ≥ 8 required for classification as gout*	Categories	Score
Pattern of joint/bursa involvement during symptomatic episode(s) ever	Joint(s) or bursa(e) other than ankle, midfoot or 1st MTP (or their involvement only as part of polyarticular presentation)	0
	Ankle OR midfoot (as part of monoarticular or oligoarticular episode without MTP1 involvement)	1
	MTP1 (as part of monoarticular or oligoarticular episode)	2
Characteristics of symptomatic episode(s) ever: 1.Erythema overlying affected joint (patient-reported or physician-observed 2.Can't bear touch or pressure to affected joint 3.Great difficulty with walking or inability to used affected joint	No characteristics	0
	One characteristic	1
	Two characteristics	2
	Three characteristics	3
	One typical episode	1
	Recurrent typical episodes	2
Clinical evidence of tophus: draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g. Achilles)	Absent	0
	Present	4
Serum urate: Measured by uricase method. Ideally should be scored at a time when the patient was not taking urate-lowering treatment and patient was beyond 4 weeks of the start of an episode (i.e., during intercritical period); if practicable, retest under those conditions. The highest value irrespective of timinig should be scored.	< 4 mg/dl	-4
	4 — < 6 mg/dl	0
	6 — < 8 mg/dl	2
	8 — < 10 mg/dl	3
	≥ 10 mg/dl	4
Synovial fluid analysis of a symptomatic (ever) joint or bursa Should be assessed by a trained observer	Not done	0
	Monosodium Urate (MSU) negative	-2
Imaging evidence of urate depositions in symptomatic (ever) joint or bursa: Ultrasound evidence of double-contour sign or dual energy computed tomography (DECT) demonstrating urate deposition	Absent OR Not done	0
	Present (either modality)	4
Imaging evidence of gout-related joint damage: Conventional radiography of the hands and/or feet demonstrate at least one erosion	Absent OR Not done	0
	Present	4
TOTAL SCORE =		

Treating a gout attack

Except for medication, the treatment should also include:

- reducing the strain on the extremity with the affected joint
- the extremity should be comfortable and the joint area should be exposed in order to reduce tenderness
- using cold compresses
- proper hydration (it will allow to lower the concentration of uric acid).

Pharmacotherapy:

- **Colchicine** — an alkaloid extracted from the autumn crocus plant (Colchicum autumnale), which reduces inflammation, although its effects are not yet fully known. The medication is taken during the

first day of the attack in an initial dose of 1.0mg, 0.5mg after an hour and, if need be, 0.5mg after 12 hours. In the following it is recommended to take 0.5mg three times a day, until the symptoms resolve. Contraindication for the use of colchicine are: renal or hepatic failure, pregnancy, blood disorders, heart function disorders, serious gastric and intestinal disorders. The medication shouldn't be combined with macrolides, statins, or cyclosporin. The most common adverse effects include gastro-intestinal symptoms, like stomach ache, nausea, and diarrhea. The medication can cause liver and kidney dysfunction and may be myelotoxic.

— **Nonsteroidal anti-inflammatory drugs (NSAIDs)** with the exception of aspirin (which increases the concentration of uric acid in blood serum) are alternatives to colchicine, if they are used in the maximum recommended therapeutic dose.

— **Glucocorticosteroids (GCs)** — recommended for patients with colchicine and NSAID contraindications, administered intra-articularly if possible. If this is difficult or impossible due to multi-joint inflammation, the medication is administered orally, initially at 0.5mg of prednisone per kg of body mass, usually over the course of 5 days with a gradual reduction of the dosage.

— **Canakinumab** — a human, monoclonal IL-1β antibody (unavailable in Poland) intended for patients with frequent attacks ($\geq$ 3 per year), who have colchicine, NSAID and GC contraindications [5].

Treatment of chronic gout

In the case of recurrent attacks (> 2/year), the presence of gouty tophi, chronic arthritis, and concomitant diseases, such as chronic nephropathy, hypertension, ischemic heart disease and heart failure a treatment targeted at lowering uric acid concentration should be considered. The aim is to achieve a uric acid concentration of < 6mg/dl and in the case of gouty tophi and/or chronic arthritis in the course of gout, < 5mg/dl. The treatment should be started no earlier than 2 weeks after the attack has subsided, due to the risk of another attack.

— **Allopurinol** (a xanthine oxidase inhibitor) is a first line treatment to reduce uric acid concentration in blood serum, used at an initial dose of 100mg/day, which is gradually increased, usually every 4 weeks, until the optimal dose of 300–600mg/day is reached, which should reduce the uric acid concentration to 6mg/dl.

— **Febuxostat** — as an alternative to allopurinol, in case it's ineffective or causes adverse effects. The initial dose is 80mg/day and can be increased up to 120mg/day [6].

In case of a gout attack, patients who regularly take antihyperuricemic medication, like allopurinol (Allupol, Milurit) or febuxostat (Adenuric), should not stop their treatment, since this would increase the risk of future attacks. Due to the mechanism of medications that decrease the level of uric acid, which may cause a gout attack, in the initial phase of the treatment it should be taken in combination with colchicine at a dose of 0.5mg/day or with NSAIDs.

An addition or alternative to antihyperuricemics are urisuric medications, like probenecid or benzbromarone, which are unavailable in Poland. Losartan and fenofibrate are known to have a weaker urisuric effect and should be considered, especially for patients with hypertension and dyslipidemia. [7, 8]

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REVIEW ARTICLE

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Limitations of molecularly targeted therapy

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ABSTRACT

Personalized medicine is an extension of traditional medicine is based on a highly individual approach to each patient. One of the most important tools that allow this approach is targeted therapy. It focuses mainly on blocking cancer cell's proliferation and angiogenesis capabilities by interfacing with specific molecules that are involved in the growth and progression of the tumour. Small-molecule inhibitors and monoclonal antibodies are the main drugs that are currently in use in order to affect the specific biochemical pathways in cancer cells. However, likewise any other cancer therapies, targeted therapy has its own limitations. For instance, identifying a molecular target needed to begin treatment is one of those hardships. A specific molecule is crucial in this way of treatment. The other limitation is the toxicity that appears during the treatment, the same as in the case of traditional chemotherapy and radiotherapy. Furthermore, the cost of this therapy is significantly higher compared to classical treatments. However, the main obstacles are mechanisms of cancer drug resistance which are often developing in response to given drugs. In many cases, it makes further treatment impossible. This article is focusing on the limitations of molecularly targeted therapy.

Key words: molecularly targeted therapy, anti-cancer drugs, cancer drug resistance, the toxicity of anti-cancer drugs

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Introduction

The purpose of modern anticancer therapies is to overcome the difficulties resulting from insufficient knowledge of the tumour genome, its high diversity and instability. Rapidly expanding knowledge of molecular biology and cancer genetics has provided us with tools that make personalized medicine possible. Molecularly targeted therapy focuses on the identification of molecular changes on the level of a single patient, and also on optimization and individualization of treatment, as well as individual characteristics of the tumour microenvironment [1–3].

The presuppositions of such therapy are to block the proliferation of cancer cells by interfering with specific molecules necessary for the successful tumour growth and development. Drugs are designed in such a way to affect a specific, targeted biochemical pathway [4]. The first and most crucial step in planning an effective treatment is to find specific molecules that serve as a molecular target. One of the methods is to identify proteins present in a tumour, but absent or exhibiting a decreased expression in normal, healthy cells. Another approach is to look for changed proteins that drive cancer progression. These can be fusion proteins located in altered cells — the cause of genetic instability. Each cell has specific cell-surface receptors, which are responsible for activation of a response to extracellular stimuli. Often these proteins are used as the target of therapy because they show a relatively high frequency of mutation or overexpression [1–4].

Molecularly targeted cancer therapy

Molecular targets

An example of a protein that is a target of molecular therapy is Vascular Endothelial Growth Factor (VEGF), one of the most important factors regulating the development of tumour blood vessels, thereby modulating the process of angiogenesis. The angiogenesis process provides nutrients and oxygen for cancer cells, contributing to the formation and growth tumour. In addition, it allows the spread of cancer cells — VEGF stimulates the secretion of more proteases, contributing to the degradation of the basal membrane. [5] Inhibition of VEGF makes it possible to arrest the growth of blood

vessels and cut off cancer cells from nutrients and oxygen [6]. There are two approaches used to disrupt VEGF signalling, i.e. including ligand blockade and pharmacological blocking Vascular Endothelial Growth Factor Receptor (VEGFR).

Another example of a molecular target is Epidermal Growth Factor Receptor (EGFR). EGFR is a transmembrane glycoprotein that is overexpressed on the surface of numerous tumour cells. Binding of the receptor to the ligand leads to the activation of a signalling cascade modulating proliferation, adhesion, migration, angiogenesis and metastasis. The use of monoclonal antibodies directed against EGFR causes binding and blocking of signalling pathways, which results in inhibition of tumour growth development and also in the prevention of metastases [6].

The next protein used as the molecular target is Human Epidermal Growth Factor Receptor 2 (HER2), is characterized by the external activity of tyrosine kinase. Gene amplification and overexpression of this protein is identified in approximately 20% of breast cancer cases, it is also a negative prognostic factor. HER2 is a key mediator of cell growth and differentiation. HER2-positive tumours show a higher degree of malignancy than other subtypes. Inhibition or binding of this receptor may prevent the activation of signalling pathways, thus also the proliferation of the changed tissue [7].

An example of gene serving as a target in personalized therapy is B-Raf Proto-Oncogene (BRAF). B-Raf protein is a kinase from the RAF family of proteins and participates in intercellular signalling. *BRAF* mutations as *BRAFV600E* and *BRAFV600K* occurs with a high frequency in various types of cancer, may be inherited or acquired during postnatal development. This kinase is part of the MAPK signalling pathway, which continuous activation leads to increased proliferation, higher invasiveness and survival of cancer cells, and also increases the probability of metastasis. Modern drugs inhibit the activity of the altered protein by inhibiting this kinase [8].

Mechanism of action

Two action mechanisms of a targeted anti-cancer treatment can be distinguished. The first of these is blocking proliferation through the use of small molecule tyrosine kinase inhibitors (TKI) which causes impeding the activation of the signalling pathway by blocking the action of an abnormal protein (Tab. 1) [1, 2].

The second type of treatment uses monoclonal antibodies that bind specifically to the target proteins, which leads to inhibition of their activity (Tab. 2). Through the use of genetic engineering, humanized and fully human monoclonal antibodies are produced and are used in the treatment of cancer [10].

Toxicity of drugs used in targeted therapy

Inhibitors of the Epidermal Growth Factor Receptor (EGFR)

Epidermal growth factor receptor inhibitors are approved for treatment of early-stage cancers, such as non-small cell lung cancer, colorectal cancer, breast cancer, pancreatic cancer, head and neck cancer and squamous cell carcinoma. They include intravenous monoclonal antibody treatment or oral therapy with small tyrosine kinase inhibitors. EGFR is expressed in the structures of the skin, so inhibition is associated with a number of adverse skin complications [11]. It is believed that this is related to the inhibition of EGFR in basal keratinocytes and hair follicles. They exhibit similar expression of EGFR as in cancer cells [12].

In clinical practice, one of the most commonly observed skin reactions is an acne-like eruption. It manifests itself with blister-like papules or pustules that occur in clusters. Aforementioned changes can cause itching, smarting, pain and irritation. In the first stage of treatment both, erythema and edema can be present. Papules may occur between the 2nd and 3rd week, and after about a month, persistent erythema, dryness and telangiectasia are commonly noted. In extreme cases, it is necessary to reduce the dose or completely terminate the treatment. Some patients notice an involution in post-treatment changes, but there are also cases in which severe and persistent acne-like reactions often develop [11, 13]. Research regarding this subject reports a correlation between the occurrence of a rash and the effectiveness of treatment. It has been confirmed that acne-like changes in the treatment with the use of gefitinib and erlotinib may be an effective clinical indicator for predicting responses in patients with small cell lung cancer [14].

Another common side effect of EGFR inhibitors is Hand-Foot Syndrome or Palmar-Plantar Erythrodysesthesia. In the case of sorafenib and sunitinib therapy, the intensity of these side effects is proportional to the dose [14]. Syndromes range from erythema, edema and burning, to hyperkeratosis. Those can significantly affect the well-being of the patient during therapy. Other skin complications include observable pathological changes in hair and nails, resulting in hair loss and brittleness, also nail brittleness, as well as discolouration or curling. [15]. Other side effects associated with EGFR inhibition include dry skin, pruritus, atrophy of the natural barrier protecting against infection, seborrheic dermatitis, subungual hemorrhage, photosensitivity or paronychia, manifested by purulent inflammation around the nails [11, 12].

Trastuzumab, a monoclonal antibody directed against HER2, is mainly applied in breast cancer. The most common side effects are chills, fever, asthenia and nausea. However, cases of extensive and toxic

cardiovascular complications or even fatal pulmonary complications have also been reported. These severe events include primarily; dyspnea, pneumonia, lung infiltrates, edema, insufficiency or hypoxia. Usually, treatment termination can take place if initial symptoms indicating pulmonary complications occur [16, 17].

Inhibitors of B-RAF serine-threonine kinase

Skin lesions observed during treatment with EGFR inhibitors may also occur during targeted melanoma therapy. Increased risk of skin complications during vemurafenib or dabrafenib therapy has been observed in the range of 8 to 36 weeks after administration of the first dose [18]. During BRAF inhibitors monotherapy, skin toxicity is observed in 92–99% of patients, the most common being acne-like lesions, maculopapular or exudative rashes [19]. In addition, painful wart-like lesions most commonly occur after 4 weeks of treatment. Another frequent side effect is the Hand-Foot Syndrome described earlier. Most patients taking BRAF inhibitors suffer from hypersensitivity to ultraviolet A radiation (UVA). Side effects associated with exposure to UVA are manifested by severe sunburns, pain or blisters. Other side effects that occur during treatment of melanoma include alopecia, seborrheic dermatitis, follicular keratosis, or epidermal cysts [19, 20]. Treatment of skin lesions most often involves the use of antibiotics and corticosteroids, which carries additional toxicity to the patient. All described Dermatologic Events (DEAs) exert enormous influence on the mental, social and physical health of patients and affect their overall quality of life [18].

Other possibly dangerous complications, occurring during treatment with drugs such as dabrafenib or vemurafenib are fever, skin lesions, hepatic toxicity and lymphopenia. Lymphopenia makes it difficult to initiate an immune response and thus leads to numerous infections. The late identification of infections caused by pathogens can lead to particularly severe and potentially fatal diseases [21].

Inhibitors of Vascular Endothelial Growth Factor (VEGF)

In addition to skin complications, molecular targeted therapy can cause a number of other side effects. Tyrosine Kinase Inhibitors like sorafenib, sunitinib, imatinib ora axitinib may have side effects associated with hypothyroidism:

— thyroid atrophy by inhibiting its vascularization,
— preventing the binding of VEGF to normal thyroid cells,
— reducing the synthesis of thyroid hormones,
— inhibition of iodine uptake,
— sdrug-induced thyroid atrophy [22, 23].

Moreover, in 2010, thyroid dysfunction was described in patients treated with gefitinib [23]. These events were related to its mechanism of action, as it affects a lot of tyrosine kinases and binds VEGFR. The result of such interaction may be thyroid dysfunction occurring after less than a month of administrating the drug, it may have a place earlier than in the case of sorafenib or sunitinib [24].

VEGF plays a key role in the development of vascular blood vessels, which is why anti-angiogenic

Table 1. Examples of kinase inhibitors used in targeted therapy [8]

	Mechanism of action	Target	Therapeutic indications
Dabrafenib	Selectively binds B-raf protein.	BRAF	melanoma
Vemurafenib	Selectively binds to the BRAP ATP binding site.	BRAF	melanoma
Lapatinib	Reversibly blocks the phosphorylation of EGFR, ErbB2, ERK-1 and-2 and AKT kinases.	EGFR HER2	breast cancer
Erlotynib	Reversibly binds to the intracellular catalytic domain of the EGFR receptor.	EGFR	NSCLC, pancreatic cancer

Table 2. Examples of antibodies used in targeted therapy [8]

	Mechanism of action	Target and type of monoclonal antibodies	Therapeutic indications
Cetuximab	Binds to the intracellular domain of EGFR.	EGFR chimeric IgG1	colorectal cancer, HNSCC
Bavacizumab	Inhibiting receptor activation by binds to VEGF.	VEGF humanize IgG1	cervical cancer, NSCLC, glioblastoma, ovarian cancer, kidney cancer, colorectal cancer
Trastuzumab	binds HER2 on the surface of tumor cells, bring cell-mediated cytotoxicity in relation to tumor cells that overexpress HER2.	HER2 humanize IgG1	Stomach or esophageal adenocarcinoma, breast cancer

therapies focus on inhibiting this factor. Numerous inhibitors have been approved by the U.S. Food and Drug Administration (FDA) they show potential benefits but also cause significant dose-related complications. In 2011, the FDA withdrew the permission to use bevacizumab in case of treatment of breast cancer because the benefits did not outweigh the risks of the treatment [25, 26]. Due to the mechanism of action, the majority of adverse reactions resulting from anti-VEGF therapy is associated with vascular disease. These include cardiac infarction, cerebral stroke, heart failure, hypertension, thromboembolism or proteinuria [25].

Hypertension is considered to be a frequent consequence of undergoing VEGF inhibitors therapy [25]. Induction of hypertension may be connected with inhibition of nitric oxide production in endothelial cells. It usually is asymptomatic, but it can be a risk factor for cardiovascular disease or renal failure [27]. Another common consequence of using anti-angiogenic drugs is proteinuria, most likely caused by the inhibition of VEGF paracrine signalling [25], or acute hypertension [12]. Proteinuria is associated with overproduction of abnormal proteins that can cause nephrotoxicity. The above side effects accompanying anti-VEGF therapy may correlate with each other or may be a result of long-term therapy. In the elderly, they are not a prognostic factor [25].

There is also a risk of arterial thromboembolic complications, as VEGF inhibition may negatively affect blood dust and von Willebrand factor, and consequently lead to the activation of the hemostasis system [12]. All agents directed against VEGF are associated with an increased risk of bleeding [28, 29].

Anti-cancer drug resistance

Drug resistance can be one of the most significant limiting factors during anti-cancer treatment. The resistance may result from the adaptation of tumour cells caused by regular drug application or from the presence of pre-existing changes at the molecular level [30, 2]. Congenital cellular resistance is characterized by a lack of response to drugs from the beginning of their use. The acquired one, however, appears sometime after the start of therapy, most often after 12 or 18 months. Most patients develop resistance at one of the stages of treatment. There are many mutations and disorders that may result in the cell not being sensitive to targeted treatment [2, 31]. Asic K., in his work from 2016, divided the resistance mechanisms into:

- disturbances of drug penetration inside the cell — changes occurring in genes coding for target proteins,
- addiction to the alternative signalling pathway — activation of a protein that performs a similar function, causing further growth of cancer cells,
- changes leading to further activation of the target path — mutations or changes of genes encoding proteins below or above the target molecule,
- replacement/imitation of the target function,
- activation at Multidrug Resistance (MDR) [31].

Inhibitors of the Epidermal Growth Factor Receptor (EGFR)

In the case of treatment of non-small cell lung cancer (NSCLC) with erlotinib, all previously mentioned mechanisms have been observed, both congenital and acquired cellular resistance. During the treatment of colorectal cancer with cetuximab, in the case of congenital resistance, compensation of the EGFR function and changes in the regulation of the target signal pathway have been demonstrated. This resulted in the further activity of the EGFR molecule. In the example of acquired resistance, changes indicating contact with the drug have been shown [31, 32]. The primary problem in NSCLC therapy is the activation of alternative, parallel signalling pathways that cause the blockade created by the drug to be bypassed. One of the additional mechanisms of potential resistance is the activation of the insulin-like receptor 1 (IGFR1) [33].

Similarly, targeted therapy for HER2 overexpression in the treatment of breast cancer using monoclonal antibodies may contribute to all of the previously mentioned mechanisms of cellular resistance. In the case of acquired resistance, MDR was excluded as well as replacement/imitation of the target function. When kinase inhibitors are used, further activation of the target signalling pathway and replacement/imitation of the target functions by activation of another protein or MDR may also occur [31]. Trastuzumab is an example of a drug that allows considerable clinical advances in the treatment of breast cancer. The impediments, however, is not fully understood. Changes in the cell cycle, DNA repair mechanisms, PI3K signalling pathway, as well as inhibition of the extracellular protein domain or HER2 degradation are indicated. In the case of trastuzumab, the mechanism of impaired binding of the drug to the receptor may refer to the formation of a truncated HER2 protein, devoid of the extracellular domain. Receptor cloning by MUC4 glycoprotein has also been described. The loss of the PTEN suppressor gene (Phosphatase and Tensin Homolog), or excessive activation of the PI3K-AKT pathway, results in the change of the signalling pathway into its alternative counterpart [33].

Inhibitors of B-RAF serine-threonine kinase

Mechanisms of congenital resistance occurring during treatment of melanoma with the *BRAFV600E* mutation using vemurafenib, include dependence on

alternative signalling pathways, further activation of the target pathway and imitation of the target function. In acquired resistance, it is also possible to make difficult contact with the drug by incomplete binding to the cancer cell. The use of sunitinib is associated with the occurrence of all the previously mentioned mechanisms of congenital cellular resistance, with the exception of the blockade of contact with the drug. Likewise, further activation of the target path was excluded from the acquired resistance [31]. In addition, it has been shown that by reducing tumour vasculature when using sunitinib, cancer cells acquiring resistance more often form distant metastases [34].

Under physiological conditions, ERK signaling is regulated by feedback mechanisms to preserve homeostasis of the body and normal cell growth. In tumors with the *KRAS* or *BRAF* mutation, this signaling disorders are often noticed and the phenomenon of overexpression of the path prompted researchers to use inhibitors of this ERK signaling as a therapeutic agent - dabrafenib and vemurafenib. Treatment has shown that effectiveness correlates with the braking force of signaling. This is related to the rapid adaptation of the tumor to the inhibited pathway through mechanisms leading to RAF dimerization and the increased level of ERK signaling. Vemurafenib and dabrafenib require a monomeric RAF protein for inhibition. Therefore, when it is dimerized, the action of drugs is inhibited. Furthermore, tumor heterogeneity influence to the development of resistance to individual factors [35].

The cost of targeted therapies

The main premise of targeted therapies requires the use of state-of-the-art diagnostic technologies, blood and tissue banks, and the use of extended clinical knowledge, which significantly influences the cost of the final treatment. Drugs used in such therapies are designed to work on a specified biochemical pathway and require extensive trials, often limited to selected patient populations. Therefore, except for the biological barriers, which are often related to the mechanisms of resistance, also incomplete understanding of signaling pathways and further search for useful biomarkers, the widespread use of personalized medicine is limited by the economic barrier. There are various reasons why investors have doubts about the profitability of personalized treatment. One of the main sources of hesitation is the problem of identification of appropriate diagnostic technologies that would be both, effective and at the same time inexpensive [36].

Expensive studies can be profitable only if, due to their high accuracy, they bring significant health benefits to well-identified target groups. Standard breast cancer treatment is based on chemotherapy and hormonotherapy. In targeted treatment, other than the standard characteristics of a tumor, such as size, lymph node metastases, or hormone levels, tests are performed in order to detect the expression of tumor genes and protein levels. An example is the HER2 receptor study to select candidates for trastuzumab treatment. It is recommended to apply either routine immunohistochemistry (IHC) or Fluorescent *in situ* Hybridization (FISH). However, they differ in accuracy and efficiency, so researchers often have to do carry out both tests. Only patients with a HER2-positive result are classified for this therapy [37].

A relatively expensive study in targeted therapy at HER2 is a Histopathological analysis which uses antibodies or Gene Expression Profiling (GEP); as a tool for risk stratification. GEP includes gene analysis that uses either DNA microarray technology or polymerase chain reaction in real time (Reverse Transcriptase PCR, RT-PCR) [37, 38]. Total cost of therapy for trastuzumeb of early-stage HER-positive breast cancer averages around $ 67,800 [39]. Treatment with trantuzumab with HER-positive stomach cancer is estimated at $ 90,000 a year [40].

FDA-approved Vemurafenib, used in the treatment of metastatic melanoma in patients with the BRAF mutation, is implemented instead of the standard dacarbazine treatment. Curl et al. compared the cost-effectiveness of both treatments. It was shown that the cost of using vemurafenib is inadequate to its results [41].

Comparative analysis indicates that the overall cost of targeted therapy may outweigh the benefits of the treatment. In 2011, the majority of targeted drugs approved by the FDA, assuming a 12-month treatment, required a cost of $ 20,000, which resulted in insurance companies starting to withhold their expenses for treatment. The costs of targeted therapy fell completely on the patient, which in many cases led to stressful situations resulting from the loss of financial liquidity an example may be bevacizumab approved for treatment, among others colorectal cancer, NSCLC or ovarian cancer. The annual cost of the treatment is estimated around $ 50,000, which in some cases can amount to $ 100,000. Finally, the monoclonal antibody was withdrawn from the treatment of breast cancer due to proven ineffectiveness compared to standard therapy, while the cost of treating the patient for one year could be as high as $ 500,000. Another drug, the use of which requires large financial outlays is cetuximab, approved for the treatment of among others NSCLC. Patient's therapy with its use costs about $ 800,000 a year. Even if there are funds for treatment, this does not ensure survival, but it may have many side effects that adversely affect the patient's well-being [40]. Another problem that consumes large financial outlays is the costs of mitigation or treatment of side effects. In contrast to diagnostics, they are not included in the estimated cost of therapy [41].

Conclusions

Molecular Targeted Therapy is one of the modern tools used in the fight against such cancers as melanoma, breast cancer or colorectal cancer. The condition for its use is accurate diagnostics which enables the characterization of cancer cells. The most important element of this therapy is to find a molecular target. Novel, highly reliable markers for targeting cancer cells with a specific phenotype are still being sought.

In most patients, drug resistance appears after a certain time, despite the initial effectiveness of the implemented therapy. After the acquisition of resistance, it seems almost impossible to overcome the mechanisms allowing cancer cells to further undisturbed proliferation. Most often in this case the treatment with personalized therapy is completed and the patient is treated with standard methods. There have also been attempts to circumvent resistance mechanisms through the use of combination therapies, but this is always associated with increased costs of treatment.

Another problem in the use of personalized therapy is high toxicity. Although the effect of therapy is targeted, it still affects normal cells. Some cells in the body show expression of molecules that serve as a molecular target, but not as pathological as in cancer cells. For this reason, drugs directed against EGFR or HER2 most often cause dangerous skin changes, anti-angiogenic drugs, and cardiovascular complications. The increase of side effects is associated with the reduction in the dose of the drug or, in extreme cases, termination of therapy. Mechanisms of resistance and toxicity of therapy chiefly reduce its effectiveness.

The additional factor is the costs of diagnostics, medicines and combating side effects. They predominantly contribute to the unprofitability of treatment. If the effects are inadequate to the incurred costs and they additionally reduce the patient's quality of life, the drugs are not approved, and even though they were previously registered, they are removed from circulation.

The limitations of molecular targeted therapy are in many cases greater than with standard anti-cancer therapies. Meeting the requirements for reducing side effects and costs with simultaneously higher efficacy would require using molecules that are found on cancer cells as a molecular target, but are absent on normal cells (Fig. 1). Expanding our knowledge of the resistance mechanisms and signaling pathways in tumors would increase the chance of success for targeted therapy. It is equally important to look for new methods of drug production and diagnostic tests that would minimize the cost of treatment.

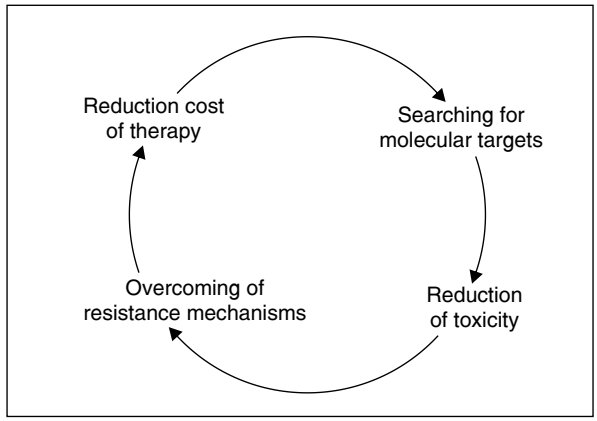

Figure 1. Perspectives for Molecularly targeted therapy

Disclosure of interest

The authors declare no conflict of interest.

List of abbreviations

BRAF — B-Raf Proto-Oncogene
DEAs — Dermatologic Events
EGFR — Epidermal Growth Factor Receptor
FDA — Food and Drug Administration
FISH — Fluorescent In Situ Hybridization
GEP — Gene Expression Profiling
HER2 — Human Epidermal Growth Factor Receptor 2
HNSCC — Head and neck squamous cell carcinoma
IGFR1 — Insulin-Like Growth Factor 1
IHC — Immunohistochemistry
MDR — Multidrug Resistance
NSCLC — Non-Small-Cell Lung Carcinoma
PMPY — Per Member Per Year
PTEN — Phosphatase And Tensin Homolog deleted on chromosome ten
RT-PCR — Reverse Transcriptase PCR
TKI — Tyrosine Kinase Inhibitor
UVA — Ultraviolet A
VEGFRs — Vascular Endothelial Growth Factor Receptor
VEGR — Vascular Endothelial Growth Factor

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VIA MEDICA

REVIEW ARTICLE

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Self-reported questionnaires for a comprehensive assessment of patients after acute coronary syndrome

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ABSTRACT

Effective patients' preparation for discharge is expected to improve adherence to long-term treatment and functioning in chronic faze of coronary artery disease-ameliorating clinical outcome. This paper is aimed to introduce the strategy of comprehensive post-ACS in-hospital patients' evaluation regarding readiness for hospital discharge, as well as a post-discharge assessment of adherence to pharmacological treatment and functioning in the chronic phase of the coronary artery. A system of diagnostic tools allowing assessment of patients during hospitalization and after discharge has been developed. The Readiness for Hospital Discharge after Myocardial Infarction Scale (RHD-MIS) was designed for in-hospital evaluation, while the Adherence in Chronic Diseases Scale (ACDS) and the Functioning in Chronic Illness Scale (FCIS) for examination during follow-up visits. They are expected to reflect the effectiveness of different aspects of patient-medical staff collaboration. Use of questionnaires seems to be a method of choice for this purpose because of the simplicity, easiness of their application, and low cost. Self-reported questionnaires allow comprehensive in-hospital and post-discharge assessment of patients after ACS.

Key words: self-reported questionnaire, adherence to treatment, coronary artery disease

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Introduction

Therapy consistent with medical guidelines after acute coronary syndrome (ACS) has been shown to effectively reduce the prevalence of adverse cardiovascular events, however, the adherence to long-term pharmacotherapy tends to be insufficient [1–3]. Therefore, extensive in-hospital education should be a standard of care in patients with ACS [4,5]. To ensure patient understanding, satisfaction and safety, discharge planning, including the assessment of patients' readiness for discharge, should be applied [6–8]. Such an evaluation allows a personalized definition of needs for additional educational intervention [9]. It is expected that effective patients' preparation for discharge will improve adherence to long-term treatment and functioning in chronic faze of disease improving clinical outcome [6, 7, 10].

This paper is aimed to introduce the strategy of comprehensive post-ACS in-hospital patients' evaluation regarding readiness for hospital discharge, as well as a post-discharge assessment of adherence to pharmacological treatment and functioning in the chronic phase of the coronary artery.

Methods

Self-reported questionnaires are suitable for common use allowing identification of patients with ACS of insufficient preparation for discharge from hospital, subjects of increased risk of low adherence to treatment after discharge as well as bad functioning in chronic illness [3, 11, 12]. Therefore a system of diagnostic tools allowing assessment of patients during hospitalization and after discharge has been developed. A comprehensive, multi-stage assessment of patients should improve the quality of medical care by personalizing educational and therapeutic interventions after ACS [13–15]. The Readiness for Hospital Discharge after Myocardial Infarction Scale (RHD-MIS) [7] was designed for in-hospital evaluation, while the Adherence in Chronic Diseases Scale (ACDS) [16, 17] and the Functioning in Chronic Illness Scale (FCIS) [18] for examination during follow-up visits.

Assessment of readiness for hospital discharge

The discharge from the hospital is a multifactorial, interdisciplinary, individualized process of transition

from hospital to outpatient care, requiring efforts aimed to meet patients' expectations and needs as well as to negotiate the agreement regarding a therapeutic plan for the post-discharge period [19–22]. Therefore a tool enabling the efficient assessment of the patients' knowledge, expectations, and concerns, as well as indicating the field requiring additional intervention in clinical conditions should be widely applied. The previously developed Readiness for Hospital Discharge Scale (RHDS) was tested in a sample of adult medical-surgical patients without any specific illness [20]. The recently validated RHD-MIS was designed for subjects after myocardial infarction [7]. The validation procedure was performed in 201 patients recovered for ACS and treated with the percutaneous coronary intervention (PCI). The questionnaire consists of 23 questions: 18 self-reported by patients (the subjective assessment of patients' knowledge — 7 items, expectations of patient — 9 items) and 7 assessed by the medical staff during a consultation with the patient (the objective assessment of patients' knowledge — 7 items), each scored from 0 to 3 points. The additional five not-scored items reflect the patient's situation and do not measure the intensity of any feature. The internal consistency of the entire RHD-MIS was satisfactory with an α-Cronbach coefficient of 0.789. The RHD-MIS fulfilled the assumption of factor analysis: the determinant of the correlation matrix was 0.001, Kaiser-Mayer-Olkin (K-M-O) statistic was 0.723, and the Bartlett' test of sphericity was statistically significant. The analysis of the internal consistency of the three areas confirmed the rightness of the distinguishing of three subscales. According to our knowledge, the RHD-MIS is the first validated survey taking into account the specificity of patients with ACS. It was developed as a tool aimed to improve the quality of the discharge process, including additional personalized education and motivation [7]. Further investigation is needed to assess the potential impact of RHD-MIS scoring on long-term outcome.

Assessment of adherence to long-term medication

Poor adherence to long-term medication is known to reduce the effectiveness of applied therapy making it a critical issue in high-risk populations [16, 23]. Interventions aimed to improve adherence are expected to ameliorate the clinical outcome in patients after ACS [24]. Hence, there is a need for a reliable tool allowing identification of subjects prone to not follow the ordered therapy. Several self-reported questionnaires were developed for this purpose. The survey should be simple and easy to apply in everyday practice. Moreover, it should determine the most common reasons of non-adherence. The ACDS has been validated in 401 patients with stable coronary artery disease [16]. Initially, it has been designed as an 8 — items self-reported questionnaire to reflect the actual implementation of the treatment plan in terms of provided pharmacotherapy as well as facilitate identification of mechanisms determining adherence in adult patients with chronic illnesses. All the questions refer to determinants of adherence associated with behaviours and determinants that can indirectly influence the adherence and are related to situations and patients' convictions. According to the results of the validation procedure, one question has been excluded. Finally, the internal consistency for the remaining 7 items was satisfactory with an α-Cronbach coefficient of 0.752. The determinant of the correlation matrix was 0.211, the value of K-M-O statistic was 0.848 and Bartlett's test of sphericity was statistically significant [16]. We believe that the ACDS indicating subjects of low adherence has the potential to improve patient — a health care professional communication and relationship, which are the key points providing higher adherence to the specific therapy. However, further studies are required to assess the correlation between the ACDS results and actual adherence to medication. Several language ACDS versions (Portuguese, Spanish and Turkish) currently undergo validation procedures.

Recently, a variant of the ACDS — the ACDS-diet has been also developed. It is dedicated for evaluation of adherence to the diet. The results of ongoing simultaneous validation studies of Polish and Portuguese versions are expected at the end of 2019.

Assessment of functioning in the chronic illness

The impact of the disease essentially covers all areas of human functioning, including physical activity, emotional and spiritual sphere, and functioning in society resulting in lower self-value perception, deterioration in well-being, an increase of anxiety and uncertainty about the future [25–28]. However, the available tools are aimed to evaluate only single aspects of the chronic disease impact on human life e.g. quality of life, physical and mental functioning, level of disease acceptance, self-efficacy or health self-control location [29–32]. Therefore, a new diagnostic tool to assess the overall functioning of the patient in chronic disease has been created. The FCIS has been designed to evaluate the impact of the disease on the patient, the patients' impact on the disease and the impact of the disease on patients' attitudes [18]. It has been validated in 366 coronary artery disease patients previously treated with PCI. The questionnaire consists of 24 questions divided into three parts, with a catalogue of 5 answers added to each question. The value of the α-Cronbach coefficient for the entire questionnaire was 0.855 indicating that the questionnaire is reliable and homogenous. The set of all 24 questions fulfilled the requirement of the factor analysis, i.e. the value of the determinant of the

correlation matrix was 0.001, K-M-O parameter was 0.843 and the Bartlett' test of sphericity was statistically significant [18]. According to our knowledge, FCIS is the first tool allowing the comprehensive assessment of physical and mental functioning dedicated for patients with chronic diseases. The FICS allows the assessment of various aspects of patients' functioning with chronic disease in a quick and simple way, without the use of several different tools. Such an approach should allow diagnosing deficit areas in order to implement appropriate therapeutic and educational interventions [33]. The Portuguese versions of this questionnaire are currently validated.

Discussion

The described strategy of comprehensive in-hospital and post-discharge evaluation of patients after ACS has been implemented into several clinical protocols [34–36]. However, all these tools (RHD-MIS, ACDS, and FCIS) were designed to improve the quality of every-day clinical practice. They are expected to reflect the effectiveness of different aspects of patient-medical staff collaboration. Use of questionnaires seems to be a method of choice for this purpose because of the simplicity, easiness of their application, and low cost. Moreover, questionnaires may also be helpful for differentiation of mechanisms of resistance to treatment [37–39]. Questionnaires are population-specific and need validation in specific clinical settings [40, 41]. All presented tools were tested in patients with coronary artery disease after ACS treated with PCI [7, 16, 17, 18, 42]. Their application in populations with different diagnosis or in other cultural and language environment needs additional validation to ensure consistency and reliability of results.

Conclusion

Self-reported questionnaires allow comprehensive in-hospital and post-discharge assessment of patients after ACS.

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VIA MEDICA

CASE REPORT

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Cardiovascular effects of cocaine

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ABSTRACT

A case of a 39-year-old man, who was taking cocaine 2-3 times a week for several years. The article contains the possible impact of cocaine use on the cardiovascular system and differential diagnosis in this patient.

Key words: cocaine, cardiovascular

Med Res J 2019; 4 (2): 110–115

Introduction

Cocaine is one of the most commonly used illegal drug worldwide. It is highly psychologically addictive, but it has no physical withdrawal effects. The main mechanism action of cocaine is the inhibition of noradrenaline and dopamine re-uptake from the synaptic cleft which causes overstimulation of alpha and beta-adrenergic receptors. [1] Cocaine abuse may cause acute and chronic cardiovascular diseases — myocardial ischemia, myocardial infraction, arrhythmias, cardiomyopathy, myocarditis, hypertension, aortic dissection. (Fig. 1.) Cocaine users have 4–8 times higher mortality compared to the general population. It is also the most common cause of drug-related deaths.

Case report

A 39-year-old male with pneumonia and heart failure (de novo), with no previous of cardiac problems, presented shortness of breath. He admitted that he was taking cocaine 2–3 times a week for several years by inhaling it cocaine through his nose. Three weeks ago he underwent a laryngological surgery due to chronic sinusitis.

During the physical examination, the patient had a blood pressure of 105/70 mmHg and his heart rate was 110 beats/min and regular. In cardiac auscultation, a high-pitched holo-systolic murmur on the apex, radiating to the armpit could be heard. Electrocardiogram revealed sinus rhythm with left ventricular overload and hypertrophy, negative T in leads I, II, aVL, V4–V6 (Fig. 2).

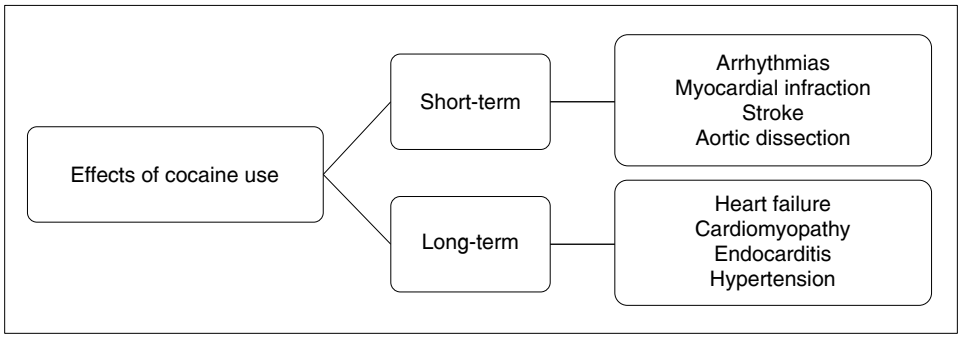

Figure 1. Short-Term and long-term effects of cocaine use

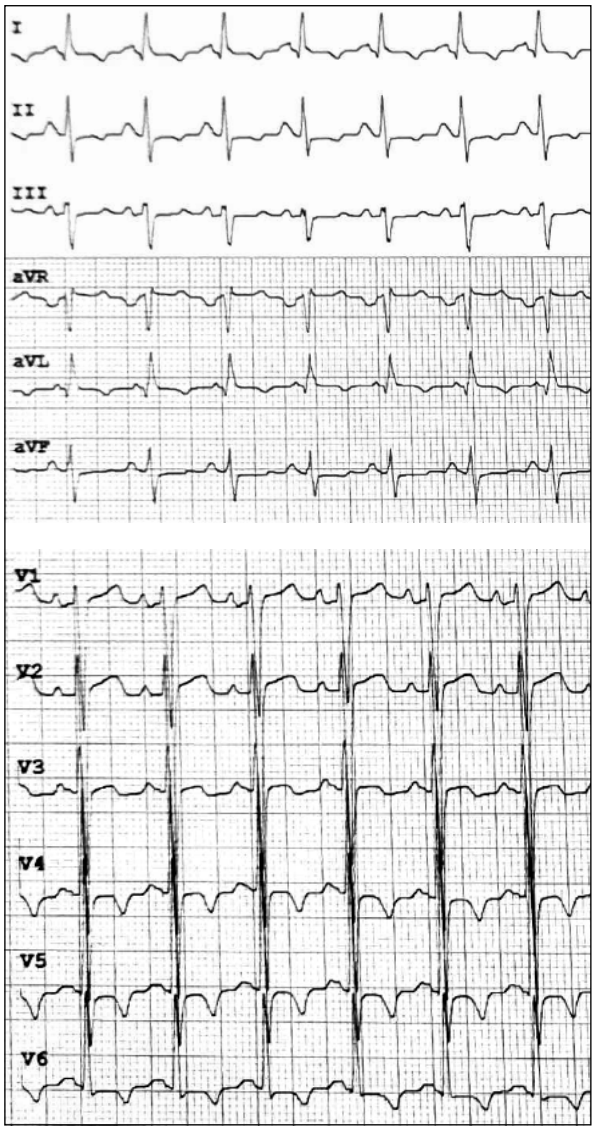

Figure 2. ECG of presented patient

Troponin I levels peaked at 77 ng/ml, creatine was 0,97 mg/dl, Btype natriuretic peptide was 2003 pg/ml. A chest X-ray revealed an enlarged cardiac silhouette (Fig. 3). An echocardiogram demonstrated akinesis of the apex, anterior wall and interventricular septum, hypokinesis of other left ventricular walls, enlargement of all heart cavities, left ventricular ejection fraction of 25%. Coronarography didn't show any abnormalities in coronary vessels (Fig. 4). Cardiac MRI showed dilation and severe retardation of the systolic function of both chambers with no underlying cause. There wasn't contrast enhancement typical to inflammation or myocardial ischemia.

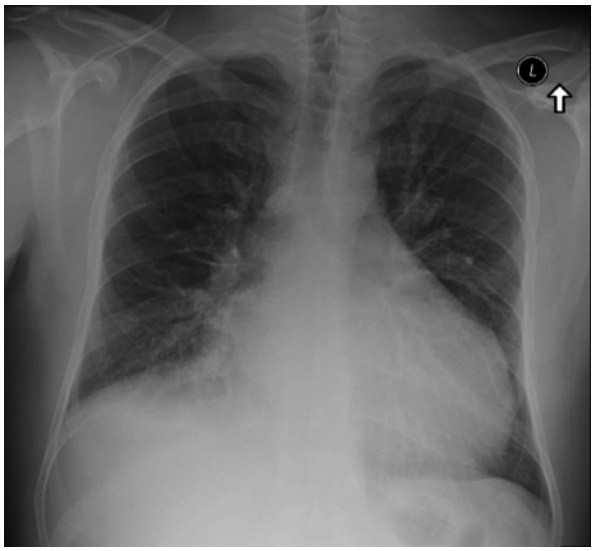

Figure 3. Chest X-Ray of a presented patient

Cocaine-inducted acute myocardial infraction

Overstimulation of beta-adrenergic receptors, caused by cocaine, increases contractility and heart rate, which leads to a higher oxygen request [2]. Moreover, cocaine is causing overstimulation alfa-1 and alfa2 receptors, which causes coronary artery spasm. The ischemic effect appears when heart rate and blood pressure is higher, requiring more oxygen supply (Fig. 5). Cocaine also activates platelet aggregation, which is leading to the formation of blood clots in the coronary vessels. It also accelerates atherosclerosis [3].

However, coronarography may not show any abnormalities in coronary vessels [4]. In patients with cocaine-related pain, a heart attack occurs in 6% of cases. Cocaine inducted acute myocardial infraction is the most common among the population of patients between the ages of 18-45 [5–6]. It needs to be suspected in young patients with chest pain.

The risk of a heart attack increases 24 times directly after using cocaine. Most infractions happen during the first 3 hours after cocaine use [7]. Complications rarely occur after 12 hours, so patients should be monitored by ECGs and cardiac troponins for at least 12 hours [8]. Cocaine is affiliated with an increased risk of acute coronary syndrome even without the presence of coronary heart disease, due to coronary artery spasms.

The treatment is similar to the one that is used in an acute myocardial infraction. Until recently it was considered that it is not recommended to use B-blockers in treatment, because of vasoconstriction properties. How-

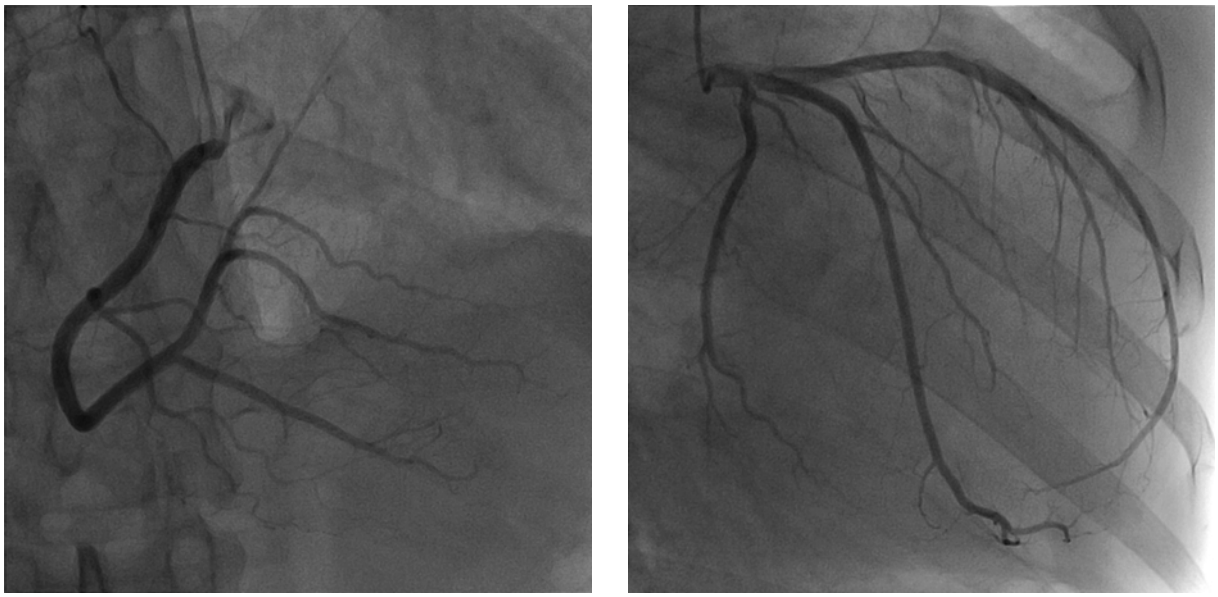

Figure 4. Coronarography of the presented patient

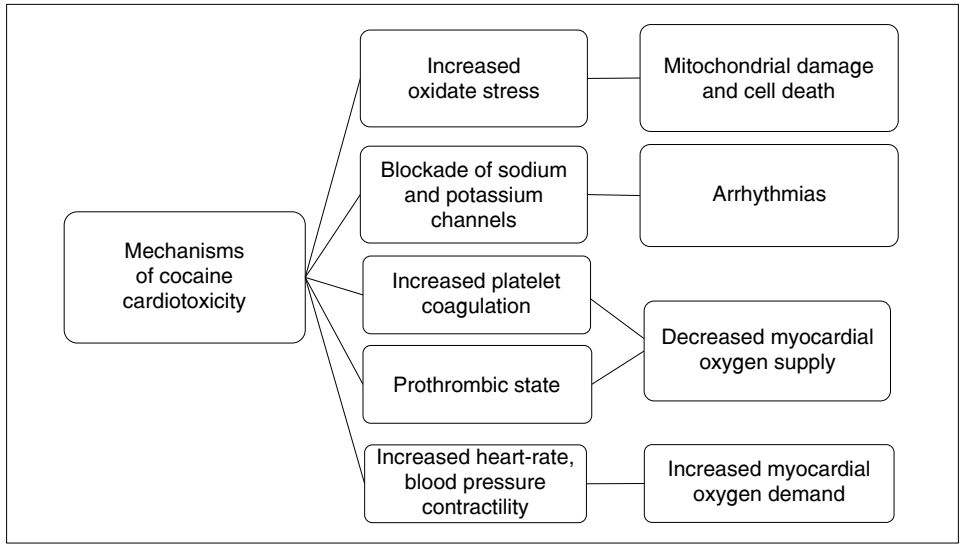

Figure 5. Mechanisms of cocaine inducted cardiotoxicity

ever because of the fact, that a lot of patients didn't admit that they used cocaine, received B-blockers and they didn't affect them negatively, but even they had a beneficial effect. [9] B-blockers are causing a lower request for oxygen. Treatment was associated with lower rates of deaths. The guidelines of ACC/AHA from 2012 states that it is acceptable to use Bblockers at the patients with hypertension or tachycardia if they received vasodilator drug [7]. Additionally, it is recommended to use benzodiazepines for the patients who are hyper excitable with hypertension and tachycardia [10]. Benzodiazepines reduce the hemodynamic effects of cocaine. Sedation is also indicated in patients with psychomotor agitation.

The lack of coronary artery stenosis in coronarography, especially in young patients with the acute coronary syndrome, should lead to suspicion of taking cocaine as a cause. The guidelines of ACC/AHA from 2008-2012 recommended to using bare-metal stents in cocaine abusers. [7]

The psychological state and euphoria associated with cocaine use, reduce the number of patients, who were referred to a hospital. That is why the reports on the number of heart attacks caused by cocaine use are underestimated.

With regard to the case report, the possibility of myocardial infarction was ruled out because of the lack

of chest pain and slightly increased TnI without typical dynamic, characteristic for the myocardial infraction.

Coronarography didn't show any abnormalities in coronary vessels.

Aortic dissection

Cocaine induces the apoptosis of smooth muscle cells, which build the vessel wall, making them more susceptible to damage [11]. Sudden increase of blood pressure up to high values, after exposure to cocaine, may cause aortic dissection. It is estimated that 0.5% is connected with cocaine usage. Should be expected aortic dissection especially in young patients with chest pain. First line treatment is controlling blood pressure, heart rate and level of pain. Further therapy is surgery. Patients have a high risk of dangerous complications and even death.

In this particular case report, aortic dissection is not expected because there was no chest pain. Also, there was no evidence of aortic dissection in imaging studies.

Cardiomyopathy

Cardiomyopathy in cocaine users is caused by a direct toxic effect on myocytes, oxidative stress, calcium channel dysfunction and also excessive adrenergic stimulation. Toxic influence of cocaine is causing inflammation of the heart muscle, fibrosis and as a result heart failure. Oxidative stress has a toxic effect on the myocardium. It is caused by high level of peroxides and free radicals, which are damaging all components of cardiomyocytes. [12] Raised calcium inflow into smooth muscle cells results in increased contraction force, but when it is chronic, it weakens the myocardium, causes overgrowth and decreases the left ventricle ejection fraction. [13] Excessive adrenergic stimulation caused by the inhibition of noradrenaline and dopamine reuptake causes an increase in heart rate and elevated blood pressure. [14] This affects the remodelling of the myocardium. Improvement of the left ventricle ejection fraction is possible after reaching total abstinence from cocaine.

Cocaine-associated cardiomyopathy should be suspected in young patients with heart failure. Symptoms reported by patients are similar to those with dilated cardiomyopathy. Mostly it is dyspnea and fatigue. [15] However it was revealed that symptoms such as leg oedema are much less intense. Cardiomyopathy usually has a more severe course. Usually, patients also present symptoms of increased adrenergic stimulation, such as tachycardia, hyper-tension and those associated with the psychotropic action of cocaine. In a physical examination, it's possible to notice symptoms of cocaine usage — depending on the route of administration of the drug such as scars after intravenous injections or damage of the nasal septum.

It is reasonable to use B-blocker treatment in patients with cocaine-related cardiomyopathy who had abstinence for more than 6 months, as standard therapy of the left ventricular dysfunction.

The clinical picture of this patient led to the diagnosis — cardiomyopathy. The patient presented dyspnea and impaired of effort tolerance. It was confirmed by the results of additional tests that includes among others echocardiography and MRI.

Arrhythmia

Cocaine increases the risk of arrhythmia, due to excessive adrenergic stimulation and it also affects the blockage of sodium and potassium channels. In small doses the effect of stimulation of the adrenergic system dominates, in large doses, it blocks ion channels. [16] Usage of cocaine induces ventricular and supraventricular arrhythmias. It can cause sinus tachycardia or atrial fibrillation when arrhythmia is the result of excessive adrenergic stimulation. The blockade of potassium channels causes QT interval prolongation, which can lead to ventricular tachycardia, including *torsade de pointes*. Cocaine-induced myocardial ischemia can cause ventricular tachycardia or ventricular fibrillation. [17]

The first-line treatment is B-blockers in combination with alpha-blockers. Sodium bicarbonate and lidocaine are also used. Have Cablockers been shown to reduce arrhythmia? It is important to correct electrolyte disturbances. Arrhythmias resistant to pharmacological treatment can be corrected by cardioversion or defibrillation. It has been proven that ablation is feasible, safe and effective in patients with drug-resistant cocaine-induced tachycardia. [18] The most common cause of sudden death in people addicted to cocaine is ventricular fibrillation. [19] The main therapeutic goal of a patient experiencing cocaine-related arrhythmia is the abstinence of using cocaine.

During the hospitalization of the patient in the ECG monitoring, no arrhythmias were recorded.

Endocarditis

Cocaine is one of the most commonly used drugs for intravenous use. This route of administration is associated with a high risk of endocarditis.

Cocaine also has a damaging effect on the vascular endothelium. Endocarditis in drug users is mostly on the tricuspid valve. [20] Treatment consist of multi-week antibiotic therapy but the most important goal is to stop using cocaine.

The results of laboratory tests and the result of MRI allowed to rule out endocarditis at the patient.

Stroke

Strokes occur most often in older patients. However recently there was an increase in a number of incidences among younger people, which is related to the use of illegal drugs. Cocaine increases the risk of ischemic and hemorrhagic stroke. [21] The most common causes of ischemic strokes in patients using cocaine are atherosclerotic stenosis of the large artery and occlusion of the small cerebral vessels.

Vasoconstriction and prothrombotic properties increase the risk of ischemic stroke. The use of cocaine accelerates the process of atherosclerosis. [22] Long-term use of cocaine increases the risk of stroke, including endothelial changes, atherosclerosis and vasculitis. Most ischemic cocaine-related strokes occur in people with a distant history of cocaine use.

Hemorrhagic strokes are associated with a sudden rise in blood pressure after cocaine ingestion. They are more common in active cocaine users. The most common cause is rupture of the aneurysm. [23] It has been proven that brain aneurysms are likely to happen to people who use cocaine. The use of cocaine is associated with a greater probability of hemorrhagic stroke than ischemic stroke. [24]

The patient did not show symptoms of neurological deficit. Diagnosis for stroke has not been extended.

Conclusion

As demonstrated, cocaine has many negative effects on the cardiovascular system. One of the main goals of treatment is total abstinence. An important aspect is to make patients aware of the consequences of further cocaine use. Cocaine use can cause both short-term and long-term effects.

In young patients presenting cardiovascular disease symptoms, but not having any other loads, the drug use should be considered in the diagnosis, because it is most often occurs in this age group.

In this case report, the patient was diagnosed with toxic cocaine cardiomyopathy. The direct cause of the disease was long-term and regular use of this drug.

The patient was qualified for ICD implantation as the primary prevention of sudden cardiac death.

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VIA MEDICA

CASE REPORT

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Gastrointestinal bleeding and the prevention of thromboembolism

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ABSTRACT

About 2 percent of developed countries population use vitamin K antagonists (VKA), such as warfarin. These anticoagulation drugs are commonly prescribed for the purpose of thromboembolism prevention, in cases of atrial fibrillation, mechanical heart valves, deep vein thrombosis, pulmonary embolism and etc. The frequency of VKA prescription is massively increasing in the whole world. The main reason for it is the ageing of the population. As the usage of anticoagulants is increasing, doctors more often get to encounter patients with gastrointestinal bleeding taking anticoagulating drugs. The treatment of these patients is difficult because there are several important factors that have to be considered while choosing the tactic of treatment, such as the intensity of bleeding, coagulation, thrombotic risk and endoscopic findings. Even if practical guidelines partially indicate the main principles of actions for similar cases, the treatment of bleeding patients taking anticoagulants remains seriously challenging. This article contains clinical case report and the discussion of the treatment that has been chosen in this case, based on practical guidelines provided by American Society for Gastrointestinal Endoscopy (ASGE), European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Cardiology (ESC). This topic is also addressed in guidelines from the American College of Gastroenterology, the American College of Chest Physicians, the American College of Cardiology, which give similar recommendations.

Key words: anticoagulants, warfarin, bleeding, thromboembolism, anticoagulation, endoscopy

Med Res J 2019; 4 (2): 116–119

Introduction

About 2 per cent of developed countries population use vitamin K antagonists (VKA), such as warfarin. These anticoagulation drugs are commonly prescribed for the purpose of thromboembolism prevention, in cases of atrial fibrillation, mechanical heart valves, deep vein thrombosis, pulmonary embolism and etc. The frequency of VKA prescription is massively increasing in the whole world. The main reason for it is the ageing of the population. As the usage of anticoagulants is increasing, doctors more often get to encounter patients with gastrointestinal bleeding taking anticoagulating drugs. The treatment of these patients is difficult because there are several important factors that have to be considered while choosing the tactic of treatment, such as the intensity of bleeding, coagulation, thrombotic risk and endoscopic findings. Even if practical guidelines partially indicate the main principles of actions for similar cases, the treatment of bleeding patients taking anticoagulants remains seriously challenging. This article contains clinical case report and the discussion of the treatment that has been chosen in this case, based on practical guidelines provided by American Society for Gastrointestinal Endoscopy (ASGE), European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Cardiology (ESC). This topic is also addressed in guidelines from the American College of Gastroenterology, the American College of Chest Physicians, the American College of Cardiology, which give similar recommendations.

Case report

52 years old woman having the complaints of vomiting with blood clots, black fieces and general weakness has been delivered to the emergency department.

A day before hospitalization the patient got nausea after coughing, had vomited blood with clots. One day later vomiting occurred once again, black fieces showed up as well. The patient has been delivered to the emergency department by ambulance and has been hospitalized for more detailed examination and treatment.

The patient had rheumatism, mitral valve was replaced with a mechanical prosthesis in 2008. She also

had a myocardial infarction and coronary arteries bypass in 2008. Artificial cardiac pacemaker (ECS IKDVR) was implanted in 2011. The patient also has arterial hypertension, permanent atrial fibrillation, type II diabetes.

The patient permanently takes metformin, gliclazide, metoprolol, spironolactone, torasemide. She also often takes diclofenac to reduce the pain of her joints. To prevent thromboembolic events which can occur because of mechanical mitral valve prosthesis and permanent atrial fibrillation, the patient takes warfarin.

During the physical examination, the patient was fully conscious, oriented and available for contact. The skin and visible mucous membranes have been pink, the tongue has been dry, covered with white plaque. Breathing rate has been 16 per minute. Breath sound in the lungs has been vesicular, without crackles on both sides. Heartbeat has been arrhythmic with the sound of a mechanical valve's prosthesis. Arterial blood pressure 110/80 mmHg, heart rate 150 times per minute. The abdomen has been soft, but sensitive in the whole area. The percussion of kidneys hasn't been painful. There have been no oedemas in her legs.

Blood test results: red blood cells (RBC) 3,27 x 10^{12}/l, haemoglobin (Hb) 103 g/l. Coagulation tests: SPA 25 %, INR 2,19.

Endoscopy showed a bleeding gastric ulcer in the angular area, which has been around 0.7 cm in size and with a clot underneath. The bleeding has been stopped by clamping. The treatment has been continued with esomeprazole/pantoprazole 80 mg bolus intravenously, continuing 8 mg per hour by automatic syringe pump for 3 days.

A blood test was repeated after the endoscopy and it showed that the amount of haemoglobin was getting lower (100•88•81 g/l). The patient had a blood transfusion, 2 units of red blood cells mass were given.

Next morning the health state of the patient was improved, general weakness seemed to be reduced, there were no signs of bleeding.

The treatment has been continued with Sol. Esomeprazole 40 mg twice a day intravenously for 2 days, later Caps. Omeprazole 20 mg twice a day orally were prescribed.

In case of gastrointestinal bleeding, the decision to stop taking warfarin and change it with low molecular weight heparin (LMWH) was made, so the patient has started getting Sol. Nadroparin 2850 IU twice a day subcutaneously.

Tab. Tardyferon 80 mg once a day orally has been prescribed additionally to treat anaemia.

The patient was discharged from hospital after a week. On the day of discharge, her health was improved, there were no signs of recurrent bleeding. Heartbeat has been arrhythmic with the sound of a mechanical valve's prosthesis. Arterial blood pressure 90/64 mmHg, heart rate 64 times per minute. Breath sound in the lungs has been vesicular, without crackles on both sides. The abdomen has been soft, slightly sensitive in the epigastric area.

It has been recommended to continue the treatment with Caps. Omeprazole 20 mg twice a day orally, Tab. Tardyferon 80 mg once a day orally, Sol. Nadroparin 2850 IU twice a day subcutaneously. Also to avoid nonsteroidal anti-inflammatory drugs (NSAID), to use Caps. Tramadol if severe pain occurs. It has been planned to repeat endoscopy after a month and then decide if warfarin using should be restarted.

Endoscopy was repeated after a month, the healed ulcer was observed and nadroparin was changed with warfarin again. Warfarin resumption was started after more than a month since gastrointestinal bleeding occurred. There has been found *Helicobacter pylori* infection and it has been treated with antibiotics. It was also recommended to continue taking iron preparation to treat and prevent anaemia.

Discussion

The patient is 52 years old woman with the signs of gastrointestinal bleeding- vomiting with blood clots and melena. The patient also uses warfarin, because she has mechanical mitral valve prosthesis and permanent atrial fibrillation, which are dangerous because of increased risk of thromboembolism. Anticoagulant warfarin certainly contributes to avoiding thromboembolic events, yet significantly increases the risk of bleeding. Gastrointestinal bleeding that occurred for the patient might be the result of warfarin usage. Based on literature sources, in cases of active and heavy bleeding, the usage of anticoagulants should be discontinued, except minimal rectal bleeding. [1, 2] In case of this specific patient, bleeding has been active, with a decreasing amount of haemoglobin, consequently, warfarin has been discontinued, according to the recommendations of literature sources.

Early endoscopic intervention is the main measure to stop gastrointestinal bleeding, so this procedure should be organized immediately. [2] Anticoagulants users' blood coagulation, which is mainly reflected by the international normalized ratio (INR), can be over the therapeutic value, that is why it is important to measure INR during the patient preparation for the endoscopic procedure and to take additional means for restoring normal coagulation. According to ASGE practical guidelines, in cases when bleeding is active, but INR value fits in therapeutic range (< 2.5), it is not recommended to postpone endoscopic procedure in the purpose of restoring coagulation. However, if INR is > 3, there is a need to take actions to normalize coagulation of blood. Vitamin K, prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) might be a choice in

this case. For all the patients, except those with minimal rectal bleeding and those with INR < 5, VKA should be discontinued and administered Vitamin K. A decision to give PCC (or FFP if there is no possibility to use PCC) should be taken depending on patient's bleeding intensity, INR value, the timing of endoscopic procedure and individual risk for thrombosis. PCC should be given to intensively bleeding, critical state patients with persistent or permanent haemodynamic instability, even in those cases when INR value fits the therapeutic range. INR should be measured every 20–30 minutes until the end of the PCC infusion. If INR remains > 1.5, one more dose of PCC should be given. After 6–8 hours INR should be measured again, and then once a day until the situation stays critical. It is recommended to administer Vitamin K together with PCC to avoid coagulopathy which can occur 12–24 hours after INR normalization when infused coagulation factors are eliminated from an organism (the half-life of warfarin is 20–60 hours, PCC 6–8 hours, FFP 1,5 hours- 2 days). Actively bleeding, haemodynamically stable patients with therapeutic INR value should be given only intravenous Vitamin K, which is enough in cases like these. If INR is over a therapeutic range, PCC or FFP should be considered. Urgent restoring of coagulation is not necessary for minor bleeding that does not cause anaemia. If TNS > 5 low dose of Vitamin K can be given orally (1–5 mg) or intravenously (1–2.5 mg). [1, 3, 4]

In the described situation, INR value has been in the therapeutic range [2, 19]. This INR value does not require additional coagulation recovering actions, such as Vitamin K, PCC or FFP. Those means have not been taken and endoscopy has been arranged immediately. Endoscopy has shown a bleeding gastric ulcer, which has been clamped and bleeding has been stopped. Patients with gastrointestinal bleeding are usually treated with proton pump inhibitors (PPIs). When gastrointestinal bleeding is suspected, intravenous PPIs should be administered empirically (e.g. 80 mg esomeprazole bolus i/v, continuing 40 mg twice a day intravenously) and continued until the exact location of bleeding is detected. [5] The patient has been treated with esomeprazole/pantoprazole 80 mg bolus intravenously, continuing 8 mg per hour by automatic syringe pump for 3 days. The chosen treatment matches recommendations, though it suggests initiating administration of PPIs as soon as gastrointestinal bleeding is suspected. Later on, treatment was continued by Sol. Esomeprazole 40 mg twice a day intravenously for 2 days and Caps. Omeprazole 20 mg twice a day orally afterwards.

After bleeding is stopped endoscopically, a patient should be carefully monitored in case of recurrent bleeding. If the patient used to take anticoagulating agents, it is important to evaluate thrombotic risk and decide whether taking those drugs has to be restarted. Anticoagulants are usually restarted for patients who are haemodynamically stable and the risk for recurrent bleeding is low (based on Forrest classification). [6]

The timing of resuming anticoagulating agents depends on the specific drug, that patient has been using before. Both ASGE and ESC practical guidelines indicate, that if warfarin has been used, it can be restarted at the same evening of the procedure, only if there are no signs of recurrent bleeding. To reach therapeutic effect might take a few days. [6, 4]

It is recommended to give bridging therapy with heparin for patients who have a high risk of thrombosis. The main point of this therapy is the relatively short half-life of heparin (1.5 hours), which allows discontinuing the usage of preparation immediately if bleeding occurs. Bridging therapy should be started patients who used to take warfarin in these cases:

1. Embolic stroke or systemic embolic event within the previous three months
2. Mechanical mitral valve
3. Mechanical aortic valve and additional stroke risk factors
4. Atrial fibrillation and very high risk of stroke (e.g., $CHADS_2$ score of 5 or 6, stroke or systemic embolism within the previous 12 weeks, concomitant rheumatic valvular heart disease with mitral stenosis)
5. Venous thromboembolism within the previous three months
6. Recent coronary stenting
7. Previous thromboembolism during interruption of chronic anticoagulation [7]

There are 2 kinds of heparin that can be used for bridging therapy: low molecular weight heparin (LMWH) or unfractionated heparin.

LMWH is recommended for patients with very high (e.g., rheumatic heart disease, permanent atrial fibrillation with recent embolic stroke, mechanical heart valve) or moderate (e.g., active oncological process) arterial thromboembolic risk. Unfractionated heparin is a better choice in case of renal failure or haemodialysis because it is dosing does not depend on renal function. [7]

Heparins can be given in prophylactic, therapeutic or intermediate doses. Therapeutic doses are the best for patients with a potential source of arterial thromboembolism (e.g., atrial fibrillation, mechanical heart valve) or venous thromboembolism, which occurred within the last month. [7]

Intermediate dosing can be applied for patients with atrial fibrillation or venous thromboembolism, which occurred within the last month, but there is a greater concern of bleeding. [7]

Prophylactic dosing is not applicable for patients with atrial fibrillation, because there is no evidence of its efficiency in this case. Doses like these can be applied

for patients who had venous thromboembolism within 3–12 month. [7]

Bridging therapy is just a temporary solution, which allows reducing thrombotic risk during the acute, life-threatening period. Observational studies' findings show that resuming Vitamin K antagonists is the best choice after the acute bleeding period is gone, though the most appropriate timing to do so is not that well studied.

3 clinical studies compared the patients, who resumed Vitamin K antagonists after gastrointestinal bleeding and those who did not. Resuming of Vitamin K antagonists has been associated with a significantly lower risk of thromboembolic events and death. Furthermore, the risk of recurrent bleeding has remained similar. [1]

The ideal timing of resuming anticoagulation drugs after gastrointestinal bleeding is poorly studied. Practical guidelines do not specify when to restart using anticoagulants and recommend to do it as soon as cardiovascular complications' risk exceeds the risk of bleeding. One of the studies mentioned earlier divided 653 patients into intervals by the time of resuming anticoagulation after bleeding (< 7 days; 15–21 days; 21–30 days; > 30days). Mortality was lower in those cases, when anticoagulation was resumed < 7 days, 15–21 days and 21–30 days, compared to those, that resumed coagulation > 30 days. Patients who started using warfarin after 7d., had approximately 2 fold higher risk of recurrent bleeding and slightly lower risk of thromboembolism, compared to those, who did it after > 30 days. The incidence of recurrent bleeding was similar in all groups that resumed anticoagulation after > 7 days, thus it seems that second week after gastrointestinal bleeding might be the most reasonable timing to restart Vitamin K antagonists. Nevertheless, patients in this study were not divided based on a specific risk for thrombosis and recurrent bleeding. [1]

The patient in the described case, that has permanent atrial fibrillation and mitral valve prosthesis, uses warfarin for prevention of thromboembolic events. According to literature sources, 3 factors have to be considered, while planning to resume anticoagulation- the risk of recurrent bleeding, specific anticoagulant, that patient used to take before, and thrombotic risk. Endoscopy has shown a bleeding gastric ulcer with a clot underneath, so the risk of recurrent bleeding reaches 10–20 %. The prosthetic mitral valve is a factor for high thrombotic risk, moreover, she has permanent atrial fibrillation, which means that there is a need for LMWH therapy. [8, 6] The patient has started getting Sol. Nadroparin 2850 IU twice a day subcutaneously.

On the day of discharge from the hospital, the usage of warfarin was still suspended and recommended to continue the treatment with Sol. Nadroparin 2850 IU twice a day subcutaneously and decide whether to restart using warfarin after endoscopy, which was planned after almost a month from the day of discharge. However, available sources show that it is safe to restart warfarin after > 7 days from gastrointestinal bleeding. Studies have not shown a significantly higher risk of bleeding compared to those cases when warfarin was restarted after a month, so it would be reasonable to restart it earlier than it has been done.

All things considered, the treatment for this patient has been chosen wisely, but based on the latest knowledge, more modern viewpoint on restarting anticoagulating drugs could be applied. Even though gastrointestinal bleeding is a serious life-threatening situation, which requires urgent treatment and careful monitoring, since active bleeding period had passed, more concern should be given to the prevention of thromboembolic events.

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Abstracts

1. The effect of an educational campaign on stroke symptoms recognition among primary school kids

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Background: Stroke is the third leading cause of disability among adult patients. Poor awareness regarding stroke emergencies and symptoms limits its effective therapy. School promotion of the essential knowledge about stroke manifestations may be beneficial, however little is known about its efficacy among Polish pupils. Therefore we aimed asses the effects of education campaign on of stroke knowledge among primary school kids.

Methods: Dedicated educational campaign entitled "uDARuj Zdrowie" including 45 minutes lesson with movie presentation has been performed among pupils from III class of primary school. Kids answered the questionnaire of: 9 one-choice questions concerning stroke awareness and first aid procedures and 1 question regarding typical stroke symptoms before and +/- 12 months after the lesson.

Results: 287 kids participated in lessons, and 145 responded the questionnaire after the follow up. Median of correct answers regarding stroke awareness and first aid procedures were 5 (0–5) before and 6 (1–9) after the follow up ($p < 0.01$), including: cause of a stroke 32.12% vs. 37.41% ($p < 0.01$), immediate call for ambulance 62.21% vs. 82.44% ($p < 0.01$) and therapeutic time window 89.21% vs. 95.83% ($p < 0.01$). Median of recognized stroke symptoms was 2 before and 4 after the follow up ($p < 0.01$).

Conclusions: Dedicated educational campaign improves kids knowledge about stroke symptoms and procedures. Basic stroke education should be implemented in primary education.

2. Predictors of an early diagnosis of total occlusion of infarct-related artery in patients with non-ST-elevation myocardial infarction (NSTEMI)

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Background: Some patients with non-ST-elevation myocardial infarction have a total occlusion (TO) of infarct-related artery (IRA). Thereupon, acute coronary occlusion (ACO) may also present as non-ST-elevation myocardial infarction (NSTEMI) and thus veil the real threat. The prevalence and impact of TO of IRA on outcomes in patients with NSTEMI remain unclear. The purpose of the study was to analyse the incidence of total occlusion of IRA and to assess the predictors of total occlusion of IRA in patients with NSTEMI.

Methods: The study was conducted as a retrospective cross-sectional analysis of 399 consecutive patients with NSTEMI ($M = 293$, mean age 70.3 ± 10.1) hospitalised and treated by primary percutaneous coronary intervention (PCI) in the 1st Chair and Clinic of Cardiology, Medical University of Silesia in Katowice in 2017. The study population was categorized into patients with TO of IRA and with hemodynamically significant culprit coronary lesion (non-TO) on coronary angiography. Demographic and clinical data, including laboratory test results and

electrocardiographic parameters, were acquired by means of meticulous review of discharge summaries and electronic health records. TO of IRA, in-hospital and 12-month mortality were the outcomes.

Results: TO was found in 138 (34.6%) patients with NSTEMI. Patients with TO had a greater incidence of diabetes mellitus ($p = 0.003$) and atrial fibrillation ($p = 0.02$). Coexistence of serum triglicerides level ($p = 0.001$), glucose level ($p = 0.0005$) and baseline troponin level ($p = 0.004$) corresponded with the highest incidence of TO of IRA. The left circumflex artery (LCx) was the major IRA in the TO group (39.1%), whereas the left anterior descending artery (LAD) was more commonly the IRA in the non-TO group (48.5%). Multivariate analysis revealed that LCx as the culprit lesion (OR 0.53 [0.41–0.68], $p < 0.0001$) was an independent predictor of IRA flow in TIMI scale. In-hospital and 12-month mortality were significantly higher in the TO group than non-TO group (2.8% vs. 1.1%, $p = 0.007$ and 6.1% vs. 2.5%, $p = 0.0003$).

Conclusions: The identification of NSTEMI patients with total occlusion of infarct-related artery is challenging. In the population of patients with NSTEMI, TO of IRA represents a considerably frequent phenomenon and corresponds with established clinical markers of impaired outcome. These patients may require different clinical approach than typical NSTEMI patients. Therefore, the utmost caution should be paid to prevent delay of coronary angiography in NSTEMI patients with higher baseline troponin levels and metabolic disturbances who represent the increased risk of acute coronary occlusion.

3. The use of body composition analysis in diagnosing heart failure — comparison with brain natriuretic peptide

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Background: Heart failure (HF) concerns 26 million people around the globe and is one of major causes of hospitalisations in Europe. Currently, one of the recommended by European Society of Cardiology (ESC) methods of screening is checking the brain natriuretic peptide (BNP) level. It is a very non-specific test however, as its increase may also occur due to left ventricle hypertrophy, hyperthyroidism, renal failure or other causes. This made us look for a way that is faster, cheaper and would allow to detect HF earlier, thus giving opportunity to start the treatment in an earlier stage, when prognosis is better. To do so we have tried to prove relation between body water content and presence of HF.

Methods: The approach we are exploring is use of body content analysis done thanks to bioimpedance, since other studies show close relation between percentage of water in a body mass and management of acute HF and this is a good non-invasive method to determine that factor. Study group consists of hospitalised stable adult patients admitted for diagnostics towards HF detection. During the hospitalisation the necessary diagnostic tests were performed and additionally body content analysis using bioimpedance method. During the hospitalisation laboratory tests and imaging examinations were performed as required for diagnostic and treatment purposes, as well as body content analysis using bioimpedance method specifically for the study. Twenty seven patients were encircled to the study, with total of 100 planned.

Results: According to the current data from the group of 27 patients, there was a significant negative correlation between BNP and BMI ($R = -0.529$, [i] $p = 0.005$ [/i]) and a significant positive correlation between BNP and fat-free tissue ($R = 0.549$, [i] $p = 0.004$ [/i]), total water ($R = 0.463$, [i] $p = 0.017$ [/i]) and extracellular ($R = 0.576$, [i] $p = 0.002$ [/i]). Increased BNP level was associated with left ventricular dysfunction ([i] $p = 0.022$ [/i]) and atrial fibrillation ([i] $p = 0.025$ [/i]). There was no correlation between body content and left ventricular ejection fraction (LVEF). Furthermore, there was no relation between body content and systolic or diastolic left ventricular dysfunction.

Conclusions: Current results indicate bioimpedace body content analysis may be a method to assist in the diagnosis of HF. However, it is necessary to analyze results from the planned group of patients. At this point basic limitations of our research are monovariable analysis and small count of the study group.

4. The effect of Homocysteine on fibrinolytic and proteolytic parameters depends on the intraluminal thrombus thickness

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Background: Increased levels of homocysteine (Hcy) have been implicated as risk factor for cardiovascular disease and there is some evidence that may be associated with an increased risk of having an abdominal aortic aneurysms (AAA). Homocysteine was suggested to enhance the proteolysis as well as disturbance of the coagulation/fibrinolysis system, which in turn may promote local proteolytic degradation of the aortic wall. In the majority of cases, the aneurysmal walls are covered by the intraluminal thrombus (ILT). It was suggested that depending on the thickness, ILT shows the significant differences in the activity of proteolytic and fibrinolytic processes, which emphasizes that such peculiar structure may influence the pathogenesis and development of the disease. The aim of this study was therefore to investigate the effect of incubation of homocysteine on proteolytic and haemostatic activity in individual aneurysm compartments.

Methods: Aneurysmal aortic specimens were obtained from 36 patients (27 men and 9 women), who were diagnosed with the presence of both thick (≥ 25 mm) and thin (≤ 10 mm) intraluminal thrombus in one aneurysm sac. The obtained aneurysm tissue samples were divided into four groups: thick thrombus; thin thrombus; wall adjacent to thick thrombus; wall adjacent to thin thrombus. In a series of experiments, the thick and thin ILT as well as adjacent walls were separately incubated in medium, in the presence of DL-homocysteine (100 μmol/L or 500 μmol/L). Untreated aneurysm fragments were used as controls. After treatment, tissue samples were collected for protein extraction and the concentration of t-PA (ng/mg,) and TF (pM/mg) were determined using immunoenzymatic test (ELISA). The MMP-2 (μM/mg) activity was performed using fuorescence resonance energy transfer (FRET) assay.
Results: Incubation of thin thrombus fragments with DL-Hcy resulted in an increase of t-PA concentration compared to control tissue (1.39 ± 1.65 vs. 0.84 ± 0.74, p = 0.024). Whereas, in thick ILT sections, MMP-2 activity as well as t-PA concentrations was decreased (respectively, 2.53 ± 2.02 vs. 3.28 ± 2.65, p = 0.006; 0.67 ± 0.57 vs. 0.96 ± 0.91, p = 0.021). Moreover, DL-Hcy induced the activity of MMP-2 in the wall underlying thin IL T in comparison to control tissue (9.54 ± 5.88 vs. 7.44 ± 4.48, p = 0.011). In turn, in wall adjacent to thick thrombus the activity of both MMP-2 and TF were decreased in contrast to controls (respectively, 5.89 ± 3.39 vs. 7.26 ± 5.49, p = 0.046; 67.13 ± 72.59 vs. 114.46 ± 106.29, p = 0.007).
Conclusions: These data demonstrate that homocysteine increases the activity of both haemostatic and proteolytic parameters in thinner AAA segments, which suggested that Hcy may enhance damage of arterial wall in this part of aneurysm. Those results might be significant for future AAA studies in the context of predictive tools of disease severity, risk of rupture as well as potential targeted therapy.

5. The importance of focal adhesion in coronary artery endothelial cell activation and barrier function

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Background: Maintaining the integrity of the endothelial barrier is a prerequisite for homeostasis. This is possible due to the involvement of proteins that sustain normal cell-cell and the cell-extracellular matrix (ECM) contacts. In the case of the endothelium, the basic protein involved in adherence junctions is VE-cadherin, while talin is closely associated with the focal adhesion. It is postulated that in the endothelial cells mainly talin-1 is expressed, whereas talin-2 homolog is characteristic for cardiac muscle cells. It is possible, however, that talin-2 may also occur in endothelial cells, but its role remains unknown. The aim of the study was to elucidate the involvement of both talin homologues and focal adhesion in the inflammatory response of vascular endothelial cells.
Methods: We used primary human coronary artery endothelial cells (pHCAECs) derived from healthy 23-years old white male treated with tumour necrosis factor alpha (TNFα). Endothelial cells were activated with 100 nM concentration of TNFα. Tropomyosin-1 (TPM1) expression was regulated using the CRISPR/Cas system. Alterations in cell-cell and cell-ECM contact were confirmed by fluorescence labeling of junctional and focal adhesion proteins together with the actin cytoskeleton. Proteins levels were assessed using western blot technique. The angiogenic potential was investigated using in vitro tube formation assay. All results obtained on the fixed cells were analyzed in relation to those from live-cell imaging. Morphology of migrating cells was investigated using correlated fluorescence and holotomography microscopy.
Results: TNFα-activated pHCAECs change F-actin organization pattern from star-like into linear stress fibres. Simultaneously, TNFα induces formation of angiogenic-dependent migrasome-like structures, which can be released to the medium and stay in the place of previous strong cell-cell junction, attached to the place of strong focal adhesion site or taken up by surrounding cells. This suggests their role in cell communication. These changes can be prevented by stabilizing the actin cytoskeleton structure. Stabilization of actin filaments was achieved using CRISPR systems regulating the naïve expression of TPM1. We showed that activation of TPM1 expression dismissed inflammatory response of pHCAECs maintaining endothelial integrity and inhibiting in vitro tube formation, whereas knockout of TPM1 increased the inflammatory response of pHCAECs leading to loss of endothelial integrity and enhanced in vitro tube formation. Furthermore, our experiments showed that activation of TPM1 inhibits focal adhesion of pHCAECs, even after their activation with TNFα. On the other hand, knockout of TPM1 enhanced focal adhesion of TNFα-activated pHCAECs. It resulted in the increased expression of talin-2 and vinculin but not talin-1. Moreover, the activation of TPM1 inhibited cleavage of VE-cadherin in pHCAECs, even after their activation with TNFα and promoted α-catenin-based stabilization of cell-cell junction continuity, especially in TNFα-activated cells, while knockout of TPM1 induced high expression of β-catenin in TNFα-activated pHCAECs.
Conclusions: TNFα-induced activation of pHCAECs leads to F-actin cytoskeletal rearrangement promoting angiogenesis. CRISPR systems regulating the expression of TPM1 can be used to control F-actin stabilization and endothelial integrity by the maintenance of both focal adhesion and cell junctions. The increase in talin-2 expression in cells with actin cytoskeleton rearrangement may indicate the involvement of this protein in the migration of activated endothelial cells due to enhanced traction force. However, the activation of TPM1 expression dismisses the inflammatory response of pHCAECs and protects endothelial integrity, while the knockout of TPM1 leads to cellular changes characteristic for angiogenesis.

6. Science-fiction or the future of medicine: how using all-day cardiological telemonitoring can help diagnose the coronary heart disease

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Background: Advancement in healthcare technologies, such as tele-ECG provides easier and faster medical contact for cardiology patients. Tele-ECG followed by telephone consultation should identifies first signs of heart diseases exacerbation, resulting in better clinical outcomes. However, there is lack of data comparing efficiency of telemonitoring in patients after percutaneous coronary procedures. Therefore, the aim of this study was to evaluate long term clinical outcomes between patients with or without telemonitoring support.
Methods: This is a multicentre, retrospective registry of 400 consecutive patients, who undergone percutaneous coronary procedure (PCI) from 10.2016 to 06.2018. 202 of them were provided with teleECGdevice and telephone consultations, while 198 patients did not agree for telemonitoring. Patients with both acute coronary syndrome and stable angina were included. The average time of telemonitoring was 312 days.
Results: At baseline, patients in monitored group were more often presented with myocardial infarction (50% vs. 35 %; $p = 0.01$), especially STEMI (18% vs. 9%; $p < 0.01$). After one year, the incidence of hospitalization due to myocardial infarction (3.8 vs. 4.7%; $p = 0.16$) and all couse death were numerically lower in monitored group, however the difference was not statistically significant. The rate of hospitalizations with heart failure exacerbation were significantly lower in monitored group (2% vs. 4.10%; $p = 0.04$). The incidence of arrhythmias and rePCI/CABG were significantly more common in study group (7.4% vs. 2%; $p < 0.05$ and 9% vs. 5%; $p=0.04$ respectively) were more often in monitored group.
Conclusions: Our study suggests that exacerbation of heart disease in patients supported with telemonitoring were diagnosed earlier. It might result in lower incidence of more serious medical conditions. Further studies with larger and more comparable groups are needed to proof this hypothesis.

7. Knowledge and adherence of patients on warfarin therapy toward their treatment regimen in Alshaab and Ahmed Gasim Hospitals, Sudan, 2018

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Background: Warfarin is commonly used oral anticoagulation which is needs to be continuously monitored both clinically and laboratory due to its narrow therapeutic index and potentially life threatening complications. this study aims to assess knowledge and adherence of patients on warfarin therapy toward their treatment regimen and to identify barriers that prevent patients to take their warfarin therapy regulary.
Methods: A cross-sectional survey was conducted at Alshaab teaching hospital heart section and Ahmed Gasim hospital Khartoum, Sudan. The systematic random sampling method was used in sample selection and interview based questionnaires were used to determine the socio-demographic characteristics, the patient's knowledge of warfarin therapy and medication adherence.
Results: Male patients (52.5%) exceeded females (44.8%), the mean age was 48.79. About 68.4% of the studied patients received education regarding Wafarin Oral anticoagulant by their physician. 43% of the studied patients had moderate overall knowledge score, while more than half of them had either satisfactory or good adherence levels (62.2%). There were negative significant correlations between patients' adherence to Warfarin Oral Anticoagulant and their level of knowledge ($r = 0.035$*). There were significant differences between patient's education, sex, occupation and their level of knowledge, whereas no significance differences between patient's sex/age and their level of adherence were found. There were three barriers prevent the patients from taking their medication. Forgetting (43.7%) was found to be the main reason followed by drug unavailability (36.8%) and high cost (19.5%) respectively.
Conclusions: The majority of the studied patients had moderate overall knowledge score about Warfarin Oral Anticoagulant, and more than half of them had either satisfactory or good adherence levels. There were negative significant correlations between patients' adherence to Warfarin Oral Anticoagulant and their level of knowledge.

8. Selected haemostatic factors in patients with abdominal aortic aneurysm

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Background: Abdominal aortic aneurysm (AAA) has increasingly been recognized as a significant cause of mortality in older adults. It is suggested that the mechanism contributing to aneurysm rupture is the imbalance between the fibrinolytic system and the activation of the coagulation system. In many research, haemostatic markers were examined for the association with the AAA growth, size of AAA, as well as ILT size. However, the results are inconsistent. The aim of our study was the evaluation of selected haemostatic markers in patients with AAA and controls; and evaluation of the correlation with AAA diameter and thrombus thickness.
Methods: The study included 36 patients with AAA, treated in the Department of Vascular and General Surgery and Angiology of PUM in Szczecin, and 30 controls with normal diameter (< 3 cm). Venous blood samples were obtain from control group and each patient with AAA

before elective repair of aneurysm. Whole blood was collected into tubes with plasma citrate to assay D-dimer and tissue plasminogen activator (t-PA). Whereas plasminogen activator inhibitor-1 (PAI-1) was measure in CTAD plasma. The ELISA or ELFA method were used to determine the concentration of all factors.

Results: Concentrations of D-dimer (ng/mL) and t-PA (ng/mL) were significantly higher in patients with AAA (respectively: 2673 ± 1824 vs. 1125 ± 895, $p = 0.002$; 5.2 ± 2.5 vs. 4.2 ± 1, $p = 0.039$). PAI-1 (ng/mL) levels did not show a significant difference (12.0 vs. 13.0; $p = 0.586$). The correlation showed negative relationship between t-PA and ILT thickness ($r = -0.53$; $p = 0.001$) and t-PA and aneurysm diameter ($r = -0.38$; $p = 0.023$).

Conclusions: The higher plasma concentrations of D-dimer and t-PA may support the hypothesis that the secondary fibrinolysis plays an important role in the pathogenesis of the AAA formation and strong negative correlation between t-PA concentration and ILT thickness, suggests that coagulation-fibrinolysis imbalance may accelerate ILT formation and possibly aneurysm progression.

9. A pilot study of chromogranin B in patients undergoing off-pump coronary artery bypass grafting

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Background: Chromogranin B (CgB) belongs to a family of acidic proteins called granins, that are widely distributed in many cell types. It has been shown that CgB is also produced by the ventricular myocardium and can become a potential biomarker of heart failure. The clinical value of CgB for evaluating myocardial disease progression or treatment response is still poorly understood. The aim of the study was to assess CgB concentrations in patients undergoing off-pump coronary artery bypass grafting (OPCABG).

Methods: The study included 30 male patients (mean age 63) with coronary artery disease (CAD) who underwent elective, first-time isolated OPCABG and 20 healthy, nonsmoking, age-matched males (mean age 59). Patients with left ventricular ejection fraction (LVEF) < 40% were excluded. Venous blood samples from patients were collected twice: on the day of surgery and seven days later. CgB concentrations were evaluated by enzyme-linked immunosorbent assay.

Results: CgB concentration in patients scheduled for surgery was similar to observed in healthy males (Me = 77.04 ng/mL vs. Me = 82.56 ng/mL, p = NS). CgB concentrations 7 days after OPCABG were significatly higher than in the day of surgery (Me = 87.54ng/mL vs. Me=77.04 ng/mL, $p = 0.004$). We found no difference in CgB concentrations, depending on the surgical procedure: no-touch OPCABG vs. touch (traditional) OPCABG. Nevertheless, CgB levels in patients after touch surgery were higher (Me = 88.73 ng/mL) than in patients after no-touch surgery (Me = 82.01 ng/mL). Additionally, there were no differences in CgB concentrations in subgroups of patients divided according to the presence of diabetes mellitus, hypertension, dyslipidemia or cigarette smoking. We found no relations between CgB concentrations and age, body mass index (BMI), procedure duration and number of grafts.

Conclusions: Off-pump coronary artery bypass surgery increases circulating CgB concentrations, regardless of the surgical technique. This phenomenon may be associated with the release of CgB from ventricular myocardium and deserves further investigations.

10. ECG-based apnea-hypopnea index in acute ischemic stroke patients

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Background: Obstructive sleep apnea (OSA) is a breathing disorder during sleep regarded as cardiovascular risk factor associated with increased mortality. The Apnea–Hypopnea Index (AHI) is represented by the number of apnea and hypopnea events per hour of sleep. ECG seems to be potentially the most practical, non-invasive tool for screening for sleep disordered breathing (SDB). In patients with AHI > 15 risk of SBD is significant. OSA is important, modifiable risk factor of acute ischemic stroke (AIS) which is responsible for majority of neurological disabilities in adults. The aim of our study was to estimate AHI based on ECG in patients with cryptogenic AIS and in healthy subjects. We wanted to measure if the episode of AIS leads to increased AHI.

Methods: The study group consisted of 92 patients diagnosed with first symptomatic cryptogenic AIS (age: 60 ± 14; 51% males) hospitalized in Neurology Department, Leszek Giec Upper-Silesian Medical Centre of the Silesian Medical University in Katowice in years 2015–2018. Patients were divided into 2 groups: TACI (anterior ischemia) and non-TACI (posterior ischemia). Each patient had 7-days Holter recording. Control group contained 50 healthy people (age: 55 ± 9; 66% males) after Holter ECG monitoring in 1st Chair and Clinic of Cardiology in Upper Silesian Medical Centre in Katowice. Data was analyzed and automated algorithm was used to estimate patients' AHI. AHI thresholds of < 5 and > 15 were used to indicate low and high probability of OSA.

Results: AHI was significantly increased in AIS patients in comparison to control group ($p = 0.001$). AHI in non-TACI patients (14 ± 5.3) was higher than in TACI (10.5 ± 4.8) and control group (8.5 ± 8.4). AHI > 15 occurred in 29% AIS patients and in 16% from control group
Conclusions: Patients after AIS are more likely to have higher AHI and higher probability of OSA. Non-TACI AIS is significantly more predisposing factor of SDB which might be related to localization of ANS respiratory center.

11. How do the patients with thoracic aortic dissection assess their quality of life after bentall procedure?

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Background: Post-surgical quality of life is an important factor in every post-operative patient management. It affects not only patients but also clinical practice in making treatment decisions. The aim of the study was to assess the short-term and long-term quality of life of the patients with acute thoracic aortic dissection who underwent Bentall procedure between January 2012 and January 2018. We wanted to measure the effects of disease and medical intervention on the individuals' attitude towards future life.
Methods: We gathered data from medical records of 218 patients from Department of Cardiac Surgery, Leszek Giec Upper-Silesian Medical Centre of Silesian Medical University in Katowice-Ochojec, diagnosed with ICD-10: I71.0 [Dissection of aorta (any part)] between January 2012 and January 2018. After excluding patients with Marfan disease and reoperation, we contacted patients, who survived the surgery and were still alive. We managed to contact and interview 40 patients, who were in different time after surgery. In March 2018 they filled in The World Health Organization Quality of Life Questionnaire (BREF). WHOQOL-BREF consists of 26 questions, due to measure the following domains: physical health, psychological health, social relationships and environment. We compared the similarities and differences corresponding to the number of years after the operation.
Results: The results show that the average patient after the Bentall procedure assessed the physical health lower and social relationships higher than the rest of the measured aspects. Women scored their quality of life higher than men in all age groups. Pain prevents patients from everyday activities to little extent. They are rather satisfied with their sleep. Moreover, they are content with access to health services. They seldom feel anxious or depressed.
Conclusions: Patients are very content with their social relationships and support from their family and friends. They are much less satisfied with their work capacity and physical condition, which is corelated with lower subjective qality of life after the surgery. After the operation they became more dependent on health care services and they need regular medical check-ups. However, they believe that their life is meaningful and they value their life more than before the surgery.

12. Extracellular matrix cylinder reconstruction of tricuspid valve in patient with dual-chamber implantable cardioverter-defibrillator (ICD-DDD)

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Background: Extracellular matrix valve protheses have been getting more attention in recent years, for their advantage over the other commonly used materials. Bioscaffolds, by inducing the host tissue growth, reduce significantly thrombogenicity and inflammatory foregin-body response of the organism, show a significant antibacterial activity, as well as they are more resitant to calcification and overall degradation. Therefore extracellular matrix is a reasonable option for high-risk patients with various co-exhisting conditions. This case concerns a patient diagnosed with a severe tricuspid regurgitation found after the dual-chamber implantable cardioverter-defibrillator (DDD-ICD) replacement procedure.
Methods: 65-year old male patient was urgently admitted to the cardiac surgery unit with a severe tricuspid regurgitation after the dual chamber implantable cardioverter-defibrillator (DDD-ICD) replacement procedure. The patient was immidiately qualified for TVR surgery. Tricuspid valve native cusps were resected and tubular prothesis made of small intestinal submucosa-derived extracellular matrix (ECM) was subsequently implanted. 12-month follow-up observations of patient's conditions have been collected, including echocardiographic examinations.
Results: Post-operative echocardiogram showed a proper function of the cylinder ECM tricuspid valve, with a small thin central jet, without any leakage around the prothesis. The patient was discharged from the hospital 9 days later in good condition, without neurological deficits, cardiovascularly and respiratorily stable. 12 months after the surgery echocardiographic examination shows the same findings; the patient leads a normal life and has no problems with executing everyday tasks.
Conclusions: Extracellular matrix cylinder reconstruction can be successfully performed in patients with ICD-DDD, without damaging the electrode passing through the heart chambers. The material that was used for the reconstruction is a very good option for high-risk patients with many comorbidities or foreign bodies inside the heart (stents, electrodes), in order to reduce thrombogenicity, calcification, acute immune response or bacterial infections.

13. Broken heart syndrome — a case study of 67-years-old female cancer patient

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Takotsubo cardiomyopathy, known also as Broken Heart Syndrome, is a rare acute heart failure syndrome affecting 2–3% of people. 90% occurs in women, mostly postmenopausal. It can be induced by physical or emotional trigger factor.

67-years-old woman with the history colon cancer (2016) was admitted to surgical ward with sub-obstructive symptoms (26.05.2017). Subsequently laparotomy was performed. During surgery patient needed continuous iv catecholamines infusion due to hypotonia. After the surgery, she demonstrated acute circulatory and respiratory failure, cardiac arrest (VF mechanism) and cardiogenic shock. She was transferred to cardiology ward with diagnosis of ST-elevation myocardial infarction (STEMI) of anterior wall. Blood tests showed raised cardiac biomarkers: CK-MB, Troponin T. Coronary angiography did not reveal significant stenosis in coronary arteries. Pulmonary embolism was excluded in angio-CT. In transthoracic echocardiography (TTE) there was generalized hypokinesis with LV EF reduced to 10–15%. Due to cardiogenic shock, Intra-aortic balloon pump (IABP) was utilized. Patient was diagnosed with MI type 2 and transferred to Intensive Care Unit. Four weeks later, in control TTE, the LV EF was 60% with mild mitral and trigeminal valve regurgitation. During following months, the recurrence of cancer was diagnosed and she received oncological treatment. At one-year follow up, woman reported fatigue, dizziness, malaise and presyncope symptoms. Holter-ECG performed in outpatient clinic, revealed short episodes of 2nd degree AV block, Mobitz II and she was qualified for pacemaker implantation. The patient had urine stagnation (09.2018). Histopathological exam showed urothelial cancer. Recently, her cardiology status remains stable and she continues therapy.

Takotsubo cardiomyopathy is characterized by symptoms imitating acute coronary syndrome, so it can be easily mistaken and treated as such in the initial period. In this case the trigger factor could be surgical procedure, elevated catecholamines, serious illness(cancer), chemotherapy or mental stress associated with cancer. The prevalence of Takotsubo cardiomyopathy can be underestimated due to lack of awareness of this rare diagnosis.

14. Safe inhibition of P-glycoprotein as a potential prolonger of treatment response to levodopa in Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative condition characterized by the progressive loss of dopaminergic motor neurons in the midbrain. Therefore replenishing the depleted dopamine supply in the brain is the target of current PD-directed therapies. As exogenous dopamine cannot cross the blood-brain barrier, levodopa, a precursor of dopamine that can permeate this barrier, is the drug of choice for treating PD patients. However, only 5–10% levodopa is available for the neurons as the rest is effluxed by P-glycoprotein, an ATP-dependent transporter of the multidrug resistance family of transporters. Indeed, P-glycoprotein-mediated efflux is the cause of multidrug resistance in several diseases, including cancer. Therefore, current therapies are being designed to overcome the drug efflux, for example, by using other competitive substrates of the transporter such as verapamil.

In this review, we have discussed PD, the blood-brain barrier, and the ongoing research on improving the bioavailability of levodopa in the brain, while considering the potential drawbacks of these approaches.

We believe that this will provide a comprehensive picture of the current scenario regarding PD treatment and highlight the scope for improvement.

15. The current approach of arterial hypertension based on recent recommendation of ESC

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Background: Arterial hypertension is one of the most important and modifiable risk factors for cardiovascular disease in Europe and worldwide. As a major contributor to worldwide morbidity and mortality, it poses a massive socioeconomic burden. Blood pressure control is still inadequate in most of the hypertensive patients (< 140/90 mm Hg) even though great progress in perception, diagnosis and treatment of hypertension is made. The intention of this research paper consists on analyzing and comparing guidelines through the current years in order to generate an updated definition, diagnostics and treatment about arterial hypertension regarding the population standards. Performing a literature search for new evidence on hypertension in general would inform for the reaffirmation of the current guidelines used in our hospitals.

Methods: The PubMed and ESC/ESH guidelines were searched. The searches were limited to articles of adult ages published between 2013–2018 in English language. The studies were reviewed and controlled to get the best extract. Determination of risk factors, lifestyle and demographic characteristics tends to give a full overview of the patient and define the proper treatment scheme.

Results: In a comparison, the current guidelines refer more lifestyle modifications especially in uncomplicated hypertension. Drug treatment is considered afterwards depending on hypertension grade with its main purpose to lower blood pressure. By how much the blood pressure should be lowered is currently a matter of controversy. The 2013 European and German national guidelines recommend a target blood pressure of < 140/90 mm Hg for most patients. The 2018 European Society of Hypertension guideline recommends as the first objective lowering blood pressure < 140/90 mm Hg for all patients and afterwards hypertension target values should be < 130/80 mm Hg for most patients.
Conclusions: The most efficient treatment of hypertension is reached knowing your patient, classifying the level of hypertension and determine risk factors for cardiovascular disease. As it always starts with lifestyle modifications, the drug treatment preferably starts with a two drugs combination except the hypertension Grade I. As an addition to resistant hypertension treatment is a low dose of spironolactone or another diuretic therapy like higher dose of thiazides or a loop diuretic or bisoprolol.

16. Improvement of the quality of resuscitation among students and doctors after applying electrodes with a pressure sensor

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Background: Correct chest compressions significantly increase the coronary perfusion pressure, which increases the chance of survival of patients. High quality CPR is carried out in accordance with the recommendations, i.e. with a depth of compressions of 5-6 cm and a frequency of 100-120 per minute. During the study, we focused on two elements: depth and the frequency of compressions.
Methods: 96 people participated in the study: students of CM UMK in Bydgoszcz (37 people) and doctors from No. 1 Jurasz University Hospital in Bydgoszcz (59 people). Defibrillators equipped with real-time monitoring of the quality of pressure were used. Every participant in this study initially began to compress the manikin with which the electrode with the pressure sensor was used, but without feedback. Then he proceeded to oppress the second manikin, which also possessed an electrode with a pressure sensor, from which he received real-time feedback on the depth of pressure of the chest, with what frequency and if there was relaxsation after each pressure.
Results: The effect of using feedback on the quality of pressure is the increase in the quality of chest compressions from 10 to over 50%. The average depth of pressure without feedback was above the norm given in the guidelines, and after the hint exercise decreased to the normal value. The average frequency was within the normal range but as many as 40 out of 48 people who initially had an incorrect frequency with feedback were in the range of 100–120 per minute.
Conclusions: The use of an electrode with a pressure sensor significantly increased the quality of CPR conducted among both doctors and students, and the improvement was at a similar level in both groups. Interestingly, the results of students conducting CPR without hints were higher than doctors. It could be related to the fact that students were in the recently of first aid and/or emergency medicine classes.