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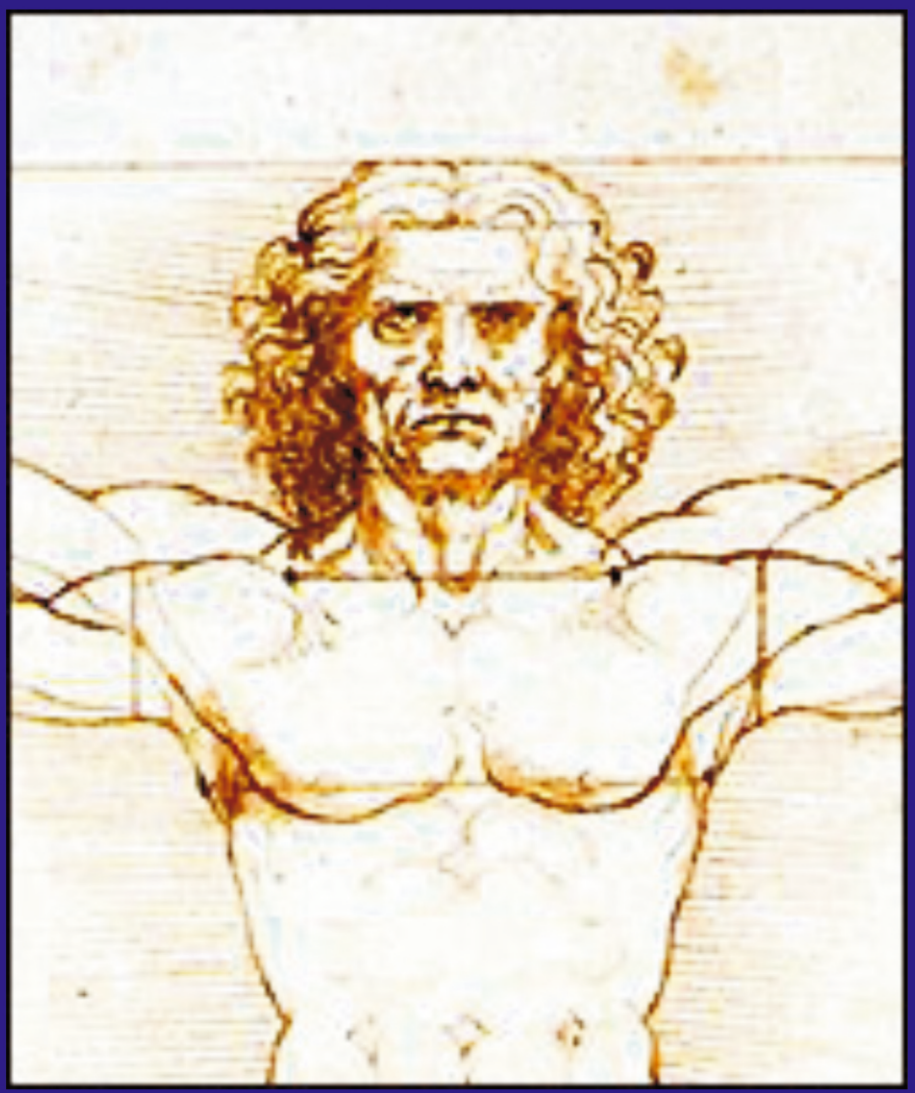

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UTILITY OF REPEATED DRUG LEVEL MEASUREMENTS AFTER HIGH DOSE METHOTREXATE INFUSION FOR TREATMENT PLANNING IN PEDIATRIC LEUKEMIA

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Abstract: **Introduction:** Although high-dose Methotrexate (MTX) is a successful chemotherapeutic agent used in the treatment of acute lymphoblastic leukemia in childhood, life-threatening toxic effects are rarely seen. Therefore, frequent follow-up of drug levels is recommended. The study researched the necessity of drug level measurement and a minimum safe number of measurements.

Materials and Methods: The files of pediatric patients with Acute Lymphoblastic Leukemia receiving high-dose MTX treatment in a single center between 2018 and 2021 were retrospectively reviewed. The treatment protocol was: 3000 mL/m^2 alkaline hydration fluid was continued until the 72nd hour together with 2 gr/m^2 continuous MTX infusion in the low-risk group and 5 gr/m^2 in moderate and high-risk groups, and 15 mg/m^2/dose folinic acid was given at the 42nd, 48th and 54th hours.

Findings: 456 MTX treatments were evaluated in 114 patients. Similar results ($p > 0.05$) were obtained in the MTX level measurements performed at the 24th, 42nd, 48th, and 54th hours after MTX administration. In the repeated measurements, the data at the 42nd hour were similar ($p = 0.021$). The number of cases that were > 150 µmol/L at the 24th hour of methotrexate infusion and above 1 µmol/L at the 42nd, 48th, and 52nd hours were found to be similar in the repeated measurements.

Conclusion: Although recommended, frequent follow-up of MTX levels might not always indicate toxicity. In centers with limited laboratory facilities, the MTX level measured at the 42nd hour in the first treatment might be a practical approach to guide the management of other MTX treatments.

Keywords: leukemia, methotrexate, toxicity, drug level.

INTRODUCTION

The most frequent type of cancer in childhood is acute leukemia. 80% of this is acute lymphoblastic leukemia (ALL). Methotrexate (MTX) is the principal chemotherapeutic agent used in the treatment of ALL and also for the prevention of relapse (1-5). One of the main factors increasing the treatment success in childhood ALL is dose intensity, and it is established that MTX administered in high doses positively affects prognosis (6, 7).

The mechanism of the MTX effect is to bind to the methylenetetrahydrofolate reductase enzyme, preventing the conversion of dihydrofolate to tetrahydrofolate, the active form of folic acid. With single-carbon presentation, tetrahydrofolate is indispensable in the synthesis of purine nucleotides and thymidylates. The effect of MTX, therefore, is to inhibit DNA synthesis and repair and prevent cell proliferation (8). MTX prevents the proliferation of rapidly proliferating healthy cell types, such as bone marrow, oral and intestinal mucosal cells, and urinary bladder cells, as well as malignant cells. One of the main drugs in the treatment of acute lymphoblastic leukemia, MTX, may cause life-threatening toxic effects, such as liver toxicity, nephrotoxicity, bone marrow suppression, and especially oro-intestinal mucositis, in 2-12% of the patients, even if the effect of MTX is therapeutically curtailed by calcium folinate treatment within 18-24 hours after the administration of MTX in high doses (9).

Standard doses have been determined for the amount of folic acid to be administered. However, the amount and number of doses are estimated according to serum MTX levels (9-11). In studies conducted to date, a wide range of recommendations based on MTX level has been made, ranging from "this measurement is not required" to "a single measurement is sufficient" or "a follow-up at six-hour intervals is needed until MTX level falls below the determined level" (9, 12-14). This study reviewed the similarities and differences among the repeated MTX levels in pediatric patients who were given repeated high-dose MTX due to ALL and researched the utility of these repeated measurements.

MATERIALS AND METHODS

MTX levels of pediatric patients treated according to ALL IC BFM 2009 protocol in a single Pediatric Hematology and Oncology Clinic, Basaksehir Cam and Sakura Training and Research Hospital, Istanbul 2018-2021, were evaluated. Each patient received four cycles of high-dose MTX. Complete blood count, creatinine, and alanine aminotransferase values were checked for suitability for MTX administration before each cycle. The treatment protocol was: 3000 mL/m^2 alkaline hydration was given together with 2 g/m^2 continuous MTX infusion in the low-risk ALL group and 5 g/m^2 in moderate and high-risk ALL groups for 24 hours. Hydrationfluids were continued until the 72nd hour. MTX clearance was determined by measuring the MTX level from peripheral blood samples four times at the 24th, 42nd, 48th, and 54th hours from the beginning of the first MTX infusion, and 15 mg/m^2/dose folinic acid was administered at the 42nd, 48th and 54th hours. From the 42nd hour, an additional dose of folinic acid of 15 mg/m^2/dose, if MTX is higher than 1 μmol/L, 30 mg/m^2/dose if higher than 2 μmol/L, 45 mg/m^2/dose if higher than 3 μmol/L, 60 mg/m^2/dose if higher than 4 μmol/L was given. Calcium folinate was continued until the MTX level in the peripheral blood fell below 0.25 μmol/L. Regular 6-hour follow-up MTX measurement was stopped in patients who showed sufficient clearance of MTX. The results of these measurements were compared.

MTX level was measured by a homogeneous competitive binding immunoassay based on competition between MTX in the sample and reagent containing MTX labeled with glucose-6-phosphate dehydrogenase (G6PDH) enzyme to bind to the anti-MTX antibody (Ark^{TM}Metotrexateassay). As the latter binds the antibody, G6PDH enzyme activity decreases. In the presence of the drug in the sample, enzyme activity increases, and this is directly proportional to the sample drug concentration. Uninhibited G6DPH enzyme converts coenzyme nicotinamide adenine dinucleotide (NAD) to NADH which is measured spectrophotometrically as the rate of change in absorbance. Endogenous serum G6PDHdoes not interfere with the results because the coenzyme NAD operates only with the bacterial G6PDH enzyme used in the assay.

Approval for this study was obtained from the hospital ethics committee (23.09.2021; 2021.09.190). All procedures performed in the study were in accordance with the institutional and national research committee's ethical standards and with the 1964 Helsinki declaration and its later amendments.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows, version 22.0 (IBM Inc., Armonk, NY, USA). The normality of the distribution of the variables was analyzed by the Kolmogorov-Smirnov test. Data with normal distribution are presented as mean ± standard deviation (SD), and those with non-normal distribution are shown as median (minimum-maximum). Independent groups were compared with the Student T-test and Mann Whitney U-Test and Kruskal-Wallis test, as appropriate, and the repeated measurements were compared with the Friedman tests. Chi-Square Test and Fisher's Exact Test were used to compare ratios. A $p < 0.05$ was considered significant.

RESULTS

During the study, 456 MTX levels following high-dose therapy in 114 patients were analyzed. The median age of the patients was 6 (2-17) years. Most (68; 60%) of the patients were male. The majority (101; 89%) were diagnosed with B cell ALL, of whom 14 (13.9%) were low-risk, 76 (75.25%) were moderate-risk, and 11 (10.9%) were in the high-risk groups. The remaining 13 (11%) patients were diagnosed with T cell ALL and 10 (76.9%) were in the moderate-risk group, and 3 (23.1%) were in the high-risk group.

In the level measurements performed four times at the 24th, 42nd, 48th, and 54th hours following each MTX cycle (given at two-week intervals), no statistically significant difference was found from cycle to cycle at each of the four-time points (Table 1). Analysis of the data indicated that the values at the 42nd hour were similar (p = 0.021) and that the 42nd-hour measurement of the first MTX treatment was guiding for determining the level in other MTX treatments (Table 1). The number of cases that were > 150 μmol/Lat at the 24th hour of the methotrexate infusion and above 1 μmol/L at the 42nd, 48th, and 52nd hours were similar in the repeated measurements at the same time points in the subsequent infusion cycles (Table 2).

Table 1. *Median interquartile MTX levels at the 24th, 42nd, 48th, and 54th hours by the cycle of treatment*

Hour of measurement	Cycle of high-dose methotrexate				
	First	Second	Third	Fourth	*p**
24	31.8 (41)	24.5 (42.6)	33.4 (42.1)	20.1 (15.9)	0.123
42	0.63 (0.62)	0.5 (0.32)	0.45 (0.43)	0.48 (0.4)	0.135
48	0.38 (0.24)	0.44 (0.21)	0.3 (0.13)	0.24 (0.37)	0.064
54	0.27 (0.2)	0.26 (.69)	0.26 (0.45)	0.21 (0.24)	0.937

Kruskal - Wallis test

Table 2. *Number of cases above 150 µmol/L24 hours after the infusion and above 1 µmol/Lat the 42nd, 48th, and 52nd hours after the first, second, third, and fourth cycle of high dose MTX*

	Time of measurement (hour)	Cycle of high-dose methotrexate				
		First	Second	Third	Fourth	*P*
> 150 micmol/L	24	74	47	45	34	NA
> 1 (micmol/L)	42	64	73	73	63	0.224
	48	79	66	58	50	NA
	52	66	46	33	27	NA

Chi-square; NA, not applicable.

Severe toxicity requiring hospitalization developed in three (2.6%) patients, consisting of nephrotoxicity in two and severe mucositis in one. Serum creatinine values prior to MTX infusion of the patients who developed nephrotoxicity were within the normal range (0.4-0.6 mg/dL). One was on the third high-dose MTX cycle, and when the 42nd-hour serum MTX level was found to be 34 µmol/L, serum creatinine was 1.3 mg/dl. Later, on the eleventh day, when the serum MTX level was 0.98 µmol/L, serum creatinine was persistently high at 0.72 mg/dL. MTX level and creatinine levels continued to decrease gradually and correlatedly during these 11 days. On the twelfth day, when the MTX level was 0.13 µmol/L, serum creatinine normalized for the first time at 0.47 mg/dL. No toxicity was observed when this same patient underwent their fourth MTX treatment. In the other patient with nephrotoxicity, the MTX level was 29.5 µmol/L when serum creatinine was 2.04 mg/dL after the fourth high dose of MTX. Although both levels were persistently high and correlated for 11 days, serum creatinine returned to normal (0.5 mg/dL) for the first time on the eleventh day of follow-up, when the MTX level was 0.28 µmol/L. Acute renal failure developed with elevated serum creatinine in both of these patients, but indications for dialysis, such as persistent hypercalcemia, acidosis, or uremic symptoms, did not develop and no permanent damage was observed in their follow-up.

DISCUSSION

In pediatric patients receiving MTX (2 to 5 g/m^2) for ALL, terminal half-life is known to change between 0.7 to 5.8 hours. Renal excretion is the primary way of elimination through active tubular secretion with glomerular filtration after iv administration, and 80% to 90% of the administered dose is excreted unchanged within 24 hours, while 10% or less of the administered dose is excreted via the biliary route. To detect delayed drug clearance, it is recommended to measure plasma MTX concentrations three times, at the 24th, 42nd, and 48th hours after the start of the MTX infusion; furthermore, the folinic acid recovery dose and regimen are determined with these measurements (15, 16, 17). The level of drug measured at the end of the first 24 hours following MTX infusion is important to assess the risk of toxicity at a time point 18 hours before the first calcium folinate treatment would be given. Drug level measurement is frequently used, especially in drugs with antidotes, to predict the toxic effects of the drugs. However, practical guidance is needed as it is not generally possible to get reliable results in a few hours in centers with limited laboratory facilities. In this study, the results of the repeated MTX level measurements were assessed to guide the safe administration of high-dose MTX treatment in pediatric patients with ALL. Moreover, the ethical territory requires the bioethical reflect, argue and provide constructions of knowledge

towards the choices and decisions made in concrete cases and situations (18).

Several studies have suggested that serial monitoring of drug levels until the MTX level becomes < 0.1 μmol/L is critical for the successful management of MTX-related toxicity (9, 10, 11). However, some studies have reported that a safety/toxicity balance can be obtained through clinical and laboratory findings in centers where level monitoring cannot be carried out, while other studies have suggested that only one or two post-infusion blood MTX measurements are sufficient (14, 16, 19). Vaishnavi et al. monitored 100 MTX cycles and reported that administration of 3 or 5 g/m^2 MTX without measuring MTX levels is safe by monitoring long-term hydration, additional leucovorin doses, and serum creatinine and urine pH (12). In a study conducted with 32 pediatric patients, Sari et al. analyzed 68 treatment cycles following ≥ 1 g/m^2/day MTX administration, two measurements were carried out at the 24th and 48th hours, and no correlation was found between the MTX level and clinical toxicity in these measurements (20). In the study by Dhingra et al., consisting of 184 patients, it was reported that a single plasma drug level measurement at the 54th hour, together with long-term hydration, was sufficient for the safe management of MTX in 89% of the 598 MTX treatments (14). In another study, 231 MTX infusions given to 61 pediatric patients were analyzed, and it was declared that pharmacokinetic parameters could be determined precisely and accurately by two-level measurements at the 24th and 48th hours, and thus the time when MTX concentration reached the prescribed threshold could be predicted (16). Our study also shows that the benefit of repeated measurements is extremely low after analysis of 456 high-dose MTX levels over four cycles in 114 patients.

Studies indicating that serum creatinine levels can be used to predict MTX nephrotoxicity have been published (21-24). In a study where high-dose MTX treatments given to 264 pediatric patients with acute leukemia were examined, it was concluded that an increase of more than 50% in serum creatinine level was a better guide for delayed MTX elimination than serum MTX level (20). In a similar study, it was reported that serum creatinine and creatinine clearance were closely correlated with plasma MTX concentrations after high dose MTX and that it could be used in follow-up (21). In the study by Howard et al., it was reported that urine pH, serum creatinine value, urination, and examination of mucous membranes twice a day allowed the administration of hundreds of high-dose MTXcycles without too much toxicity (14). In our study, we also found that serum creatinine levels were increased only in two patients, and this resulted in acute renal failure, that MTX level and serum creatinine levels were high in the measurements at the same time and decreased to normal levels simultaneously. We also found that serum creatinine was compatible with MTX concentration when MTX level measurements could not be conducted.

To avoid the toxic effects of MTX, alkaline hydration and folinic acid are used, as well as MTX level measurements (12). As more than 90% of MTX is eliminated by the kidneys and dissolves poorly at acidic pH, alkaline hydration is performed (10, 19, 25). Alkaline hydration was reported to last for a minimum of three days (12, 26, 27) and in our study, hydration was also given for this duration. Folinic acid was started at the 42nd hour as it will neutralize MTX. However, studies have shown that the risk of relapse may increase when given in high amounts with additional doses (5, 10). In contrast, it has been questioned whether long-term folinic acid is harmful or reduces the efficacy of MTX (28). In the present study, folinic acid was administered to the patients at the 42nd, 48th, and 54th hours of MTX infusion, and only those with higher blood MTX levels than expected were given additional doses.

The probability of side effects increases with the increase in the dose of MTX (29). Mucositis is the most frequently reported toxic effect of MTX (12, 26, 29-31). MTX-related toxicity may require hospitalization (27, 29). In our study, only three individuals of the 114 patients had side effects requiring hospitalization and subsequent delay in the next chemotherapy cycle. In these three, nephrotoxicity was more frequent than mucositis, but the numbers are too small to draw any firm conclusion.

Despite the delayed clearance of MTX, considering that toxicity symptoms rarely develop in patients, it was observed that drug levels might not be directly related to toxicity, although measurements are still clinically useful. However, although high-dose MTX has been used without level follow-up, if MTX levels are available but repeated testing is not possible, it seems advisable to perform at least a limited number of MTX level measurements after infusion. As a preventive measure, it may be reasonable to follow up on MTX levels earlier and use more measurements in patients with toxicity in earlier high-dose MTX cycles. Although more comprehensive studies are required, this study showed that MTX level measurement at the 42nd hour in the first MTX treatment cycle might offer reliable guidance. Thus, we believe this may be a pragmatic solution to repeated measurements in a resource-limited setting, enable better planning for other subsequent treatments, and provide an effective, reliable, and cost-efficient solution to the problem of

repeated MTX measurement when giving high-dose treatment.

A limitation of this study was that, due to the retrospective nature of the study, some data was missing from the comparison of the levels between the four sequential cycles.

Conclusion

It was considered that in the high-dose MTX treatments after the first dose, the contribution of the blood MTX levels measured every 6 hours to the forming of the treatment was extremely limited. MTX level measured at the 42nd hour in the first treatment might be a practical approach to guide the management of other MTX treatments.

Abbreviations

MTX — Methotrexate
ALL — Acute Lymphoblastic Leukemia
G6PDH — Glucose-6-Phosphate Dehydrogenase
NAD — Nicotinamide Adenine Dinucleotide

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Sažetak

KORISNOST PONOVLJENIH MERENJA NIVOA LEKA NAKON INFUZIJE VISOKE DOZE METOTREKSATA ZA PLANIRANJE LEČENJA KOD PEDIJATRIJSKE LEUKEMIJE

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Uvod: Iako je visoka doza metotreksata (MTX) uspešan hemoterapeutski agens koji se koristi u lečenju akutne limfoblastne leukemije u detinjstvu, toksični efekti opasni po život retko se primećuju. Zbog toga se preporučuje često praćenje nivoa leka. Studija je istraživala neophodnost merenja nivoa leka i minimalnog bezbednog broja merenja.

Materijali i metode: Retrospektivno su pregledani dosijei pedijatrijskih pacijenata sa akutnom limfoblastnom leukemijom koji su primali terapiju u visokim dozama MTX u jednom centru između 2018. i 2021. godine. Protokol tretmana je bio: 3000 mL/m^2 alkalne hidratantne tečnosti je nastavljeno do 72. sata zajedno sa 2 gr/m^2 kontinuiranom infuzijom MTX u niskorizičnoj grupi i 5 gr/m^2 u umereno i visoko rizičnim grupama i 15 mg/m^2/doza folinske kiseline je davana u 42. 48. i 54. satu.

Rezultati: Evaluirana su 456 tretmana metotreksatom (MTKS) kod 114 pacijenata. Slični rezultati ($p > 0,05$) dobijeni su u merenjima nivoa MTKS-a 24., 42., 48. i 54. časa nakon primene MTKS-a. U ponovljenim merenjima podaci na 42. satu su bili slični ($p = 0,021$). Broj slučajeva koji su bili >150 mmol/L u 24. satu infuzije metotreksata i iznad 1 μmol/L u 42., 48. i 52. satu su bili slični u ponovljenim merenjima.

Zaključak: Iako se preporučuje, često praćenje nivoa MTX možda neće uvek ukazivati na toksičnost. U centrima sa ograničenim laboratorijskim kapacitetima, nivo MTX meren na 42. satu u prvom tretmanu može biti praktičan pristup za upravljanje drugim MTX tretmanima.

Ključne reči: leukemija, metotreksat, toksičnost, nivo leka.

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PHENOTYPES OF POLYCYSTIC OVARY SYNDROME AND ACCOMPANYING HORMONAL DISTURBANCES

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Abstract: **Objective:** PCOS, which is known as a symptom complex including menstrual dysfunction (OD) and or hirsutism/androgen excess (HA), and/or polycystic ovaries (PCOM), induces women's health damage beyond this classical criteria. Subphenotypes of PCOS have different clinical properties and criteria, and the metabolical differences between these phenotypes have not been elucidated properly. Therefore, we aimed to investigate the metabolic and endocrinological differences between these sub-phenotypes.

Materials and Methods: 63 patients with PCOS followed by Istanbul Research and Education Hospital Endocrinology and Metabolism Department were included in the study. Patients were classified into subgroups according to phenotypes. The phenotype groups were compared according to blood glucose, lipid parameters, and serum hormone levels. MetS ratios between groups were also compared.

Results: Androgen excess/hirsutism was the most prominent character with a 95.2% (n = 60) rate in this study group, and ovulatory dysfunction was the least prominent one. (n = 43, 68.2%) PCOM has been detected in 50 patients (80.8%). Patients were grouped according to PCOS phenotypes. Phenotype C was the most common type, and about 65% of the patients were in this group. Triglyceride levels were statistically significantly higher in the Phenotype A group than in the Phenotype B group (p = 0.03). MetS was the highest in the Phenotype A group (45.4%) and the lowest in the Phenotype C group (34.7%).

Conclusions: Phenotype C has the highest prevalence in Turkish patients with PCOS, MetS was the highest in Phenotype A, and TG and LDL cholesterol levels were higher in Phenotype A. More studies are needed to explain these differences and their lifetime consequences.

Keywords*:* Polycystic ovary syndrome, metabolic syndrome, hyperlipidemia, hirsutism, androgens.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) increasingly attracts more interest as a disease of women of reproductive age. Classically PCOS has been known as a symptoms complex, including menstrual dysfunction (OD) and or hirsutism/androgen excess (HA) and or polycystic ovaries (PCOM). Two of the three latter criteria are sufficient to define diagnosis according to Androgen Excess Society (Rotterdam) criteria (1). Besides these clinical properties, obesity, insulin resistance, and some psychiatric diseases have been attributed to PCOS. According to a meta-analysis of 910 patients, depression and anxiety disorders were more common than in a control group of 1347 subjects (2). According to a Swedish study, 22.4% of the 22385 women with PCOS had previously been diagnosed with at least one psychiatric disorder (2). There are different criteria to define this disorder. According to these criteria, it had been found better to clearly define the PCOS sub-phenotype.These PCOS phenotypes generally include fourtypes: a) phenotype A, clinical or biochemical evidence of HA, OD (menstrual dysfunction), and PCOM; b) phenotype B: HA and OD, but not PCOM; c) phenotype C: HA and PCOM, but not OD; and d) phenotype D, with OD and PCOM, but not HA (3).

Additionally, metabolic syndrome, hyperprolactinemia, and insulin resistance could be other accom-

panying endocrine disorders in PCOS. One study has found a younger beginning and greater incidence of acne in PCOS patients with hyperprolactinemia (4). However, no study researched PCOS phenotypes and endocrine disturbances, so we aimed to document these endocrine disorders and their relationship with PCOS phenotype.

MATERIAL AND METHODS

63 patients who were routinely followed by Istanbul Research and Education Hospital Endocrinology and Metabolism Department were included in the study. The patients were diagnosed with PCOS according to Androgen Excess Society Criteria (1) and divided into subgroups according to phenotype (3). Height and weight were measured by accustomed methods, and BMI was calculated using the formula weight (in kg) divided by the square of height (in m). Serum lipid parameters, fasting glucose, and insulin were studied after 12 hours of night fasting. Serum estradiol, FSH, LH, testosterone, free testosterone, 17 (OH) Progesterone, and DHEA-S were studied at the follicular phase. Basal cortisol levels were measured at 08 00- 09 00. Overnight 1 mg dexamethasone was administered at 23 00 hrs, and serum cortisol level was measured at 08-09 00 hrs the next morning. The cut-off valuefor serum cortisol, which was less than 1.8 mcg/dl, was used to exclude hypercortisolism. The phenotype groups were compared according to blood glucose, lipid parameters, and serum hormone levels.

Institutional Ethical approval was taken from Istanbul Research and Education Hospital (27.04.2022/141)/ Helsinki guidelines were applied.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). The Chi-square test or Fischer's test was used to measure the categorical parameters. Student's t-test was used for normal distributed two-group comparisons. A one-way ANOVA test was applied to compare more than two groups. descriptive statistical methods were used to define group characteristics.

RESULTS

63 PCOS patients with a mean age of 24.69 ± 4.76 have been included. Androgen excess/hirsutism was the most prominent characteristic with a 95.2% (n = 60) rate in this study group, and ovulatory dysfunction was the least prominent one (n = 43, 68.2%). PCOM has been detected in 50 patients (80.8%).

The patients were grouped according to PCOS phenotypes. Phenotype C was the most common type, and about 65% of the patients were in this group. The study population characteristics are shown in Table 1.

There were only two patients with phenotype group D (3.2%). It is not enough to make a statistical comparison with other groups, so phenotype groups A, B, and C were analyzed to compare physical and biochemical properties shown in Table 2. In two group comparisons, triglyceride levels were found to be statistically significantly higher in the phenotype A group than in the phenotype B group (p = 0.03). This rela-

Table 1. *Study population characteristics*

Age	24.69 ± 4.76
Ovulatory Dysfunction	43/63 (68.2 %)
Androgen Excess/Hirsutism	60/63 (95.2%)
PCO morphology	50/63 (80.8%)
Phenotype A	11/63 (17.4%)
Phenotype B	9/63 (14.3 %)
Phenotype C	41/63 (65.1%)
Phenotype D	2/63 (3.2%)

Table 2. *Physical and biochemical properties of the groups*

	A	B	P-value Between A and B	C	P-value Between A and C	P-value Between B and C	p Value
Weight	77.27 ± 20.08	79.00 ± 19.30	0.84	73.32 ± 15.47	0.48	0.35	0.58
BMI	29.55 ± 6.97	31.38 ± 7.47	0.63	28.57 ± 6.99	0.72	0.35	0.72
Waist	80.80 ± 34.01	90.77 ± 22.29	0.46	82.28 ± 25.32	0.88	0.36	0.33
Glucose	86.63 ± 5.98	91.75 ± 6.40	0.09	92.62 ± 13.11	0.14	0.85	0.32
PPG	105.75 ± 21.83	79.83 ± 21.70	0.07	97.13 ± 22.63	0.36	0.09	0.12
Triglyceride	154.50 ± 84.95	78.50 ± 29.71	**0.03**	100.89 ± 54.10	0.06	0.27	**0.04**
HDL	60.00 ± 22.44	56.80 ± 9.90	0.75	58.82 ± 18.64	0.88	0.80	0.95
LDL	125.42 ± 27.31	111.75 ± 20.45	0.32	96.03 ± 23.01	**0.01**	0.07	**0.01**
Insulin	12.53 ± 9.90	14.66 ± 5.20	0.69	10.67 ± 7.82	0.72	0.30	0.59

Table 3. *Hormonal properties of the groups*

	A	B	P-value Between A and B	C	P-value Between A and C	P-value Between B and C	p Value
Testosterone	0.64 ± 0.31	0.73 ± 0.24	0.63	0.56 ± 0.33	0.58	0.30	0.53
Free Testesterone	1.53 ± 0.73	1.96 ± 0.72	0.57	1.97 ± 0.75	0.44	0.98	0.73
Estradiol	55.16 ± 11.30	35.32 ± 30.02	0.17	50.28 ± 29.46	0.69	0.24	0.30
LH	7.55 ± 3.94	6.52 ± 5.16	0.70	7.57 ± 3.09	0.98	0.50	0.79
Prolactine	23.44 ± 12.05	21.05 ± 9.26	0.64	24.94 ± 13.97	0.76	0.41	0.70
Cortisole	16.90 ± 5.41	17.70 ± 5.20	0.33	14.08 ± 3.33	0.38	0.09	0.18
DHEAS	345.16 ± 89.22	238.57 ± 59.51	0.03	311.73 ± 101.43	0.46	0.08	0.11
Metabolic Syndrome	45.4% (5/11)	12.5% (1/8)	0.03	34.7% (8/33)	0.11	0.03	0.04

tionship was found not significant between groups A and C, and between groups, B and C. LDL levels were also significantly higher in group A compared to group C ($p = 0.01$). When the three groups were compared through an ANOVA test, triglyceride and LDL levels in group A were significantly higher ($p = 0.04$ and $p = 0.01$, respectively).

Table 3 shows the comparison of the hormonal properties of the groups. Although DHEAS levels were statistically higher in group A compared to group B ($p = 0.03$), the three groups' hormonal property comparisons have shown no significant difference between phenotype groups A, B, and C.

DISCUSSION

This study has demonstrated that PCOS is predominantly found in Phenotype C, and the most common PCOS component is hirsutism and/or androgen excess. On the other side, we couldn't discover any weight or BMI difference between PCOS phenotypes. Phenotype A, which had included all PCOS criteria, had the highest TG and LDL level and, as expected, had the highest DHEAS level.

Phenotype C (HA+PCOM) was the most common phenotype. This finding was different from previous studies. Panidis et al. found Phenotype A prevalence as 48.2% (5). Another study found A in 58% prevalence (6). Metabolic syndrome was highest in the Phenotype A group (45.4 %). There have been ethnical differences according to different places and countries. For example, in contrast to the global prevalence of PCOS phenotypes, Phenotype D was found prevalent among Sudanese women (7). Diversity in frequencies of PCOS phenotypes could be clarified by whether the women were investigated in medical care or during an ordinary health control (8).

Serum triglyceride levelas a metabolic syndrome component was significantly the highest in Phenotype A, but also serum LDL cholesterol was highest in Phenotype A. Phenotype A (complete phenotype) had the highest MetS ratio (45.4 %) in the groups, Phenotype C had a similar ratio with Phenotype A (35.7%). Previous studies have found the MetS ratio in PCOS in similar proportions (6,9,10). The most common Mets Criterion was increased waist circumference by 60.3%. However, a recent study from China found low HDL was the most common MetS criterion in patients with PCOS (11). High TG was the most common in the complete phenotype (A). A study from India has found that Phenotype A had the most cardiovascular risk factors, highest waist, and BMI, but also in that study, this phenotype had the highest Clomiphene resistance (12). The difference in our study is there was no difference in weight, body mass index, and insulin levels between the groups, so the effect in blood lipids should not be affected by these parameters. Hyperlipidemia (elevated LDL Cholesterol) was more prominent in Phenotype A. A study from Poland of 93 patients also found higher LDL- cholesterol levels in patients with Phenotype A, while they didn't find a difference in TG levels (12). Total testosterone; FSH and LH and estradiol levels remained similar in phenotype groups. According to a cohort study, the PCOS phenotype didn't affect oocyte morphology and quality (13).

The importance of PCOS phenotyping lies in the fact that treatment response and cardiovascular prognosis. Adverse pregnancy outcomes were detected as more common in Phenotype A and D after in-vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) (14). Increased risk of abortion after frozen-thawed embryo transfer was found more common in phenotypes A and D (15). According to a cross-sectional study Phenotypes, A and B had weight-related problems in the quality of health, and phenotype D presented more emotional disturbance and relate health quality deteriation (16).

Limitations of this study are its cross-sectional design, small size, and of course, further studies with

more molecular investigating and treatment effects could be carried out.

CONCLUSION

Phenotype C has the highest prevalence in Turkish patients with PCOS, MetS was the highest in Phenotype A, and TG and LDL cholesterol levels were higher in phenotype A. More studies are needed to explain these differences and their lifetime consequences.

Abbreviations:

HA — Hyperandrogenism

MetS — Metabolic Syndrome

PCOS — Polycystic Ovary Syndrome

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Sažetak

FENOTIPOVI SINDROMA POLICISTIČNIH JAJNIKA I PRATEĆIH HORMONSKIH POREMEĆAJA

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Cilj: PCOS, koji je poznat kao kompleks simptoma koji uključuje menstrualnu disfunkciju (OD) i/ili hirzutizam/višak androgena (HA) i/ili policistične jajnike (PCOM), izaziva oštećenje zdravlja žena izvan ovog klasičnog kriterijuma. Subfenotipovi PCOS-a imaju različita klinička svojstva i kriterijume, a metaboličke razlike između ovih fenotipova nisu pravilno razjašnjene. Stoga smo imali za cilj da istražimo metaboličke i endokrinološke razlike između ovih subfenotipova.

Materijali i metode: U studiju su uključena 63 pacijentkinje sa PCOS-om, praćene na Odeljenju za endokrinologiju i metabolizam Istanbulske istraživačke i obrazovne bolnice. Pacijentkinje su klasifikovane u podgrupe prema fenotipovima. Fenotipske grupe su upoređivane prema glikemiji, lipidnim parametrima i nivou hormona u serumu. MetS odnosi između grupa su takođe upoređivani.

Rezultati: Višak androgena/hirzutizam je bio najistaknutiji karakter sa stopom od 95,2% (n = 60) u ovoj studijskoj grupi, a ovulatorna disfunkcija je bila najmanje izražena. (n = 43, 68,2%) PCOM je otkriven kod 50 pacijentkinja (80,8%). Pacijentkinje su grupisane prema fenotipovima PCOS. Fenotip C je bio najčešći tip, a oko 65% pacijenatkinja je bilo u ovoj grupi. Nivo triglicerida je bio statistički značajno viši u grupi fenotipa A nego u grupi fenotipa B (p = 0,03). MetS je bio najveći u grupi fenotipa A (45,4%), a najmanji u grupi fenotipa C (34,7%).

Zaključak: Fenotip C ima najveću prevalenciju kod turskih pacijenatkinja sa PCOS, MetS je bio najviši kod fenotipa A, a nivoi TG i LDL holesterola su bili viši kod fenotipa A. Potrebno je više studija da bi se objasnile ove razlike i njihove posledice tokom života.

Ključne reči: sindrom policističnih jajnika, metabolički sindrom, hiperlipidemija, hirzutizam, androgeni.

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Original article

OUTCOMES OF ULTRASOUND-MONITORED TREATMENT OF DIVELOPMENTAL DYSPLASIA OF THE HIP GRAF TYPE II

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Abstract: **Introduction:** The management of developmental dysplasia of the hips (DDH) type Graf IIa is still controversial. This study aims to examine the outcomes of ultrasound-monitored Pavlik harness treatment, as well as the effects of associated factors, such as gender, side of DDH, the age at the treatment start, and laterality on the treatment outcomes in different Graf type II subtypes.

Methods: A cohort retrospective investigation was performed on 88 ultrasound-screened infants or 125 hips diagnosed with Graf type II dysplasia during a six-month period at a single institution, the University Clinic for Orthopedic Surgery, Skopje. Subsequently, 47 infants (18 boys, 29 girls) or 73 hips who underwent Pavlik harness treatment with at least one follow-up throughout treatment monitoring were included in this study.

Results: The treatment success rate of the right DDH Graf type IIa (-) was higher (70.8%) compared to the rate of success (50%) in the treatment of left Graf type IIa (-) hips. The mean age of the infants at the treatment start in successfully treated Graf type IIa (-) hips was lower (9.12 ± 2.27 weeks) compared to the age of the infants with treatment failure at the last follow-up (11.33 ± 3.06 weeks), P = 0.04.

Conclusion: The age of treatment initiation and the side of DDH were the most relevant factors related to the treatment outcome. Infants with maturational deficit hips, Graf type IIa (-), should undergo early initiated, carefully guided, and monitored Pavlik harness treatment.

Key Words: Developmental dysplasia of the hip (DDH), Pavlik harness, Ultrasonography, Graf type II.

INTRODUCTION

Developmental dysplasia of the hip (DDH) has no single causative factor but is considered a multifactorial trait. Familiar positive history, certain racial predisposition, female gender, firstborn children, tweens, breech presentation, oligohydramnios, and presence of other orthopedic problems like postural deformities, foot deformities, torticollis, and other skeletal and muscular abnormalities are widely accepted as proven risk factors (1, 2, 3). Latest investigations suggest that prematurity is not a risk factor for DDH, but a rather protective factor for hip development (4).

The variation in the reported incidence of DDH among different populations leads to the lack of consensus regarding the treatment protocol for this condition. Many authors suggest implemetning a protocol that includes clinical and ultrasonography examinations for DDH in high-risk individuals (5, 6, 7). Because of the high incidence of DDH in our country, a combined protocol that includes universal mandatory physical examination and ultrasound hip screening up to 8 weeks of age has been accepted. Ultrasound examination of the hips enables the detection of abnormal position, instability, and dysplasia not evident by the physical examination. All infants undergo an ultrasound examination of the hips periodically (2 or 3 times after a 2 months period). Hips that featured sonographic pathology are subject to treatment and monitoring with ultrasonography. DDH treatment is still a controversial issue, and there is no current consensus on the best treatment approach. There are still controversial approaches to the treatment of Graf type IIa hips or physiologically immature hips. In these

hips, the risk of developing true dysplastic hips is about 10% (8). In Graf IIa (+) hips' physiological maturation is acceptable (alpha angle is between 55°-59° at 6 weeks of age), on the other hand, in Graf IIa (-) hips' physiological maturation is beyond acceptable limits (alpha angle is between 50°-54° at 6 weeks of age). Bilgili et al. determined the cut-off value of 55° on initial sonography as an independent predictor of worsening sonographic findings (9). It has been reported that 85% of Graf type IIa (-) hips have developed into normal hips without any treatment by the age of 3 months and then enter a plateau period during the 4 to 6th month (10). Anyway, many infants with DDH Graf type IIa remain at risk of developing true dysplastic hips if not treated, so our protocol includes Pavlik harness treatment of the maturational deficit Graf type IIa (-) hips. Our study aimed to examine the outcomes of ultrasound-monitored Pavlik harness treatment of Graf type II hips, as well as the effect of associated factors, such as gender, side of DDH, age at the treatment start, and laterality on the treatment outcome in different Graf type II subtypes (Graf IIa (-), IIb and IIc).

AIM

This study aims to examine the outcomes of ultrasound-monitored Pavlik harness treatment, as well as the effects of associated factors, such as gender, side of DDH, the age at the treatment start, and laterality on the treatment outcomes in different Graf type II subtypes.

MATERIALS AND METHODS

An institutional review board-approved retrospective investigation was performed on 88 ultrasound-screened infants, or 125 hips diagnosed with Graf type IIa(-), IIb, and IIc dysplasia during a six-month period (from September 2020 to February 2021) at a single institution, the University Clinic for Orthopedic Surgery, Skopje, R. North Macedonia. Subsequently, 47 infants (18 boys, 29 girls) with 73 DDH Graf type II hips (54 IIa (-), 9 IIb, and 10 hips IIc) who had their first ultrasound hip scan, and at least one follow-up examination throughout treatment monitoring during this period were included in the study. All infants underwent ultrasonography examination with the ultrasound system Phillips, affinity 30, Sonda L12.4. Infants with skeletal dysplasia, metabolic bone disease, and congenital coxa vara were excluded. Informed consent was obtained from the parents of the children included in the study. The data obtained from the infants' medical records were evaluated again by two independent observers. Inter-observer reliability was assessed using ICC (intra-class correlation coefficient), and the agreement was considered excellent. The Ethics Committee of the Faculty of Medicine in Skopje approved the design and the content of this study. All procedures performed in study were in accordance with the institutional and national research committee's ethical standards and with the 1964 Helsinki declaration and its later amendments.

All newborns in our country are subject to a physical examination of the hips immediately after birth in the hospital neonatology departments using Ortolani and Palmen Barlow tests carried out by an orthopedic professional to assess hip stability. Also, gluteal fold asymmetry and passive range of motion are checked for normal or reduced hip abduction. Infants with abnormal physical examination findings are referred to earlier mandatory ultrasound hip examination up to 4 weeks after delivery. Each newborn, in addition to the clinical examination, undergoes an ultrasound examination of the hips up to 8 weeks of age. The examination is carried out by orthopedic professionals trained in performing ultrasound examinations by Graf's technique (Figure1) (11). The centricity of the femoral head, the bony and cartilaginous acetabular rim, the shape of the acetabulum and its labrum, and the alpha and beta angle for measurement of the acetabular dysplasia are notified and analyzed. Data on age, sex, the existence of hereditary predisposition, the presence of risk factors during labor (breech presentation), and the diagnosis of other orthopedic abnormalities or hip instability are evidenced in the medical records and kept in the Clinic for Orthopedic Surgery.

Our protocol used in decision-making for the treatment of hip dysplasia Graf type II is as follows: Graf type I and Graf type IIa (+) hips are discharged, Graf type IIa (-), Graf type IIb and Graf type IIc hips receive Pavlik harness treatment immediately and are closely monitored by repeated ultrasound scans (in 3-4 weeks

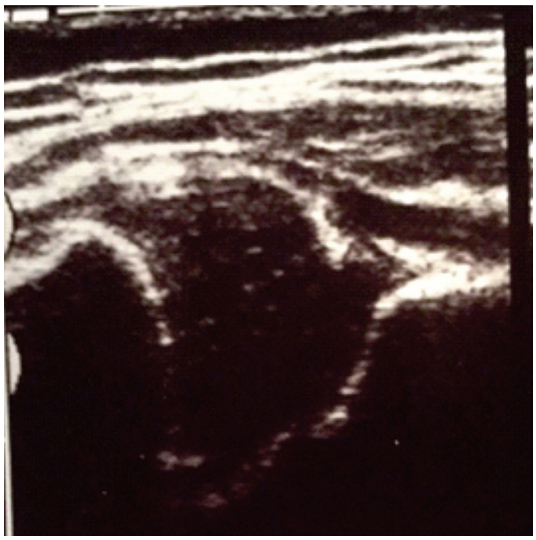

Figure 1. *Ultrasound image of DDH Graf type IIa(-)*

intervals) during the treatment period. The treatment is discontinued if the ultrasound examination reveals Graf type I or IIa+ hip. Following the termination of the treatment, we recommend a one-month extension of the treatment with 12 hours (during the night) of Pavlik harness treatment per day. First radiography for the validation of the dysplastic hip is recommended at five months of age. If residual hip dysplasia persists, radiographic follow-up of such hips is recommended at the 1st and 2nd year of age, although the risk of avascular necrosis of the femoral head is negligible in Pavlik harness treatment of Graf type II hips.

Data were statistically analyzed with SPSS for Windows (version 23 SPSS, Chicago, IL, USA). Chi-squared or Fisher's exact test was used to detect differences in treatment outcomes (success or failure) related to gender, side of pathology, and laterality. Student t-test was used to determine differences in outcomes associated with the infants' age at treatment initiation. Statistical significance was defined as $p < 0.05$.

RESULTS

During the six-month period, a total of 2958 infants underwent an ultrasound examination of the hips. In the medical records of 93 infants (29 boys, 64 girls), at least one DDH was diagnosed. On the first ultrasound scan, 99 hips in 65 infants were detected as Graf type IIa (-), 13 hips in 12 infants as Graf type IIb and 13 hips in 11 infants as Graf type IIc. Seven newborn infants had positive familial history, 25 newborns were delivered by a cesarean section and 6 newborns had a confirmed breech presentation during delivery. Subsequently, 47 infants (18 boys, 29 girls), or 73 hips with DDH Graf type II (54 hips Graf type IIa (-), 9 hips Graf type IIb, and 10 hips Graf type IIc) who underwent treatment and had at least one follow up throughout the treatment period were included in the study. Infants with at least one-sided DDH Graf type IIa (-), IIb, and IIc were subject to abduction brace and Pavlik harness treatment. The abduction brace and Pavlik harness treatment commenced immediately after establishing the diagnosis. Of the total of 47 infants with DDH Graph type II, who were monitored for a minimum of 1 to a maximum of 6 months (mean monitoring time 2.58 ± 1.31 months), success in the treatment in at least one-sided DDH Graf II hip was achieved in 25 (53%) infants. Throughout the treatment period, 42 (57.5%) of 73 monitored Graf II hips developed into normal hips. 31 hips were still considered as DDH on the last follow-up. The treatment of DDH Graph IIa (-) and Graf IIb hips showed higher success rates, 32/54, (60.4%) Graf type IIa (-) hips and 6/9, (66.7%) Graf type IIb hips developed into normal hips. Of the total of 22 Graf type IIa (-) hips diagnosed as treatment failure on the last follow-up, only 3 hips were still observed as hips with a maturational deficit, while most of these hips, 19/54 turned into true dysplastic hips Graf type IIb. The success rate of treatment of Graf type IIc hips was lower, only 4/10 (40%) of Graf type IIc hips developed into normal hips during the monitoring period.

The mean length of the ultrasound monitoring treatment period in infants with successfully treated DDH was 2.48 ± 1.07 months, almost the same as the mean length of the treatment period in infants with failure of DDH treatment on the last follow-up, 2.46 ± 1.26 months.

Gender

Of the total of 29 newborn girls with DDH Graf type II included in the investigation, success in the treatment of at least one DDH was achieved in 17 (58.6%) girls. Of the 18 included newborn boys with DDH Graf type II, success was achieved in 13 (72.2%) boys. Almost the same success was achieved in the treatment of DDH Graf type IIa (-) in male and female infants; 59% of the hips with a maturational deficit in boys and 59,4% of IIa (-) hips in girls developed into normal hips throughout the treatment monitoring period (Figures 2 and 3).

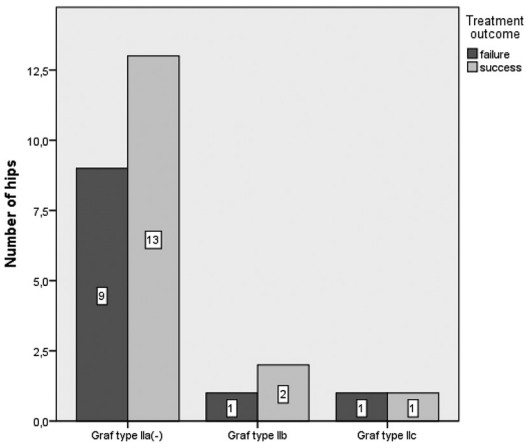

Figure 2. *Treatment success/failure by Graf type in male infants*

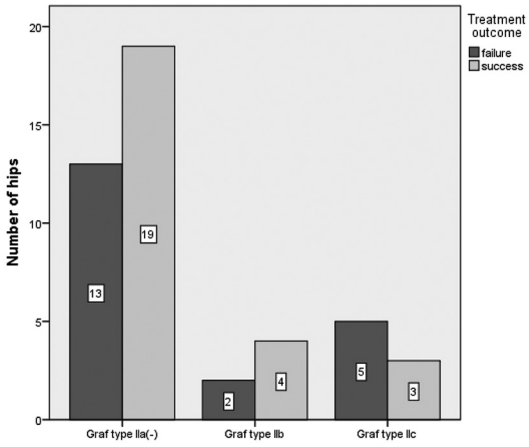

Figure 3*. Treatment success/failure by Graf type in female infants*

Side of DDH

Pavlik harness treatment was more successful in the right-sided DDH compared to the left-sided DDH. Of the total of 34 right-sided DDH Graf type II, 21 (61.8%) hips developed into normal hips, and of 39 left-sided DDH Graf type II, 21 (53.8%) hips turned into normal hips on the last follow-up (Figures 4 and 5). Even more, the treatment success rate of the right DDH Graf type IIa (-) was higher (70.8%) compared to the rate of success (50%) in the treatment of left Graf type IIa (-) hips.

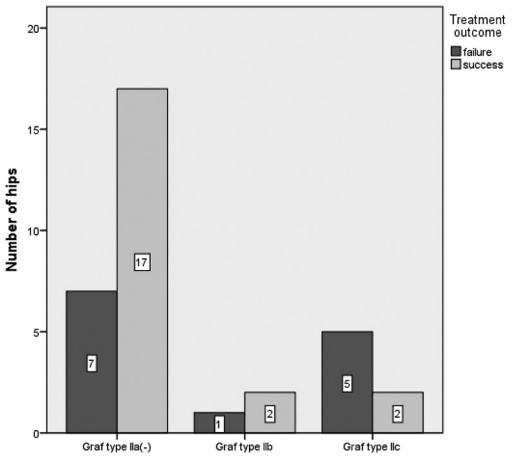

Figure 4. *Treatment success/failure by Graf type in right DDH*

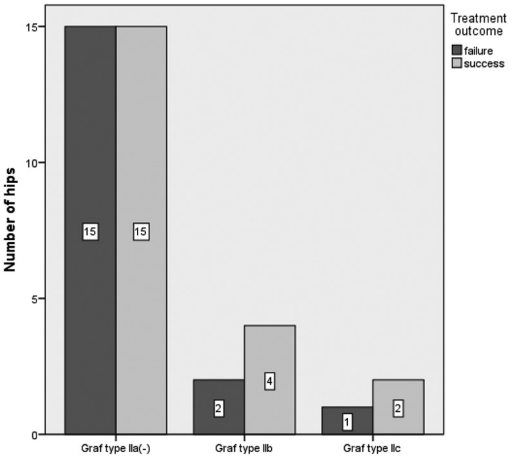

Figure 5*. Treatment success/ failure by Graf type in left DDH*

Age at the treatment start

The age of the infants at the treatment initiation was found to be statistically different (p = 0.02) between successfully treated infants, 9.52 ± 3.69 weeks, and infants with treatment failure on the last follow-up, 11.74 ± 4.02 weeks in DDH Graf type II.

The mean age at the treatment start in successfully treated infants with DDH Graf type IIa (-) was significantly lower (9.12 ± 2.27 weeks) compared to the mean age of the treatment start in infants with treatment failure at the last follow-up (11.33 ± 3.06 weeks), P = 0.04. The mean age of the treatment initiation in successfully treated infants with DDH Graf type IIb was 15 ± 4.69 weeks, while in infants with treatment failure was 18.67 ± 6.11 weeks. In infants with DDH Graf IIc, the mean age of the treatment start was significantly lower (4.5 ± 1 weeks) in infants with treatment success compared to the age of the treatment start (11 ± 1.67 weeks) in infants with treatment failure on the last follow-up, p = 0.00 (Figure 6).

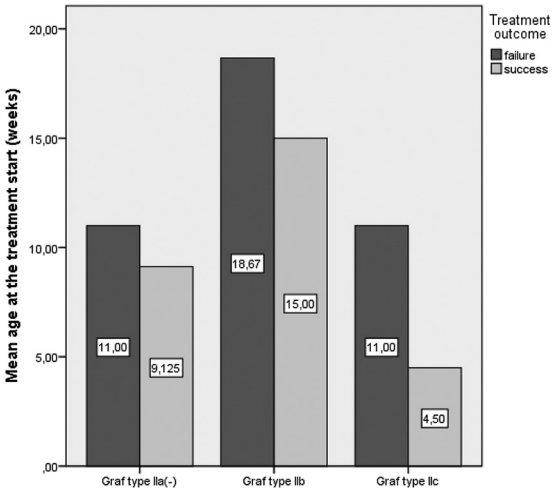

Figure 6. *Mean age of the infants at the treatment initiation in treatment failure/success of DDH Graf type IIa-, IIb and IIc*

Laterality

From 27 infants with bilateral DDH Graf type II, success in the treatment was evidenced in 14 (52%) infants. From 20 infants with unilateral DDH Graf type II, success in the treatment was evidenced in 11 (55%) infants.

DISCUSSION

Ultrasonography is not only a sensitive method for early diagnosis of DDH but a method of choice for treatment monitoring while treating DDH as well. It is a non-invasive sensitive method for visualization of bony and cartilage structures of newborn infants' hip joints. When used in treatment monitoring, it gives a possibility for multiple performances and for detecting minimal abnormalities of the hips that could not be diagnosed by a physical examination. In our country, ultrasonography is used for mandatory screening of infants' hips and treatment monitoring as well. Many European countries have also adopted universal ultrasound screening to confirm clinical findings. In North America, selective ultrasound screening is used only for infants with defined risk factors (breech presenta-

tion, family history, or clinical positive findings of hip instability). Distribution and implementation of DDH guidelines are necessary to improve the decision-making processes of pediatricians regarding the diagnosis and management of DDH (12, 13). In our study, 3.14% of infants who underwent ultrasound examination of the hips during the six-month period had at least one-sided DDH. Between the infants with DDH Graf type II, hips with maturational deficit Graf type IIa (-) were the most frequent finding (74% of DDH Graph type II) in our study. Many authors reported that 85% of DDH Grapf IIa (-) reached normality without any treatment at the end of the 3rd month of age (10). A greater number, even 35% of the hips with maturation deficit in our investigation turned into true dysplastic hips throughout the treatment monitoring period. A lot of infants with maturational deficit hips remain at risk for the development of true dysplastic hips, so we prefer to treat rather than follow up and include a routine Pavlik harness and abduction brace treatment of Graf type IIa (–) hips. For most of the infants included in the study, the treatment process had not been finished, therefore, only 57.5% of DDH Graf type II hips developed into normal hips. Our results confirm the necessity and significance of ultrasound hip screening. Experienced orthopedists can always detect dislocated and subluxated hips (Graf type III and IV), but the risk of missing Graf type IIa and Graf type IIb hips by physical examination always exists. Despite the earlier initiation of the Pavlik harness treatment in infants with DDH Graf type IIc (positive physical examination findings referred these infants to earlier ultrasound examination of the hips), the treatment success rate was lower (40%) compared to the success rate of the treatment of Graph IIa (-) and Graph IIb hips. The relatively low success rate of the treatment of Graph IIc hips in our investigation may have been due to the small number of infants included in the study and the relatively short period of treatment monitoring. Many authors reported that female gender and left-sided DDH were associated with the Pavlik harness treatment failure (10). For the hips with maturation deficit Graf type IIa (-), a lower rate of spontaneous maturation was reported in newborn girls (14,15). Our findings showed that the risk for the development of maturation deficit hips to true dysplastic hips was not associated with the infants' gender. Although Graf type IIa (-) hips have a potential for maturation, at least one follow-up after the initial diagnosis until the age of 3 months is required in order not to miss failure in the development of normal hips that remains is not a negligible number of these hips. These findings support our protocol according to which every newborn infant is referred to an ultrasound screening of the hips up to 8 weeks of age with close monitoring by repeated ultrasound scans (in 3-4 weeks intervals) during the treatment period. Graf type IIa (-) hips receive Pavlik harness treatment immediately and are closely monitored during the treatment period to avoid possible complications such as residual hip dysplasia and avascular necrosis. The entire system consists of early diagnosis, prevention, and treatment of dysplastic hip joints. The implementation of national and regional programs that promote ultrasound screening for DDH in both rural and urban areas can contribute to the early diagnosis and treatment of DDH in newborns and infants (16). Our findings showed that the treatment of physiologically immature Graf IIa (-) hips was more successful (70.8%) in the right hips compared to the rate of success (50%) in the treatment of the left DDH or the right DDH Graf type IIa (-) achieved earlier maturation and development into normal hips throughout the treatment monitoring period. Some authors found an increased rate of treatment failure in bilateral DDH (17,18), while others found no association between treatment failure and bilateral DDH (19, 20). Our findings showed no association between the treatment success and the laterality of DDH.

Most authors reported that successful treatment of DDH was associated with an early newborn hip screening at 4 to 8 weeks (21). German authors recommend replacing the current German screening guidelines for high-risk neonates with a general newborn screening for all neonates in the first week of life (22). Late detection causes an increased treatment complexity and a sevenfold increase in the short-term costs of treatment, compared to early detection and successful management in a Pavlik harness treatment (23). Our findings support the results of these studies, the younger age of the infant at the initial evaluation and treatment initiation was associated with a higher success rate of Pavlik harness treatment. The association between the treatment results and the age of treatment initiation was particularly evident in treating DDH Graf IIa (-) and IIc hips. Earlier treatment initiation could be the result of the positive physical examination in the maternity hospitals in more severe Graf types of DDH or the positive and responsible attitude of the parents who follow the instructions of orthopedic specialists and pediatric neonatologists. The parents who complied with the recommendations for early ultrasound examination of the hips are more responsible, more adapted to the use of Pavlik harness during the treatment period, and have a more serious and responsible approach to the treatment of their children. A mandatory ultrasound screening program is a sufficient tool for successful treatment results (24). Developing a program for wide health education of the newborns' parents that will in-

dicate the importance of early diagnosis and treatment of DDH could contribute to better treatment results. The limitations of this study were its retrospective design and a comparatively small number of patients.

CONCLUSION

The success in the treatment of DDH Graf type II is multifactorial, the age of treatment initiation and the side of DDH are the most prominent factors related to the treatment outcome. Infants with maturational deficit Graf type IIa (-) hips should undergo early treatment initiation, with carefully guided and monitored Pavlik harness treatment immediately after the diagnosis was established up to 8 weeks of age.

Abbreviations

ICC — Intra-class correlation coefficient
DDH — Developmental dysplasia of the hip

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Licensing

Sažetak

REZULTATI ULTRAZVUČNO PRAĆENOG LEČENJA RAZVOJNE DISPLAZIJE KUKA GRAF TIP II

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Uvod: Lečenje razvojne displazije kukova (DDH) tipa Graf IIa je još uvek kontroverzno. Ova studija ima za cilj da ispita rezultate ultrazvučno nadgledanog lečenja Pavlikovim remenima, kao i efekte povezanih faktora, kao što su pol, strana DDH, starost na početku lečenja i lateralnost na ishode lečenja kod različitih podtipova Graf tipa II.

Materijal i Metode: Retrospektivna kohortna studija je sprovedena na 88 ultrazvučno pregledanih novorođenčadi ili 125 kukova kojima je dijagnostikovana Graf tip II displazija tokom šestomesečnog perioda u jednoj ustanovi, Univerzitetskoj klinici za ortopedsku hirurgiju, Skoplje. Potom je u ovu studiju uključeno 47 novorođenčadi (18 dečaka, 29 devojčica) ili 73 kukova koji su bili podvrgnuti lečenju sa Pavlikovim aparatom uz najmanje jedno praćenje tokom lečenja.

Rezultati: Stopa uspešnosti lečenja desnog DDH Graf tip IIa (-) bila je veća (70,8%) u poređenju sa stopom uspeha (50%) u lečenju levih Graf tip IIa (-) kukova. Prosečna starost odojčadi na početku lečenja u uspešno lečenim kukovima Graf tipa IIa (-) bila je niža (9,12 ± 2,27 nedelja) u poređenju sa uzrastom odojčadi sa neuspešnim lečenjem na poslednjem praćenju (11,33 ± 3,06 nedelja) , P = 0,04.

Zaključak: Starost početka lečenja i strana DDH su bili najrelevantniji faktori u vezi sa ishodom lečenja. Novorođenčad sa nerazvijenim kukovima, Graf tip IIa (-), treba da se podvrgnu rano započetom, pažljivo vođenom i praćenom lečenju Pavlikovim remenima.

Ključne reči: Razvojna displazija kuka (DDH), Pavlikovi remeni, Ultrasonografija, Graf tip II.

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DIFFERENCES IN INFLAMMATORY MARKERS IN COVID-19 MORTALITY IN PATIENTS AGED 18-65, 65-80 AND 80 YEARS AND OLDER

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Abstract: **Background:** Since its emergence, coronavirus disease 2019 (COVID-19) has been a challenge to manage and has resulted in high mortality rates.

Aim: This study aimed to reveal the differences in the parameters at the time during the first admission, according to age groups in patients who applied due to Covid-19 and died in the hospital.

Methods: This was a retrospective, cross-sectional, and descriptive study covering the period from March 16 to May 9, 2021. The study population (1169 patients) included patients with COVID-19 who presented to the emergency department and died in the hospital. The data required for this study were obtained from the electronic medical records of the patients in the information system of our hospital. The patients were divided into three groups and analyzed.

Results: It was determined that the highest mortality rate was 547 (46.8%) in the 65-80 age group. In terms of comorbidities, there was a statistically significant difference between the three groups only in the incidence of asthma ($p = 0.037$). When the laboratory parameters and patient age groups were compared; a statistically significant difference was found in D-dimer, ferritin, WBC, platelet, and neutrophil values (respectively: $p = 0.001$, $p = 0.020$, $p = 0.005$, $p = 0.029$, $p = 0.037$).

Conclusion: The highest death rate in Covid 19 patients is seen in the 65-80 age group. In patients over 80 years of age, the presence of asthma and the increase in D-dimer and ferritin levels among laboratory parameters can be used to predict mortality.

Keywords: Age group, COVID-19, D-dimer, emergency room, ferritin, mortality.

INTRODUCTİON

Since its emergence, coronavirus disease 2019 (COVID-19) has been a challenge to manage and has resulted in high mortality rates. According to data from the World Health Organization (WHO), 5.331.019 people have died globally, and 79.813 people died in Turkey as of May 4, 2021 (1). There have been publications stating that COVID-19-related mortality is higher in older age groups. Mortality was reported to be significantly higher, particularly in patients aged > 65 years (2, 3). The guidelines published by the WHO state that the mortality rate increases by 20% in individuals aged > 80 years (3).

Many studies have been conducted on the factors that cause mortality in COVID-19 cases. While studies initially focused on viral load, inflammatory markers seem to have come to the forefront recently. As a result of these studies, the most important cause of severity and mortality in patients with COVID-19 is considered an excessive inflammatory response. Higher blood levels of inflammatory markers; including white blood cell (WBC), C-reactive protein (CRP), ferritin, and D-dimer, increased neutrophil-to-lymphocyte ratio (NLR), increased platelet-to-lymphocyte ratio (PLR), and increased serum levels of various inflammatory cytokines and chemokines have been associated with disease severity and mortality. It has also been suggested that these inflammatory cytokines, the levels of which are high in circulation, cause severe lymphopenia (2, 4). In addition, low platelet (PLT) counts, increased fibrin degradation products (D-dimer), and coagulation abnormalities are also reported to indicate poor prognosis. Organ failure of vital organs, such as the lungs, brain, heart, liver, and kidneys, due to microthrombi resulting from coagulation abnormalities is argued to be among the main causes of mortality in patients with COVID-19 (5).

This study aimed to reveal the relationship between age, inflammatory parameters, and mortality in patients who were admitted to the emergency department due to COVID-19 and died in the hospital.

MATERIALS AND METHODS

Study Group

The study protocol was approved by the Sakarya University Faculty of Medicine Local Ethics Committee, Turkey [IRB No.: 71522473 / 050.01.04 -39903-360]. This was a retrospective, cross-sectional, and descriptive study covering the period from March 16 to May 9, 2021. The study population included patients with COVID-19 who presented to the emergency department of SakaryaTraining and Research Hospital and died in the hospital.

In this study, COVID-19 was diagnosed in the emergency department based on a positive Real-time Polymerase Chain Reaction (RT-PCR) test result in patients who conformed to the definition of a probable case of COVID-19 according to the diagnosis and treatment guidelines of the WHO and the Ministry of Health of the Republic of Turkey (6). Patients with indications were admitted to the COVID-19 services or intensive care units outside the emergency department based again on these guidelines. Patients < 18 years, negative RT-PCR test results, patients not first examined in the emergency department, and patients with no available data were excluded from the study. The patients were classified into three groups in this study: Group 1 (231 patients), Patients aged 18-65 years; Group 2 (567 patients), Patients aged 65–80 years; Group 3 (371 patients), Patients aged ≥ 80 years.

Data Collection

The data required for this study were obtained from the electronic medical records of the patients in the information system of our hospital. Information on demographic characteristics, comorbid diseases, laboratory parameters (WBC count, neutrophil count, PLT, NLR, PLR, CRP levels, D-dimer levels, and ferritin levels), RT-PCR test results, and mortality was recorded as part of the study.

NLR and PLR were calculated as follows:

• NLR = ratio of neutrophil count to lymphocyte count

• PLR = ratio of platelet count to lymphocyte count

Statistics

SPSS software version 21.0 was used for statistical analysis. Median values were specified for continuous variables because they did not fit the normal distribution. Mann Whitney U and Kruskal Wallis tests were used for statistical analysis of continuous variables. Percentage values were given for the sharing of nominal categorical data, and statistical analyzes were made with the X2 test. All tests were performed with 5% two-tailed significance. Absolute and relative effects and corresponding 95% CIs for each endpoint were calculated as recommended by Altman et al. (7).

RESULTS

Our study included 1169 patients who applied to the SEAH emergency department, were diagnosed with COVID-19 by PCR, and subsequently died. The median age of the patients was 74 (66–82) years. Evaluation of the deceased patients in terms of sex revealed that male patients died more frequently, with males accounting for 62.9% (n = 735) of the mortality. The

Table 1. *Patients' demographic data, comorbidities, and laboratory parameters*

		n = 1169
Age (median; IQR)		74 (66–82)
Sex	Female (n; %)	434 (37.1)
	Male (n; %)	**735 (62.9)**
Comorbidity	Hypertension (n; %)	**376 (32.2)**
	Chronic Kidney Failure (n; %)	81 (6.9)
	Chronic Obstructive Pulmonary Disease (n; %)	110 (9.4)
	Asthma (n; %)	49 (4.2)
	Diabetes (n; %)	20 (1.2)
D-dimer (mg/L) (median; IQR)	Normal: 0–500 mg/L	**907.0 (493.5–2250.0)**
Ferritin (µg/L) (median; IQR)	Normal: 0–500 µg/L	**524.68 (246.05–1124.49)**
CRP (mg/L) (median; IQR)	Normal: 0–5 mg/L	**125.54 (66.51–198.33)**
WBC (K/uL) (median; IQR)	Normal: 4.6–10.2 K/uL	8.39 (5.86–11.65)
Platelet (10^9/L) (median; IQR)	Normal: 142.0–424.0 10^9/L	177.00 (132.85–227.00)
Neutrophil (K/uL) (median; IQR)	Normal: 2.0–6.9 K/uL	6.67 (4.46–9.72)
Lymphocyte (K/uL) (median; IQR)	Normal: 0.8–3.4 K/uL	**0.93 (0.61–1.40)**
NLR (median; IQR)		6.89 (3.92–12.85)
PLR (median; IQR)		188.50 (118.45–291.29)
Number of hospitalization (days) (median; IQR)		7 (2–13)

Table 2. *Intra- and inter group statistical analysis of the age groups*

			18-65 years n = 231	**65–80 years n = 567**	**≥ 80 years n = 371**	**p**
Sex	**Female (n; %)**		74 (32)	192 (33.9)	168 (45.3)	**0.000**
	Male (n; %)		157 (68)	375 (66.1)	203 (54.7)	
Comorbidity	**Hypertension (n; %)**		59 (25.5)	**204 (36.0)**	113 (30.5)	0.428
	CRF (n; %)		19 (8.2)	35 (6.2)	27 (7.3)	0.782
	COPD (n; %)		19 (8.2)	58 (10.2)	33 (8.9)	0.907
	Asthma (n; %)		8 (3.5)	17 (3.0)	24 (6.5)	**0.037**
	Diabetes (n; %)		1 (0.4)	14 (2.5)	5 (1.3)	0.609
Inflammatory parameters	**D-dimer (mg/L) (median; IQR)**	Normal 0–500 mg/L	790.00 (439.00–1980.00)[a]	889.00 (460.00–2015.00)[b]	1050.00 (612.50–3305.00)[a,b]	**0.000**
	Ferritin (µg/L) (median; IQR)	Normal 0–500 µg/L	542.15 (283.99–1789.67)[a]	535.53 (246.43–1187.62)	491.70 (228.06–950.25)[a]	**0.020**
	CRP (mg/L) (median; IQR)	Normal 0–5 mg/L	124.00 (65.42–182.78)	126.14 (66.32–203.02)	127.03 (67.10–201.16)	0.738
	WBC (K/uL) (median; IQR)	Normal 4.6–10.2 K/uL	7.58 (4.95–11.50)[a,b]	8.42 (6.11–11.60)[a]	8.69 (6.30–11.70)[b]	0.005
	Platelet (K/uL) (median; IQR)	Normal 142–424 K/uL	172.50 (126.00–223.00)[a]	174.10 (135.55–226.50)	182.00 (130.00–234.15)[a]	**0.029**
	Neutrophil (K/uL) (median; IQR)	Normal 2.0–6.9 K/uL	6.19 (3.77–9.46)[a]	6.66 (4.58–9.62)	5 (4.84–9.89)[a]	**0.037**
	Lymphocyte (K/uL) (median; IQR)	Normal 0.8–3.4 K/uL	0.94 (0.61–1.37)	0.92 (0.61–1.42)	0.93 (0.61–1.37)	0.806
	NLR (median; IQR)		6.54 (3.66–11.56)	6.79 (3.86–12.98)	7.30 (4.21–13.85)	0.130
	PLR (median; IQR)		169.05 (118.86–293.47)	188.37 (116.40–291.82)	194.51 (126.27–290.23)	0.303
Mortality days (median; IQR)			8.00 (4.00–15.00)	8 (2.00–4.00)	6 (1.50–11.00)	0.059

deceased patients' number of hospitalization days was 7 (2–13) days. Evaluation in terms of comorbidities revealed that hypertension (32.2%), COPD (9.4%), and CRF (6.9%) were the most commonly found comorbidities in deceased patients. As for the laboratory parameters, detailed data is provided in Table 1.

Results of intra- and intergroup statistical analysis of the age groups are provided in Table 2. Accordingly, the difference in the sex distribution between the age groups was determined to be statistically significant (p = 0.000). In terms of comorbidities, there was a statistically significant difference between the three groups only in the incidence of asthma (p = 0.037). Asthma prevalence, in particular, was found to increase in patients aged ≥ 80 years. In terms of laboratory parameters, a statistically significant difference was found between the three groups in terms of D-dimer, ferritin, WBC, platelet, neutrophil, and lymphocyte percentages. (respectively; p = 0.000, 0.020, 0.005, 0.029, 0.037, and 0.806).

In the subgroup analysis of the laboratory values in terms of age groups, a statistically significant difference was found between Group 1 and Group 3, Group 2 and Group 3 in D-dimer values (respectively; p = 0.001 and 0.004). When the subgroup analysis was conducted in terms of WBC values, a statistically significant difference was observed between Group 1 and Group 2, Group 1, and Group 3 (respectively; p = 0.013 and 0.006). Furthermore, a statistically significant difference was found between Group 1 and Group 3 in the subgroup analysis of ferritin, platelet, and neutrophil levels (respectively; p = 0.025, 0.024, and 0.036).

DISCUSSION

COVID-19 is still among the most important causes of morbidity and mortality in most countries around the world despite ongoing vaccination efforts. In particular, advanced age and male sex have been revealed to be associated with mortality. A study conducted on

this subject reported that the highest mortality rate in the group of patients aged > 60 years was among those aged ≥ 80 years (8, 9). Our study results corroborate the findings of the existing literature. Mortality was observed to be more common in the advanced age groups, particularly in those aged 65–80 years.

Considering the studies on COVID-19 in the literature, it has been previously reported that disease severity and mortality are higher in males (4, 9). This may be attributed to the higher risk of cardiovascular diseases, increased smoking, alcohol consumption, dietary differences, and decreased physical activity, in addition to the less use of healthcare services among men compared with women. Further, genetic factors may also be implicated (10, 11). Our study also showed that mortality was higher among men than women in all age groups, but this difference in mortality decreased in patients aged > 65 years. A similar study conducted on this subject found that the difference in mortality between the sexes decreased in advanced age groups, which was attributed to the decrease in the protective effect of estrogen (12). However, in our study, the difference between males and females was less in patients aged ≥ 80 years, suggesting that factors other than estrogen may be implicated.

In addition to epidemiological factors, comorbid diseases, such as hypertension, obesity, diabetes, cardiovascular diseases, chronic lung disease, CRF, and malignancy, have been reported to be associated with disease severity and poor prognosis in patients with COVID-19 (13, 14). The most common comorbid disease in patients with COVID-19 is hypertension, which has also been reported to be associated with the development of ARDS (15, 16). Although hypertension was the most common comorbidity in our study, which is consistent with the literature, the fact that asthma was also a prominent comorbid disease in our patients aged ≥ 80 years makes our study results noteworthy.

Patients with COVID-19 are known to be prone to thrombosis due to increased inflammatory response, hypoxia, immobilization, and widespread intravascular coagulation, which can be evaluated based on laboratory parameters such as D-dimer levels (17). Hence, it is stated that the age-adjusted D-dimer level threshold in patients with pulmonary embolism can be used for both diagnosis and prognosis (18). Similar COVID-19 studies have reported that different D-dimer level cutoff values, such as 1000 mg/L and 2000 mg/L, can be used to predict prognosis (19,20). Our study found D-dimer levels to be high in patients with COVID-19, as expected. However, the greatest increase was observed in patients aged ≥ 80 years. Based on this result, we believe that it would be appropriate to calculate and use age-adjusted D-dimer level thresholds to predict mortality.

Ferritin is a marker that plays a role in the inflammatory response and contributes to the cytokine storm observed in patients with COVID-19 (21). Ferritin levels are expected to increase in patients with COVID-19, and this is why it is used both as a diagnostic as well as a prognostic parameter (6, 21). Many studies have been conducted to demonstrate the success of ferritin in predicting disease severity and mortality. It has been reported that ferritin levels can indeed predict prognosis at the cutoff values of 451 ng/mL and 574.5 ng/Ml (22, 23). Our study results corroborate the existing literature, and it was observed that ferritin levels were increased in patients with COVID-19. This increase was more pronounced in those aged 18-65 years and was within the reference range mentioned in the literature for those aged ≥ 80 years. These results suggest that the threshold value should be determined according to age groups for ferritin levels as well, similar to D-dimer levels, to predict mortality.

A complete blood count is an easily accessible, relatively fast, and inexpensive diagnostic tool that can also be used in the management of patients with COVID-19 (24). The most studied parameters include WBC count, platelet count, neutrophil count, lymphocyte count, NLR, and PLR. A review of the literature suggests that an increase is expected in the WBC count, neutrophil count, NLR, and PLR, whereas a decrease is expected in lymphocyte and platelet counts (4, 25). It is noteworthy that PLR and NLR have been the most studied parameters in terms of predicting disease severity and mortality in patients with COVID-19. In fact, in a previous study on the subject, we reported that mortality could be successfully predicted using neutrophil count, NLR, and PLR at the cutoff values of 5.12 K/ul, 2.55, and 148.85 respectively (4). Other studies on the subject have also reported similar results (25, 26). The results of this study support both our previous study and the literature. Nevertheless, the fact that the most significant increases were observed in those aged ≥ 80 years makes this study a noteworthy contribution to the literature.

Limitations

Our study is retrospective and is not multicentered. In addition, the IL-6 level, which is an important parameter in COVID-19 mortality, could not be included due to the retrospective nature of the study. Besides, the lack of information about the patient's vaccination status against COVID-19 is one of the study's limitations.

CONCLUSION

The highest death rate in COVID 19 patients is seen in the 65-80 age group. In patients over 80 years

of age, the presence of asthma and increases in D-dimer and ferritin levels among laboratory parameters can be used to predict mortality.

AUTHOR CONTRIBUTION STATEMENT

1-Study concept and design: N.A. and F.G. 2-Acquisition of data: N.A., F.G., Y.Y., E.D., and N.G.G. 3-Analysis and interpretation of data: N.A., N.G.G., and E.D. 4-Drafting of the manuscript: Y.Y. and N.A. 5-Critical revision of the manuscript for important intellectual content: F.G., E.D., Y.Y., N.G.G, and E.D. 6-Statistical analysis: N.G.G., N.A. and F.G. 7 Administrative, technical, and material support: E.D., Y.Y., and F.G. 8 Study supervision: N.A., F.G., N.G.G., and E.D.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Sakarya University Faculty of Medicine Local Ethics Committee, Turkey [IRB No.: 71522473 / 050.01.04 -39903-360].

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. This research was conducted on humans in accordance with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Not applicable.

THE STANDARD FOR REPORTING:

STROBE guidelines and methodology were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available within the article.

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Conflict of Interests: The authors declare no conflicts of interest related to this article.

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Sažetak

RAZLIKE U INFLAMATORNIM MARKERIMA U SMRTNOSTI OD COVID-19 KOD PACIJENATA UZRASTA 18-65, 65-80 i 80 GODINA I STARIJIH

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Uvod: Od svog nastanka, bolest korona virusa 2019 (COVID-19) predstavljala je izazov i rezultirala je visokim stopama smrtnosti.

Cilj: Ova studija je imala za cilj da otkrije razlike u parametrima u vreme prvog prijema, prema starosnim grupama pacijenata koji su se primljeni zbog Kovid-19 i umrli u bolnici.

Metode: Ovo je bila retrospektivna, studija preseka i deskriptivna studija koja je pokrivala period od 16. marta do 9. maja 2021. Ispitivana populacija (1169 pacijenata) uključivala je pacijente sa COVID-19 koji su se javili u Službu za hitnu pomoć i umrli u bolnici. Podaci potrebni za ovu studiju dobijeni su iz elektronske medicinske dokumentacije pacijenata u informacionom sistemu naše bolnice. Pacijenti su podeljeni u tri grupe i analizirani.

Rezultati: Utvrđeno je da je najveća stopa mortaliteta 547 (46,8%) u starosnoj grupi 65-80 godina. U pogledu komorbiditeta, statistički značajna razlika između tri grupe postojala je samo u incidenci astme ($p = 0,037$). Kada su laboratorijski parametri i starosne grupe pacijenata upoređeni; utvrđena je statistički značajna razlika u vrednostima D-dimera, feritina, leukocita, trombocita i neutrofila (respektivno: $p = 0,001$, $p = 0,020$, $p = 0,005$, $p = 0,029$, $p = 0,037$).

Zaključak: Najveća stopa smrtnosti kod pacijenata sa COVID-19 zabeležena je u starosnoj grupi od 65 do 80 godina. Kod pacijenata starijih od 80 godina, prisustvo astme i porast nivoa D-dimera i feritina među laboratorijskim parametrima može se koristiti za predviđanje mortaliteta.

Ključne reči: starosna grupa, COVID-19, D-dimer, hitna pomoć, feritin, mortalitet.

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THE CORNEA AND METHODS FOR MEASURING INTRAOCULAR PRESSURE

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Abstract: **Introduction**:The study aimed to assert the relationship between central corneal thickness (CCT) and intraocular pressure (IOP) measured by: Goldmann applanation tonometry (GAT) and Dynamic contour tonometry (DCT).

Materials and Methods:The study included 150 patients with a mean age of 59.39 ± 13.12 years. Patients were divided into three groups: 50 primary open-angle glaucoma (POAG) patients, 50 ocular hypertension (OHT) patients, and 50 normal tension glaucoma (NTG) patients. IOP was determined using GAT and DCT. CCT was measured by ultrasound pachymetry.

Results: IOP measured with DCT was higher than IOP measured with GAT (19.80 ± 3.67 mmHg vs 17.71 ± 3.35 mmHg). A significant positive association between IOP measured with GAT and IOP measured with DCT was found in all patients ($r = 0.867$, $p < 0.01$). A significantly positive association between IOP measured with GAT and IOP measured with DCT in POAG ($r = 0.855$, $p < 0.01$), OHT ($r = 0.826$, $p < 0.01$), and NTG patients ($r = 0.832$, $p < 0.01$) were found. A significant positive correlation between CCT and IOP measured with GAT ($r = 0.198$, $p < 0.01$), as well as a significant positive correlation between CCT and IOP measured with DCT was found ($r = 0.198$, $p < 0.01$) in all patients. There was no correlation between CCT and IOP measured neither with GAT nor with DCT separately in three patient groups ($p > 0.05$).

Conclusion: CCT-influenced IOP was measured by both methods, GAT and DCT. DCT can not replace GAT, but it is very useful, especially in cases where errors are in the IOP GAT measurement.

Keywords: Cornea, Intraocular pressure, Pachymetry.

INTRODUCTION

Glaucoma is a chronic progressive optic neuropathy with morphological (excavation of the optic nerve head) and functional disturbances (defects in the field of vision) (1). Glaucoma is the second cause of blindness after cataracts in underdeveloped countries and after senile degeneration of the yellow spot in developed countries. It is estimated that in 2020 this disease in the world has 80 million people, and 111 million people will have it by 2040 (2).

In everyday ophthalmological practice, Goldmann applanation tonometry (GAT) is the standard method for determining intraocular pressure (IOP). GAT was first introduced by Goldmann and Theo Schmidt in 1957. Measurement of IOP with this method is done based on the force required to perform the plan, i.e. decomposition of the certain cornea (3). The Dynamic Contour Tonometer (DCT) is a contact, non-applanation method of IOP measurement based on the principle of tonometer and corneal head counts so that the head of the tonometer takes over the role of the bulb shell. This way, it directly measures the force transmitted to the bulb shell and comes from the IOP. DCT is commercially available since 2004, designed for direct and non-invasive IOP measurement, relatively

independent of inter-individual variations of corneal biomechanics (4). The value of the IOP obtained by the DCT method is the result of a four-force equilibrium: IOP, corneal rigidity, the adhesion force of the tear film, and aposition force of the tonometer (4). A piezoelectric sensor (1.2 mm diameter), mounted on the top of the tonometer head (the diameter of the head is 10.5 mm, contact diameter of 7 mm), is used for direct measuring the dynamic pulsed fluctuations in the IOP by DCT method. DCT head is similar to the GAT head and produces a constant aposition force of LG. For practical and hygienic reasons, DCT has a special silicone overlay on its head-tip (4, 5). The impact of CCT on IOP is the greatest in non-contact tonometry and the smallest in DCT (4-7).

The present study aimed to evaluate the relationship of central corneal thickness (CCT) measured by ultrasound pachymetry and IOP readings, measured with GAT and DCT, in open-angle glaucoma patients.

MATERIALS AND METHODS

The study included 150 patients with a mean age of 59.39 ± 13.12 years (range 19-83 years). Patients were divided into three groups: 50 primary open-angle glaucoma (POAG) patients, 50 ocular hypertension (OHT) patients, and 50 normal tension glaucoma (NTG) patients. The research adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

Including criteria in the study were: 1) POAG patients with elevated IOP > 21 mmHg without glaucomatous visual field defects and glaucomatous cupping of the optic disk, 2) OHT patients were with elevated intraocular pressure (> 22 mm Hg), normal visual fields and normal-appearing optic nerve heads, 3) NTG patients were with normal intraocular pressure (≤ 22 mm Hg), open angle on gonioscopy, glaucomatous visual field defects and glaucomatous cupping of the optic disk. Excluding criteria from the study were: previous intraocular surgery, corneal dystrophy or edema, pigmentary dispersion syndrome, and end-stage of glaucoma (absolute or fere absolute glaucoma).

Operating technique

Topical anaesthesia (Sol. Tetracaine 1%) was used for all measurements. IOP was determined 3 times, each consecutively, using GAT (Goldmann tonometer, Haag- Streit International AT 900, Swiss Made) and DCT (Pascal Dynamic Contour Tonometer SMT Swiss Microtechnology AG a Ziemer Ophthalmics Group Company, CH- 2562 P011 Switzerland). Tip preservative was changed before every exam during DCT measurements (Figure 1) (3). CCT was measured

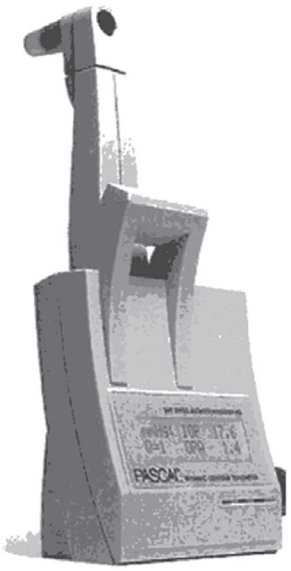

Figure 1. *Dynamic contour tonometry*

3 times consecutively using Ultrasound Pachymetry (Micro Medical Devices, Palm Scan AP 2000 Ophthalmic Ultrasound, Device Mode P2000, password 64711773, Serial # 3102, Made in USA) (4, 8).

Statistics

SPSS software 17.0. the application was used for all analyses. Statistical significance was assumed at $p < 0.05$. Data were analyzed using Student's t-test (or Mann-Whitney U test due to distribution) and Pearson's χ test (for nominal data). Variables were assessed by Pearson's parametric correlation method. When comparing three or more data sets, Fischer's variance analysis (ANOVA) was used.

RESULTS

In all patients the mean IOP measured with GAT was 17.7 ± 3.35 mmHg, and the mean IOP measured with DCT was 19.80 ± 3.67 mmHg. OHT patients had the highest mean IOP measured both with GAT and DCT, and NTG patients had the lowest mean IOP measured both with GAT and DCT (Table 1). There was a significant difference between the three groups of patients in mean IOP measured both with GAT ($F_{POAG, OHT} = 5.134$, $p < 0.05$, $F_{POAG, NTG} = 5.516$, $p < 0.05$, $F_{NTG, OHT} = 9.707$, $p < 0.01$) and DCT ($F_{POAG, OHT} = 5.220$, $p < 0.05$, $F_{POAG, NTG} = 5.341$, $p < 0.05$, $F_{NTG, OHT} = 9.644$, $p < 0.01$). The mean difference between DCT and GAT readings was 2.09 ± 1.84 mmHg. The mean difference between DCT and GAT readings was almost the same in OHT (2.16 ± 1.87 mmHg) and NTG patients (2.14 ± 1.79 mmHg), the lowest in POAG patients (1.97 ± 1.85 mmHg) (Table 2).

Table 1. *Intraocular pressure measured with Goldmann applanation tonometry and Dynamic contour tonometry in all patients and three patient groups*

Variable	Groups	Mean ± SD (mmHg)	Minimal value	Maximal value
GAT"	POAG*	17.89 ± 3.35	10	27
	OHT&	19.45 ± 2.87	14	31
	NTG	15.79 ± 2.78	8	22
	All patients	17.71 ± 3.35	8	31
DCT±	POAG*	19.86 ± 3.53	12.6	29.4
	OHT&	21.61 ± 3.31	14.8	34.3
	NTG@	17.93 ± 3.23	6.8	24.1
	All patients	19.80 ± 3.67	6.8	34.3

*"GAT = Goldmann applanation tonometry, ±DCT = Dynamic contour tonometry, *POAG = open-angle glaucoma, &OHT = ocular hypertension,@NTG = normal tension glaucoma.*

Table 2. *Mean difference between Dynamic contour tonometry and Goldmann applanation tonometry readings in all patients and three patient groups*

Variable	Groups	Mean ± SD (mmHg)	Minimal value	Maximal value
Mean difference DCT- GAT	POAG*	1.97 ± 1.85	-4.60	6.60
	OHT&	2.16 ± 1.87	-2.00	7.80
	NTG@	2.14 ± 1.79	-1.80	6.80
	All patients	2.09 ± 1.84	-4.60	7.80

*"GAT = Goldmann applanation tonometry, ±DCT = Dynamic contour tonometry, *POAG = open-angle glaucoma, &OHT = ocular hypertension,@NTG = normal tension glaucoma.*

Table 3. *Central corneal thickness in all patients and three patient groups*

Variable	Groups	Mean ± SD (µm)	Minimal value	Maximal value
Central corneal thickness	POAG*	551.76 ± 29.58	508	622
	OHT&	596.41 ± 28.32	535	684
	NTG@	544.01 ± 26.75	485	596
	All patients	564.06 ± 36.43	485	684

**POAG = open- angle glaucoma, &OHT = ocular hypertension, @NTG = normal tension glaucoma.*

A significant positive association between IOP measured with GAT and IOP measured with DCT in all patients was found ($r = 0.867$, $p < 0.01$) (Figure 2). Also, a significant positive association between IOP measured with GAT and IOP measured with DCT in POAG patients ($r = 0.855$, $p < 0.01$), OHT patients ($r = 0.826$, $p < 0.01$) and NTG patients ($r = 0.832$, $p < 0.01$) were found.

The mean CCT in all patients was 564.06 ± 36.43 µm. OHT patients had the highest mean CCT (596.41 ± 28.32 µm), and NTG patients had the lowest mean CCT (544.01 ± 26.75 µm) (Table 3). There was no significant difference in mean CCT between POAG and NTG patients ($F_{POAG, OHT} = 13.449$, $p < 0.01$, $F_{POAG, NTG} = 2.041$, $p > 0.05$, $F_{NTG, OHT} = 15.043$, $p < 0.01$). A significant positive correlation between CCT and IOP measured with GAT ($r = 0.198$, $p < 0.01$) and a significant positive correlation between CCT and IOP measured with DCT ($r = 0.198$, $p < 0.01$) were found. There is no significant correlation between CCT and IOP measured with GAT individually in POAG ($r = -0.017$, $p > 0.05$), OHT ($r = -0.096$, $p > 0.05$) and NTG patients ($r = -0.147$, $p > 0.05$), as well as CCT and IOP, measured with DCT in POAG ($r = -0.052$, $p > 0.05$), OHT ($r = -0.032$, $p > 0.05$) and NTG patients ($r = - 0.175$, $p > 0.05$). Figure 3 shows a significant positive correlation between CCT and the mean difference between DCT and GAT readings in all patients ($r = -0.288$, $p < 0.01$).

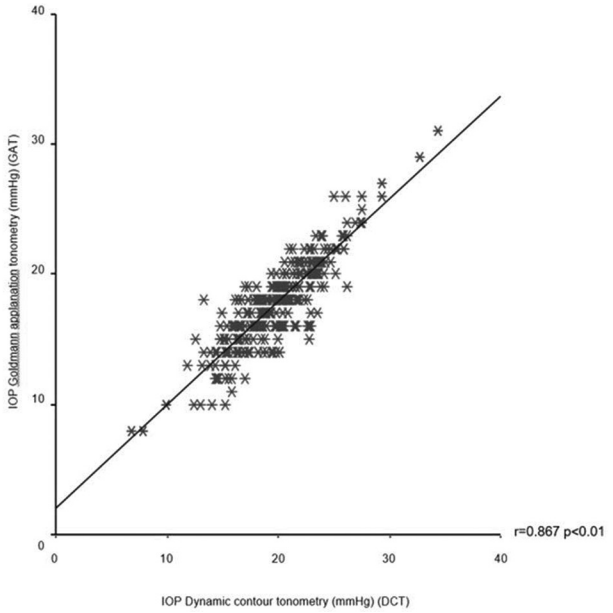

***Figure 2**. Correlation between IOP measured with Goldmann applanation tonometry and IOP measured with Dynamic contour tonometry*

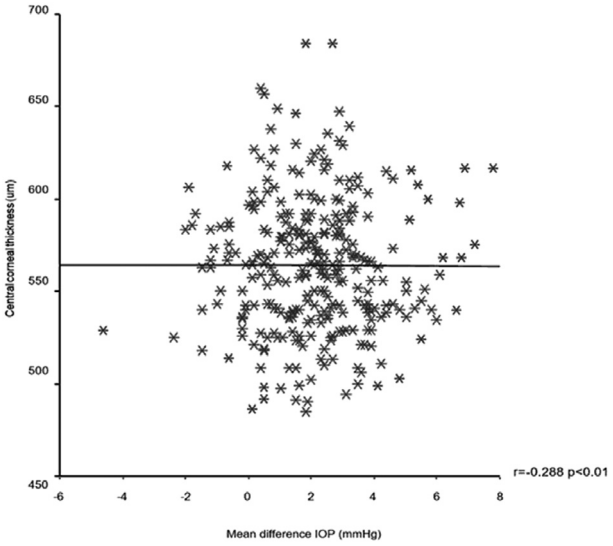

***Figure 3.** Correlation between central corneal thickness and mean the difference between Dynamic contour tonometry and Goldmann applanation tonometry readings*

But in the three groups, a significant correlation was not found. (POAG patients: r = -0.169, p > 0.05, OHT: r = 0.189, p > 0.05, NTG: r = -0.118, p> 0.05).

DISCUSSION

In the present study mean IOP measured with GAT in all patients was 17.7 ± 3.35 mmHg, mean IOP measured with DCT was 19.80 ± 3.67 mmHg which is in agreement with the findings of Ku et al. (9), Schneider and Grehn (10) while it is not in agreement with Realini et al. (11) and Barleon et al. (12) study. In our study OHT, patients had the highest mean IOP measured both with GAT and DCT, and NTG patients had the lowest mean IOP measured both with GAT and DCT, which is in agreement with the findings of Punjabi et al. (13). In the present study, the mean difference between DCT and GAT readings IOP was in agreement with findings of other authors (9, 10). In the Punjabi et al. study (13), pseudoexfoliative glaucoma patients had IOP higher and OHT patients had lower compared to our IOP findings. They conclude that the mean difference between DCT and GAT readings was higher at lower IOP values and that this difference decreases as the IOP grows. This mean difference between DCT and GAT readings obtained in our study indicates the possibility of the DCT as an adequate supplement to GAT. IOP measurement with DCT is independent of innate CCT and indicates the importance of its introduction into standard clinical practice in order to achieve an accurate diagnosis, monitoring, and glaucoma therapy. DCT is based on a completely new physical principle: when the contours of the corneal surface and the tonometer match, the pressure measured at the surface of the eye equals the pressure inside the eye. But, DCT also has deficiencies: the prolonged contact time of this tonometer and cornea head.

In the present study, a significant positive association between IOP measured with GAT and IOP measured with DCT was found in all patients and in each group. Our findings agree with the findings of other authors (9, 10, 12). Punjabi et al. (13) found a significant positive association between IOP measured with GAT and IOP measured with DCT in all groups of patients (POAG, NTG, pseudoexfoliative glaucoma, normal controls) except in OHT patients. They show that for IOP values (GAT) of 8-20 mmHg IOP (DCT) values are greater than IOP(GAT), while for IOP values > 25mmHg IOP (DCT) values are lower than IOP (GAT) (13).

Pachymetry as a method of measuring CCT is very important in diagnosing glaucoma. When Goldmann and Schmidt introduced the GAT method, they were aware that the accuracy of GAT depends on CCT. IOP measured with GAT are most precise at the CCT value of 552 μm. Various CCT-based correction tables have been proposed for the GAT (correction value of 2.5-5 mmHg per 100 μm). CCT and other biomechanical properties of the cornea have an effect on IOP measured with GAT. In clinical practice, it has been shown that the effect of CCT on IOP is the greatest in non-contact tonometry and the smallest in DCT. We found a significant positive correlation between CCT and IOP measured with GAT in all patients, which is in agreement with the findings of Ku et al. (9), Schneider and Grehn

(10), Kniestedt et al. (14). Patients with higher CCT have higher IOP measured with GAT. A significant positive correlation between CCT and IOP measured with DCT in all patients was found, which is not in agreement with the findings of Ku et al. (9), Schneider and Grehn (10), Kniestedt et al. (14). There is no significant correlation between CCT and IOP measured with GAT as well as CCT and IOP measured with DCT separately in our three patient groups which are in agreement with findings of other authors (12, 13, 15, 16).

The clinical trial has shown that by applying the GAT method on patients with thicker cornea greater IOP values are recorded compared to the standard IOP values, while in patients with thinner cornea lower IOP values are recorded. The thicker cornea and falsely recorded higher IOP indicate that there is room for the possible OHT, which had already been proven in the multicentric study: Ocular Hypertension Treatment Study (15, 16, 17). The presence of thinner cornea and falsely recorded lower IOP indicate the presence of NTG, therefore the OHT patients can be falsely diagnosed as glaucoma patients and unnecessarily treated with antiglaucoma drugs, while the NTG patients can be regarded as healthy humans that do not require treatment. In order to make the right diagnosis and apply the adequate treatment of patients suffering from glaucoma, the corneal pachymetry test is proven to be a successful method not only in clinical trials but also in every ophthalmic practice (16).

In the present study, a significant positive correlation between CCT and the mean difference between DCT and GAT readings was found that is in agreement with the findings of Ku et al. (9), Kniestadt et al. (14), De Castro OJMA et al. (18), Gvozdenovic et al. (19), Ayyildiz et al. **(**20). But when we separated patients in three groups, a significant correlation that agrees with findings of Barleon et al. was not found (12).

CONCLUSION

CCT measurement had an influence on IOP values measured by both methods, GAT and DCT. The correlation between CCT and IOP measured with DCT was small compared to the correlation between CCT and IOP measured with GAT. IOP values measured with DCT were higher in comparison with IOP values measured with GAT. GAT is still a gold standard for routine measurements of IOP. DCT can not replace GAT, but in clinical practice, DCT should become a useful complement to the classic method of IOP measurements, especially when there are errors in the IOP (GAT) measurements.

Abbreviations

CCT — central corneal thickness
DCT — Dynamic Contour Tonometer
GAT — oldmann applanation tonometry
IOP — intraocular pressure
NTG — normal-tension glaucoma
OHT — ocular hypertension
POAG — primary open-angle glaucoma.

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Licensing

Sažetak

ROŽNJAČA I METODE MERENJA INTRAOKULARNOG PRITISKA

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Uvod: Cilj ove studije je utvrditi povezanost centralne debljine rožnjače (CCT) i intraokularnog pritiska (IOP-a) izmerenog Goldmanovom aplanacionom tonometrijom (GAT) i Dinamičkom konturnom tonometrijom (DCT).

Materijal i Metode: Studija je obuhvatila 150 pacijenata prosečne starosti 59,39 ± 13,12 godina. Pacijenti su podeljeni u tri grupe: 50 pacijenata sa primarnim glaukomom otvorenog ugla (POAG), 50 pacijenata sa okularnom hipertenzijom (OHT), 50 pa-

cijenata sa normotenzivnim glaukomom (NTG). IOP je određen GAT i DCT metodom. CCT je određena ultrazvučnim pahimetrom.

Rezultati: IOP izmeren DCT metodom bio je viši u poređenju sa IOP izmerenim GAT (19,80 ± 3,67mmHg vs 17,71 ± 3,35 mmHg). Pronađena je statistički značajna povezanost IOP izmernog GAT i IOP izmerenog DCT kod svih pacijenata ($r = 0,867$, $p < 0,01$). Statistički značajna povezanost IOP izmernog GAT i IOP izmernog DCT metodom nađena je kod POAG ($r = 0,855$, $p < 0,01$), OHT ($r = 0,826$, $p < 0,01$) i NTG ($r = 0,832$, $p < 0,01$) pacijenata. Povezanost CCT i IOP izmerenog GAT ($r = 0,198$, $p < 0,01$) kao i povezanost CCT i IOP izmerenog DCT metodom ($r = 0,198$, $p < 0,01$) bila je statistički značajna kod svih ispitanika. Nije nađena statistički značajna povezanost CCT i IOP izmerenog GAT kao i CCT i IOP izmerenog DCT ($p > 0,05$) posebno u tri grupe ispitanika.

Zaključak: CCT ima uticaj na IOP izmeren obema metodama: GAT i DCT. DCT ne može da zameni GAT ali može biti jako koristan u slučajevima kada se javljaju greške prilikom merenja IOP GAT metodom.

Ključne reči: Intraokularni pritisak, Pahimetrija, Rožnjača.

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Case report

NEWBORN TREATED WITH CONTINUOUS RENAL REPLACEMENT THERAPY FOR CITRULINEMIA-TYPE 1

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Abstract: **Introduction:** Hyperammonemia occurs as a result of the inability to convert ammonia, a metabolic toxin, into urea due to a block in the urea cycle, and there resulting neurotoxicity is responsible for the pathogenesis.

Case Presentation: Our patient was 7 days old when followed up in an external center for 3 days with a preliminary diagnosis of neonatal sepsis. Lethargy, vomiting, tachypnea, and convulsions, which are frequently seen in the first neonatal forms of urea cycle disorders, were also present in our patient. He was referred to us as a result of high ammonia levels when he was examined in terms of congenital metabolic diseases. He was intubated due to the rapid development of respiratory failure. When he was admitted to our intensive care unit with hyperammonemia, light reflex could not be obtained, and widespread cutis marmaratus was developed. Continuous renal replacement therapy was started in our patient and administered intermittently for 120 hours. The glucose infusion rate was followed by high fluid. When it orally tolerated, it is supported with sodium benzoate and sodium stearyl fumarate to reduce ammonia. Nutrition was limited to protein with Basic P.

Conclusion: After staying in the intensive care unit for 30 days, our patient was discharged with the recommendation of outpatient follow-up by the pediatric metabolism physician. When our patient came for his check up after two months,there was no nystagmus and no seizures.

Keywords: hyperammonemia, newborn, sepsis.

INTRODUCTION

Hyperammonemia, which occurs as a result of the inability to convert ammonia, a metabolic toxin, into urea due to a block in the urea cycle, and there resulting neurotoxicity is responsible for the pathogenesis. Hyperammonemia can be seen due to transient neonatal hyperammonemia, hereditary causes, severe systemic diseases in the newborn, urea cycled effects, fatty acid oxidation disorders, and organic acidemias (1).

Ammonia levels should be requested from the patients who present with the clinic of decreased nutrition, respiratory failure, groaning, vomiting, and sepsis in the neonatal period (2).

In this study, we aimed to present our patient who presented with hyperammonemia, which is one of the metabolic diseases that is frequently confused in the neonatal period, and whose ammonia level was rapidly reduced with continuous renal replacement therapy, and who was diagnosed with Citrullineemia by metabolic panel tests and discharged safely.

CASE REPORT

On the 7th day of his life, our male patient was admitted to our pediatric intensive care unit (PICU) 3 days ago due to the development of respiratory failure during the follow-up of the patient, who was considered to have neonatal sepsis in the external center with complaints of sleepiness, vomiting, and rapid breathing.

We learned that he was followed up prenatally with no issues. He was born at 37 weeks with a cesarean section (C/S) with 3320 grams and was discharged after 24 hours. Parents are first-degree cousins. On PICU admission, his fever was 37.5°C, heart rate was 140 beats/min, blood pressure was 55/30mmHg, respiratory rate was 40 breaths/min, and oxygen saturation was 90% under respiratory support with a mechanical ventilator in pressure control mode. Neither pupil was reactive to light. The patient had decreased hypotony,

weakness, cold extremities, and skin pallor. In his examinations, metabolic alkalosis and lactate elevation were present. Patient's blood pressure (30/20mmHg). Rhythmic tonic-clonic movements were observed in our patient, and levetiracetam was started as an antiepileptic. Ampicillin-cefotaxime intravenous 3x50 mg/kg/dose treatments, which are broad-spectrum antibiotics started with a preliminary diagnosis of sepsis in our patient in another center, were continued.

Hospitalization tests were also noted as Ammonia (µ/dL2102, Lactate dehydrogenase (unit/L) 1712, PRO-BNP (pg/ml) 21392, Aspartate aminotransferase (unit/L) 290, Lactate (mmol/L) 9.4. Table 1 shows the examinations taken on the first day of the patient's hospitalization. A left subclavian hemodialysis catheter was placed in our patient. To initiate continuous renal replacement therapy (CRRT), the circuit was filled with cross-matched blood mixed with isotonic liquid and 5.000 units/L heparin with 30% hematocrit. Our patient's ammonia level was very high, and dialysis was started at the recommended rate of 8.000 ml/h/1.73 m^2 dialysate and replacement fluid. Our dialysis rate decreased according to the follow-ups. DIALİSAN CVVHD BG2D K2 was used as CRRT solution and its electrolyte content was revised according to the patient's electrolyte imbalance and blood gas values. The patient was intubated and followed up with prediagnoses of coagulopathy, respiratory failure, cardiogenic shock due to inotropic need, and sepsis. Adrenaline infusion was started because the patient was hypotensive; Milrinone infusion was started because heart failure was seen on echo; erythrocyte suspension, random thrombocyte, and fresh frozen plasma were given due to anemia, thrombocytopenia, and

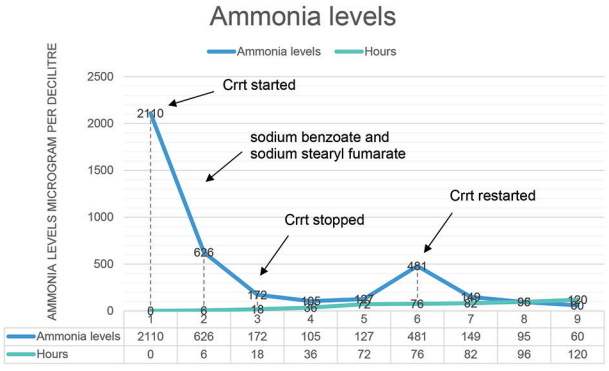

Figure 1. *Serum ammonia levels from the time of admission to the resolution of hyperammonemia. Serum ammonia levels substantially decreased with the addition of CRRT to sodium benzoate and sodium stearyl fumarate. Although both therapies effectively decreased serum ammonia levels, CRRT rate settings in the case were: blood flow of 50 ml/min, dialysate flow of 400 ml/h, and replacement flow of 400 ml/h*

Table 1. *First day of hospitalization (Biochemical and Hematologic Findings of the patient)*

White blood cell (per µL)	18400
Lymphocyte (per µL)	12000
Neutrophil (per µL)	6000
Platelet (per µL)	48.000
Hemoglobin (g/dL)	15
C reactive protein (mg/L)	1
Procalcitonin (ng/mL)	26
Urea (mg/dL)	8,6
Creatinine (mg/dL)	1.34
Aspartate aminotransferase (unit/L)	290
Alanine aminotransferase (unit/L)	162
Lactate dehydrogenase (unit/L)	1712
Ammonia (µg/dL)	2102
pH	7.5
pCO2	23
Lactate (mmol/L)	9,4
HCO3	21
PRO-BNP (pg/ml)	21392
D-dimer (ng/mL)	9.4
APTT (sec)	58
INR	2.99
Fibrinogen	104

increased INR in the tests. Thiamine was administered as 2x100 mg due to high lactate.

The dialysate and replacement fluid flow rate were started at 8000 cc/1.73 m^2/day, and the control 6-hour ammonia value quickly decreased to 626µg/dl. The ammonia levels were reduced to 2000 cc/1.72 m^2/day and dialysis was stopped when ammonia dropped below 60µg/dl. Biochemical parameters and blood gas values were monitored 4 times a day and ammonia level was observed every 6 hours. After 120 h of CRRT, each ammonia level was < 60 µg/dl, and CRRT was stopped. The ammonia values of our patient are shown in Figure 1.

Ammonia levels decreased rapidly with CRRT, and ammonia level was maintained by giving oral sodium benzoate and sodium stearyl fumarates up port and fluids with a high glucose infusion rate.

In their follow-up, he did not need inotropes on the second day; light reflex was acquired, hypotonicity decreased; blood gas values improved; On the 4th day, the patient was extubated.

Enteral nutrition of the patient whose ammonia levels decreased with sodium benzoate, sodium stearyl fumarate, and high dextrose fluid was started on the 5th day as basic-p.

The patient, who was followed up in the intensive care unit for 30 days, developed septicemia and was discharged with the recommendation of a pediatric metabolism physician.

DISCUSSION

It presents with neurological symptoms associated with hyperammonemia in the neonatal period (2). Often, 24-72 hours after feeding, the findings of acute hyperammonemia form is the main clinical picture of the patient. Lethargy, hypotonia, convulsions, coma, feeding difficulties, vomiting, dehydration, hepatomegaly, and hyperammonemia initially cause tachypnea or hyperpnea because it stimulates the respiratory center, followed by apnea and respiratory failure with respiratory center suppression (3). Hyperammonemia is a metabolic emergency and should be considered in the differential diagnosis of sepsis (4). A significant increase is observed between high ammonia levels and mortality in newborns. Unfortunately, hemodialysis in newborns is difficult due to the difficulty of vascular intervention and the High ratio of circulating blood volume to the baby's blood volume in the dialysis setting. At the same time, rebound hyperammonemia was observed after dialysis was stopped in studies, and ammonia increased again in our patient, and the need for dialysis again (5). Respiratory and cardiac failure and cardiac collapse findings developed in our patient.

In the study of Joanna M. Spinale et al., two newborns, 5 and 6 days old, were followed up with hyperammonemia; As in our case, high-dose CRRT treatment was applied, and the ammonia values at the beginning of dialysis were 1454 and 1000 µmol/L, and at the 6th hour of dialysis, the ammonia values decreased below 200 µmol/L. Our patient was 2110 µmol/L at the beginning of dialysis, and it could decrease to 626 µmol/L at the 6th hour of dialysis (6).

In the study of Christopher Markham et al. in 2 newborns with a diagnosis of hyperammonemia, the predialysis ammonia value was 1,382 µg / dl, and although it was reduced below 60 µg / dl at the 10th hour of dialysis, rebound hyperammonemia developed after dialysis was terminated, just like in our case. The family decided to redirect her goals of care to comfort measures and the patient died the next day. Her diagnostic postmortem work-up revealed a diagnosis of citrullinemia. In other cases, the initial ammonia value was 623 µg/dl, metabolic acidosis was present in the blood gas, and at the 15th hour, the ammonia value was reduced below 100 µg/dl and he was discharged with the diagnosis of organic acidemia. Although the ammonia level was still measured as 186 µg/dl at the 15th hour of our patient, the initial ammonia values were lower in both cases than in our case.

CONCLUSION

After 120 h of dialysis, each ammonia level was <60 µg/dl and CRRT was stopped. Ammonia levels decreased rapidly with dialysis, and ammonia level was maintained by giving oral sodium benzoate and sodium stearyl fumarate support and fluids with a high glucose infusion rate. The urea cycled effect was considered in the foreground because of the absence of acidosis in the blood gas of our patient and the high result of the serum amino acid citrulline level. The patient who became neurologically active was discharged after 30 days of intensive care hospitalization, and his treatments were arranged. When our patient came for the control in the 2nd month of his life, it was observed that he had head control. There was no nystagmus and no seizures.

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Conflict of Interests: The authors declare no conflicts of interest related to this article.

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Data Availability State

All patient data are stored in our hospital's data recording system.

Availability of data and material: The authors approve that all the necessary papers regarding this report can be offered upon request.

Consent to participate: Informed consent form for approved participation was obtained from the parents.

Consent for publication: Informed consent form for approved participation was obtained from the parents.

Author contributions

The manuscript has been read and approved by all the authors.

Licensing

Sažetak

NOVOROĐENČE LEČENO KONTINUIRANOM TERAPIJOM ZAMENE BUBREŽNE FUNKCIJE ZA CITRULINEMIJU-TIP 1

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Uvod: Hiperamonijemija nastaje kao rezultat nemogućnosti pretvaranja amonijaka, metaboličkog toksina, u ureu zbog blokade u ciklusu uree, a nastala neurotoksičnost je odgovorna za patogenezu.

Prikaz slučaja: Naš pacijent je imao 7 dana kada je bio praćen u drugom centru 3 dana sa preliminarnom dijagnozom neonatalne sepse. Letargija, povraćanje, tahipneja i konvulzije, koji se često javljaju kod prvih neonatalnih oblika poremećaja ciklusa ureje, takođe su bili prisutni kod našeg pacijenta. Kod nas je upućen zbog visokog nivoa amonijaka otkrivenog u sklopu pregleda zbog urođenih metaboličkih bolesti. Intubiran je zbog brzog razvoja respiratorne insuficijencije. Kada je primljen na naše odeljenje intenzivne nege sa hiperamonijemijom, nije mogao da se dobije svetlosni refleks uz razvijene promene na koži po tipu cutis marmorata.

Kod našeg pacijenta je započeta kontinuirana terapija zamene bubrežne funkcije i primenjivana je sa prekidima tokom 120 sati. Brzina infuzije glukoze je praćena visokim nivoom tečnosti. Kada se toleriše oralno, podržava se natrijum benzoatom i natrijum stearil fumaratom kako bi se smanjio nivo amonijaka. Ishrana je bila ograničena na protein.

Zaključak: Nakon 30 dana boravka na odeljenju intenzivne nege, pacijent je otpušten uz preporuku ambulantnog praćenja od stane pedijatra. Na kontrolnom pregledu posle 2 meseca, pacijent je bio bez nistagmusa i epi napada.

Ključne reči: hiperamonijemija, novorođenče, sepsa.

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Case report

METASTASIS OF SUBMANDIBULAR ADENOID CYSTIC CARCINOMA TO THE FEMUR BONE CAUSING PATHOLOGICAL FRACTURE: A CASE REPORT

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Abstract: **Introduction:** Adenoid cystic carcinoma (ACC) is a rare head and neck malignancy and is likely to be diagnosed in the major salivary glands. It's also known for its slow clinical course and prolonged survival unless no distant metastasis occurs. Even after a long period from the detection of the primary tumor, metastasis to the lung, brain, liver, and bone has a tendency to occur.

Case presentation: We report a 53-year-old man who presented with a pathological femur fracture thirteen years after the presentation of submandibular ACC. Our patient reported an improved patient-reported outcome after undergoing resection hemiarthroplasty for his bone metastasis.

Conclusion: We tried to accentuate the importance of periodical visits for the probability of distant metastasis and the work-up if it's necessary in such a rare case. It should be kept in mind that proper management of bone metastasis may lead to improvements in the quality of life.

Keywords: Adenoid cystic carcinoma, submandibular gland, bone metastasis, pathological fracture, femur.

INTRODUCTION

Adenoid cystic carcinoma (ACC) is known for a tenacious and recurrent growth pattern with an aggressive long-term course and also late-onset distant metastasis. Besides being an infrequent tumor that accounts for about 1% of all head and neck malignancies, it is common for the major salivary glands, and the most likely location is the submandibular gland (1). It's considered a high-grade neoplasm, and radical surgical resection with postoperative radiotherapy is chosen for treatment mostly.

ACC has a characteristic pattern that is a long period to metastasis after initial diagnosis with or without locoregional recurrence. Distant metastasis is often detected in the lungs, followed by bone, brain, and liver (2). We present a rare case in which metastasis to the femur bone from the submandibular ACC causes a pathological fracture as a first sign. Bone metastasis of the ACC of the major salivary glands has not been extensively discussed in the literature, and the management of these patients is indefinite. Consequently, improvements in the quality of life for our patients were obtained with proper patient management and orthopedic surgery.

CASE REPORT

A 53-year-old man underwent surgery for a left submandibular gland origin mass thirteen years ago. At the time, he had no other symptoms or complaints. Also, there was no other distant metastasis on 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) along with computed tomography (CT) scan. Once a diagnostic work-up was completed, after immediate removal of the mass, the results of the histopathological evaluation revealed adenoid cystic carcinoma (ACC). He then received adjuvant radiotherapy.

He presented to the emergency department with a left intertrochanteric fracture after falling from a standing position - low-energy trauma - a year and a half ago (Figure 1). After deepening the anamnesis, we learned that the patient had non-restrictive pain localized to his left hip area for about two or three years until a fracture occurred. He was treated with a Dynamic Hip Screw (DHS) plate for his misdiagnosed potential pathological fracture, and no other investigation for the possibility of metastasis was made. During his early follow-up, he was able to walk with no restrictions and no use of aids. Even though his fracture seemed to

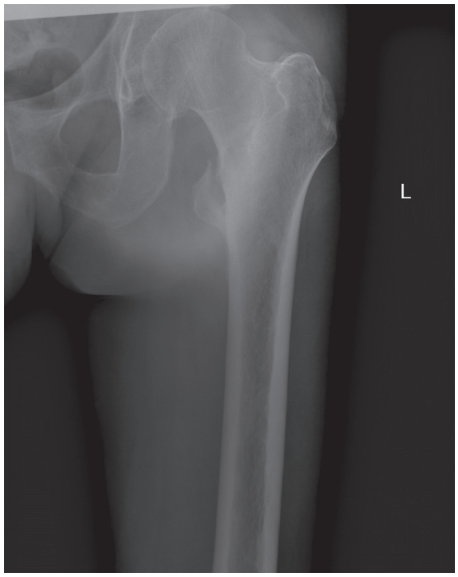

Figure 1. *Anteroposterior radiograph of the left thigh shows an intertrochanteric femur fracture with lesser tubercle avulsion*

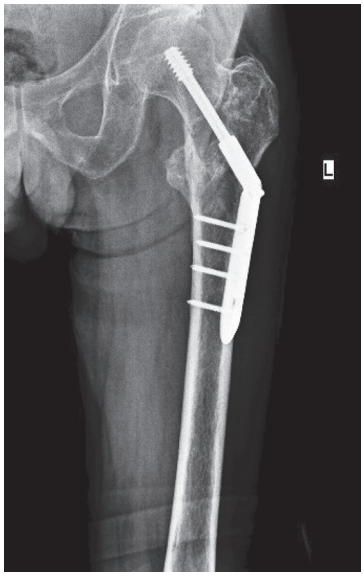

Figure 2. *Anteroposterior radiograph of the left thigh shows an appearance one year after surgery of the femur treated with a Dynamic Hip Screw (DHS) plate*

be unioned at the end of one year (Figure 2), he complained of persistent pain localized to his left proximal thigh, aggravated with motion and walking. Radiographs of the left femur showed a suspicious lytic lesion located near the lesser trochanter, which indicated the possibility of metastasis. For further investigation, CT and MRI studies were conducted on his left thigh (Figure 3 a, b, c, d).

After applying a closed bone biopsy, an 18F-FDG PET-CT scan showed multiple bone metastases and pulmonary nodules but no evidence of locoregional recurrence. Because of the pathologic fracture and

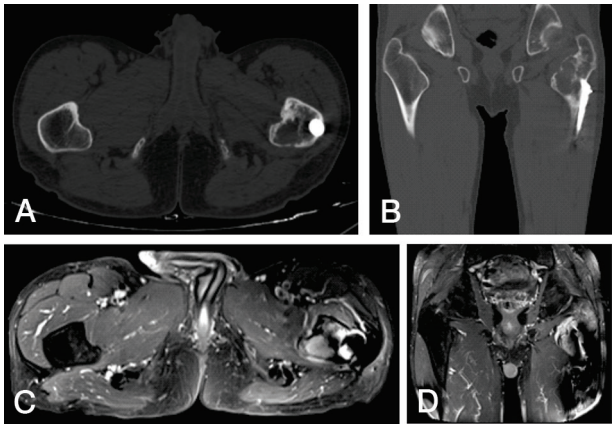

Figure 3. *Axial (A) and coronal (B) computerized tomography of the thigh shows a lytic lesion originating from the left lesser tubercle. Axial (C) and coronal (D) magnetic resonance imaging of the thigh also shows a mass arising from the left lesser tubercle that extends adjacent soft tissue*

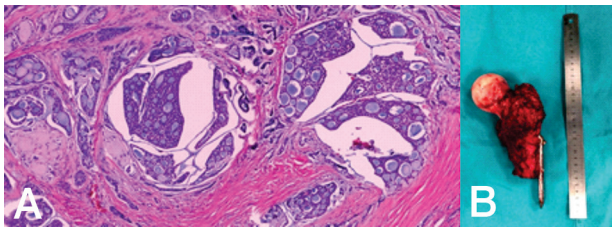

Figure 4. *(a) Histological image of the adenoid cystic carcinoma in the left proximal femur (hematoxylin and eosin X 200). (b) Surgical resection material of the left proximal femur*

persistent pain risk, the patient underwent left femoral resection hemiarthroplasty after histopathological examination of the biopsy material confirmed ACC metastasis (Figure 4 a, b). The patient was informed, and written consent was obtained.

DISCUSSION AND CONCLUSION

ACC is a rare tumor reported with a yearly 3–4.5 cases per million, accounting for 1% of all head and neck malignancies and 10% of salivary gland tumors (1). It's also known for being commonly detected in major salivary glands. ACC is much more likely to be diagnosed in the submandibular gland, which accounts for 40% of salivary gland cancers (1).

ACC is known for having a slow biological and clinical course but is an expanding and infiltrative malignancy. Authors reported that five-year survival was favorable (75%–80%), contrary survival for fifteen-twenty years was poor (10%–30%) (2). This poor survival in long term was related to insufficiency in preventing and controlling distant metastasis. Happening of distant metastasis in the earlier stage of tu-

mor growth is possible even if cured of the primary tumor in 33% of patients (2). Also, it might be seen even without the recurrence of the primary region. Our patient presented with metastasis to the bone about thirteen years after the treatment for submandibular ACC was completed. Previous studies reported that the mean time for distant metastasis is between 32 and 46 months, with a rate of 20 to 52% (2). Distant metastasis usually occurs within 5 years after treatment, but even fifteen years later, some reported (3). However, distant metastases are independent diseases and should be evaluated differently from local treatment outcomes.

Because a distant metastasis had occurred, we conducted radiological exams to detect other possible distant metastasis in case it was asymptomatic. Eventually, the 18F-FDG PET-CT scan showed that the patient had multiple metastatic pulmonary nodules and multiple bone metastases in addition to the left intertrochanteric region. Previous literature has indicated that mostly lungs, followed by bones, and less often liver and brain are the sites of distant metastasis additionally multiple metastatic sites are seen in many patients (2). Some authors suggested that previously reported incidences of distant metastasis rate to other sites, such as bone had likely higher because after a lung metastasis was seen, no additional diagnostic examinations were made (1).

There are few studies reported on bone metastasis of submandibular ACC (4, 5, 6). Two studies reported that a 52-year-old man and a 62-year-old woman had metastasis to the left great toe seven and eight years after diagnosis of submandibular ACC (4, 6). In the other case, a 54-year-old woman had multiple bone metastasis to vertebrae from surgically resected submandibular ACC (5). The patients whose metastasis to the great toe were treated with orthopedic surgery like amputation, but the patient who had metastasis to the vertebrae was treated with oral steroid therapy and decompressive palliative radiotherapy.

If a pathological fracture is evaluated as a benign fracture, it could be treated and managed like so. Finally, it results in delays in the diagnosis of malignancy (7). In this case, radiological studies showed a left intertrochanteric fracture with a lesser trochanter fracture at the patient's first emergency admission. After he was treated like it was not pathological, his fracture healed partially at the last follow-up visit. Around the fracture including the lesser trochanter, cortical bridges extended one side to another bone segment that indicated union. But after a long period of follow-ups, it was accepted as a delayed union based on the lytic lesion localized to the intertrochanteric region congruent with his persistent pain.

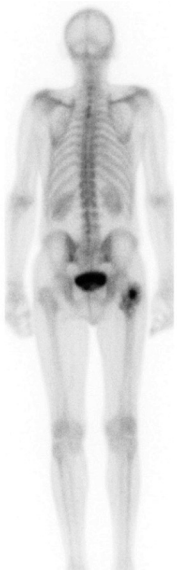

Figure 5. *Total body bone scan shows increased uptake from the left intertrochanteric femoral region*

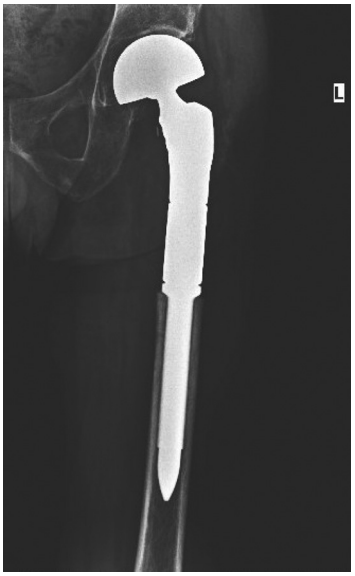

Figure 6. *A proximal femoral endoprosthesis was used to reconstruct the bone defect*

Periodical assessments are needed because of the clinical manner of ACC with late distant metastasis. While CT or MRI is recommended in the diagnostic control of the primary site for locoregional recurrence, a conventional radiograph of the chest is recommended at least annually or every two years in the detection of distant metastases (3). Accordingly, we advocated that such patients who had salivary gland origin ACC history, specifically those who have complaints regarding bone, should be examined with radiographic studies for the related areas to identify distant metastases. A simple bone scan could show the pathological uptake and could lead us to a diagnosis of metastasis (Figure 5).

Concerning this rare clinical case, prosthetic reconstruction gives the patient a chance for early weight-bearing and faster functional rehab if the patient has a satisfactory general condition but has no efficacious adjuvant treatments available (8) (Figure 6). Our patient, who underwent proximal femoral endoprosthesis replacement after resection, could walk with full weight bearing on the first postoperative day and be discharged on the third postoperative day. The patient reported substantial improvements in activities of daily living on the third-month follow-up visit with no use of crutches to walk or without restrictive pain.

Our present case is distinguished and makes additions from the previously reported ones in a few ways. It is the first reported case that presented with pathological femur fracture due to submandibular ACC metastasis and one of the longest intervals to distant metastasis by thirteen years after initial diagnosis. In parallel with the previous literature, our case implied that there is a predilection for distant metastasis from submandibular ACC and bone, one of the main sites should therefore be kept in mind.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, KB, upon reasonable request.

Licensing

Sažetak

METASTAZA SUBMANDIBULARNOG ADENOIDNOG CISTIČNOG KARCINOMA NA FEMURU KAO UZROK PATOLOŠKOG PRELOMA: PRIKAZ SLUČAJA

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Uvod: Adenoidni cistični karcinom (ACC) je retka maligna bolest glave i vrata i najčešće se dijagnostikuje u pljuvačnim žlezdama. Takođe je poznat po sporom kliničkom toku i produženom preživljavanju osim ako ne dođe do udaljenih metastaza. Čak i nakon dužeg perioda od otkrivanja primarnog tumora, metastaze u plućima, mozgu, jetri i kostima imaju tendenciju da se pojave.

Prikaz slučaja: Predstavljamo 53-godišnjeg muškarca koji se javio s patološkim prelomom femura trinaest godina nakon pojave submandibularnog ACC. Naš pacijent je prijavio poboljšani ishod nakon resekcione hemiartroplastike zbog metastaza u kostima.

Zaključak: Pokušali smo da istaknemo važnost periodičnih pregleda zbog verovatnoće udaljenih metastaza i obrada ukoliko je to neophodno u tako retkim slučajevima. Treba imati na umu da pravilno lečenje koštanih metastaza može dovesti do poboljšanja kvaliteta života.

Ključne reči: adenoidno cistični karcinom, submandibularna žlezda, koštane metastaze, patološki prelom, femur.

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Case report

CONGENITAL AFIBRINOGENEMIA IN A NEWBORN

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Abstract: **Introduction:** Congenital afibrinogenemia is a rare coagulation disorder characterized by a deficiency in the fibrinogen molecule. Fibrinogen is a hexameric glycoprotein consisting of a polypeptide chain encoded by FGB, FGA, and FGG and is required for normal hemostasis. Changes in FGA, FGB, and FGG may affect fibrinogen at different levels. As a result of these changes, fibrinogen cannot be detected in the blood. Clinical manifestations of such changes range from asymptomatic to life-threatening bleeding or thromboembolic events. Since it is an autosomal recessive disease, the risk is higher in children whose parents are related. Therefore, the disease is more common in regions where consanguineous marriage rates are high. Diagnosis is made by laboratory tests that show the absence of fibrinogen. These patients need to be treated with fibrinogen replacement therapy.

Case presentation: This study reports the case of a newborn with congenital afibrinogenemia. The baby born from a first-degree consanguineous marriage was referred to our hospital due to bleeding and ecchymosis, and afibrinogenemia was diagnosed after coagulation tests were performed. Blood samples of the patient and his parents were sent to the Genetic Diseases Diagnosis Center for a genetic diagnosis of afibrinogenemia. A new homozygous mutation of FGB exon 7: c.1220c > t (p.t407 m) (p.thr407 met) was identified in the patient. The patients' parents were heterozygous for the same mutation. Prophylaxis was not recommended for our patient who was asymptomatic in the follow-up.

Conclusions: We present the case of a hemorrhagic neonatal patient diagnosed with congenital afibrinogenemia and emphasize that fibrinogen testing should be included in the evaluation of such patients. Furthermore, congenital fibrinogen disorders may be more severe when caused due to unknown specific mutation genes. Therefore, a more center-involved genetic analysis is required to identify undiagnosed fibrinogen and fibrinogen mutations.

Keywords: Congenital Afibrinogenemia, Fibrinogen Beta Chain, Newborn.

INTRODUCTION

Congenital afibrinogenemia is a rare hematological disorder in which fibrinogen (factor I) is absent, and the patient has a tendency to bleed. It is an autosomal recessive disorder in which most patients have a history of consanguineous marriage (1). The severity of bleeding varies among patients with afibrinogenemia. The most common symptom was umbilical cord bleeding. Hemarthrosis, hematoma, and mucosal bleeding are the other types of bleeding (2).

Congenital afibrinogenemia is an autosomal recessive disease described in 1920. More than 150 cases have been reported in the literature to date. The genes responsible for this disease are located on chromosome 4 (q26-q28) and are associated with different mutations (3). So far, more than 250 mutations have been reported in online databases. A total of 1215 mutations were reported in 2016, including 626 α, 154 β, and 435 γ (http://site.geht.org/base-fibrinogene/).

In the present study, a newborn with a new homozygous mutation of FGB c.1220c > t (p.t407 m) (p.thr407 met) has been presented.

CASE REPORT

The baby was born from a consanguineous marriage by normal spontaneous vaginal delivery at a gestational age of 39 weeks and 3 days and was referred to our hospital because of ecchymosis and bleeding at the blood draw sites. The baby appeared healthy and had normal vital signs. His body weight was 3650 g (75–90p), length was 52 cm (90p), and head circumference was 35 cm (90p). Bleeding and ecchymosis were observed in the form of vascular access and injection site leakage in the arms and legs. Other ex-

amination findings were normal. History revealed no specific disease in the mother, drug use history during and before pregnancy, and no family history of similar diseases. Initial laboratory findings revealed hemoglobin of 15.5 g/dl, white blood cell of 18 000/µl, and platelet count of 220 000/µl. Prothrombin time (PT) (out of range, upper limit,16 s), pt/international normalized ratio (INR) (out of range, upper limit, 1.3), activated partial thromboplastin time (PTT) (out of range, upper limit, 35 s), and thrombin time (outside range, upper limit, 21 s). Liver and kidney function test results were normal. No evidence of hemolysis, infection, or thrombocytopenia was observed in the peripheral blood smear. The values were normal in biochemical analyses. Abdominal and cranial ultrasound findings were normal. Fresh frozen plasma (FFP) was administered to the patient, and bleeding in the form of leakage decreased. The patient's fibrinogen level was < 20 mg/dl (245–400 mg/dl). The mother's fibrinogen level was 256 mg/dl, PT was 15 s, aPTT was 28.6 s, and INR was 1.15, whereas the father's fibrinogen level was 118mg/dl, PT was 15 s, aPTT was 28.4 s, and INR was 1.17. After a definitive diagnosis, fibrinogen concentrate was administered. The test results after fibrinogen concentrate administration were as follows: PT of 14s, INR of 1, and PTT of 26s.

Blood samples taken from our patient and his family were sent to the Genetic Diseases Diagnostic Center for genetic analysis. FGB exon 7: c.1220c > t (p.t407 m) (p.thr407 met) homozygous mutation was detected in our patient. To our knowledge, this mutation has not been identified before and the parents were found to be heterozygous for the mutation.

The child was recommended vaccination following the schedule with special precautions in the use of small-diameter needles and the application of adequate pressure after injections. Our patient was told to apply to us in cases of trauma or surgery and never to use drugs that increase bleeding tendency. Vaccination was carried out in accordance with the vaccination schedule in our country. Prophylaxis was not recommended for our patient who was asymptomatic in the follow-up.

DISCUSSION

Congenital afibrinogenemia is characterized by the absence or very low levels of fibrinogen in the plasma. Partial fibrinogen deficiency (hypofibrinogenemia) is a more benign disease than afibrinogenemia. While afibrinogenemia mostly occurs in homozygous conditions, hypofibrinogenemia occurs in heterozygous conditions (4). In the genetic examination of our patient, homozygous change in the fibrinogen beta chain (FGB) gene, c.1220c > t (p.t407 m) (p.thr407 met) was detected. The FGB gene in our patient's parents was c.1220c > t (p.t407m) (p.thr407met), and a heterozygous change was detected. The relationship between the detected change and the disease has not been previously reported.

Patients with afibrinogenemia have undetectable fibrinogen levels < 10 mg/dl(200–400 mg/dl). Without consumptive coagulopathy, unmeasured fibrinogen levels diagnose afibrinogenemia (5). Bleeding may occur in patients with a fibrinogen level of < 50 mg/dl (6). According to Lak et al. 45 (85%) out of the 55 patients with congenital afibrinogenemia presented with umbilical cord bleeding (2). The fibrinogen level of our patient was < 20 mg/dl, and fresh bleeding was noticed in the places where the vascular access was opened.

The primary treatment for fibrinogen disorders is human fibrinogen concentrate. In patients with fibrinogen disorders, the target fibrinogen level is 100 mg/dl for treating minor bleeding, while the target is 150 mg/dl in patients with major bleeding (6, 7). Five fibrinogen concentrates are commercially available. In the absence of fibrinogen-containing drugs, cryoprecipitate or FFP can be administered as an emergency alternative (8). Fibrinogen concentrate was used for treating our patient, and the bleeding stopped after its infusion.

Various measures have been proposed to prevent spontaneous bleeding in patients with congenital afibrinogenemia. Weekly infusion prophylaxis is a generally accepted regimen, but monthly or biweekly infusion prophylaxis has also been used (9). Prophylaxis is not recommended in patients without spontaneous bleeding due to the high risk of blood-borne diseases, allergic reactions, and thrombotic complications. Secondary fibrinogen prophylaxis should be started after the first life-threatening bleeding event in patients with afibrinogenemia, and the target fibrinogen level should be 50mg/dl during prophylaxis (5). We did not recommend prophylaxis because our patient did not experience spontaneous bleeding during the follow-up.

In summary, prenatal diagnosis or preimplantation genetic diagnosis can help prevent disease recurrence in pedigrees. In patients experiencing bleeding from any part of the body, afibrinogenemia should be considered in the preliminary diagnosis. This case highlights the importance of testing fibrinogen levels in newborns with bleeding. Congenital fibrinogen disorders have been reported worldwide but may be higher with unknown specific mutation genes. Therefore, genetic analysis involving more centers is required to identify undiagnosed fibrinogen and fibrinogen mutations.

Abbreviations

FFP — Fresh frozen plasma
FGB — Fibrinogen beta chain
INR — International normalized ratio
PT — Prothrombin time
PTT — Partial thromboplastin time

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Licensing

Sažetak

KONGENITALNA AFIBRINOGENEMIJA KOD NOVOROĐENČETA

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Uvod: Kongenitalna afibrinogenemija je redak poremećaj koagulacije koji karakteriše nedostatak molekula fibrinogena. Fibrinogen je heksamerni glikoprotein koji se sastoji od polipeptidnog lanca kodiranog sa FGB, FGA i FGG i neophodan je za normalnu hemostazu. Promene u FGA, FGB i FGG mogu uticati na fibrinogen na različitim nivoima. Kao rezultat ovih promena, fibrinogen se ne može otkriti u krvi. Kliničke manifestacije takvih promena kreću se od asimptomatskih do životno opasnih krvarenja ili tromboembolijskih događaja. Pošto se radi o autozomno recesivnoj bolesti, rizik je veći kod dece čiji su roditelji u srodstvu. Zbog toga je bolest češća u regionima u kojima je visoka stopa brakova u srodstvu. Dijagnoza se postavlja laboratorijskim testovima koji pokazuju odsustvo fibrinogena. Ovi pacijenti moraju biti lečeni zamenom fibrinogena.

Prikaz slučaja: Ova studija prikazuje slučaj novorođenčeta sa urođenom afibrinogenemijom. Beba rođena iz prvostepenog krvnog braka upućena je u našu bolnicu zbog krvarenja i ekhimoze, a afibrinogenemija je dijagnostikovana nakon urađenih testova koagulacije. Uzorci krvi pacijenta i njegovih roditelja poslati su u Centar za dijagnostiku genetskih bolesti na genetsku dijagnozu afibrinogenemije. Kod pacijenta je identifikovana nova homozigotna mutacija FGB eksona 7: c.1220c > t (p.t407 m) (p.thr407 met). Roditelji pacijenta su bili heterozigoti iz iste mutacije. Profilaksa nije preporučena za našeg pacijenta koji je bio asimptomatski u periodu praćenja nakon što je dijagnostikovan poremećaj.

Zaključci: Predstavljamo slučaj hemoragičnog novorođenčeta sa dijagnozom kongenitalne afibrinogenemije i naglašavamo da ispitivanje fibrinogena treba da bude uključeno u evaluaciju takvih pacijenata. Štaviše, kongenitalni poremećaji fibrinogena mogu biti teži kada su uzrokovani nepoznatim specifičnim mutacijskim genima. Stoga je potrebna centralno orijentisana genetska analiza kako bi se identifikovali nedijagnostikovani fibrinogeni i mutacije fibrinogena.

Ključne reči: kongenitalna afibrinogenemija, beta lanac fibrinogena, novorođenče.

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Case report

EVALUATION OF A GIRL WITH 16p13.11 MICRODUPLICATION SYNDROME ACCORDING TO THE INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH PERSPECTIVES

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Abstract: **Objective:** To present the functional status of a child with 16p13.11 microduplication syndrome by evaluating it under the International Classification of the World Health Organization's International Framework for Functioning, Disability and Health (ICF).

Case Description: An 11-year-old girl with 16p13.11 microduplication syndrome was assessed using the tools classified according to ICF for Children and Youth (ICF-CY) categories to evaluate body function, activity participation, and environmental factors.There was a wide range of problems, from body functions to activity participation and environmental factors. Besides these problems, there were social and cognitive disorders as well.

Conclusion: Physical and cognitive problems in body function and activity together constitute great barriers to participation in daily life.

Keywords: 16p13.11 microduplication syndrome, ICF, activity, participation**,** environmental factors.

INTRODUCTION

16p13.11 microduplication syndrome is a rare chromosomal disorder associated with copy number variation on chromosome 16p13.11 locus (1). It is characterized by intellectual disability, behavioral disorders such as attention-deficit/hyperactivity, and an autism spectrum disorder. Other neurodevelopmental impairments include feeding disorder, gross motor retardation, and seizure (1). The daily activities of children with this syndrome are generally adversely affected (2). Motor activities such as rolling, walking, and sitting may take longer to develop in these children. Children with this syndrome generally receive physical therapy (3). In addition, studies have shown that some children with this syndrome have speech delay, limited use of language, and repetitive speech (3). Fine motor skills, like grasping toys and holding a bottle have also been found to be affected (2). There are studies in the literature on children with 16p13.11 microduplication syndrome, but there is no evaluation made according to the ICF approach (4, 5).

CASE REPORT

An 11-year-old girl presented to our Pediatric Neurology outpatient clinic with an intellectual disability and seizures. First parental concerns in terms of developmental milestones were noticed at the age of 8 months when she couldn't hold her head. She could control her head and sit with and without support at 8 months, 12 months, and 24 months, respectively. She was able to transfer objects from one hand to another at the age of 6 years when she also began to stand up from the floor with support. The family noted stereotypical hand movements for the last 3 years. Purposeful hand movements were not age-appropriate and complicated with task-oriented fine-motor activities. Further, she began to have seizures during sleep with sudden laughing and shouting attacks lasting up to 3 hours. During the last years, stereotypical movements, obsessive-compulsive behavior, hand clapping, and biting became prominent while the seizure frequency subsequently decreased. She was able to sit independently; however, she could not walk by herself.

She had a spastic diplegic gait with support. She had no verbal output and did not respond to her name. In general, it was observed that the patient was highly dependent on the family in activities of daily living.

The patient presented to the genetic department when she was 6.5 years old. She had features reminiscent of Rett syndromes, such as hyperventilation episodes, postural abnormalities, stereotypical hand movements, teeth-grinding, sudden laughing and screaming attacks, task-related postural and intentional tremors, and insensitivity to pain.

After the patient's mother had been informed, the family agreed to involve her in the research, and her mother allowed us to evaluate the child.

Assessment

The evaluation was made via the Zoom program as a tele-assessment due to the current pandemic conditions. To evaluate this child, we decided on assessment tools, then categorized these tools according to the International Classification of Functioning, Disability, and Health- Children and Young major categories (Table 1).

Assessment Tools

Visual Analog Scale (VAS): The VAS was used to assess the child's pain level (6).

Viking Speech Scale (VSS): The VSS was used to evaluate the child's speech (7).

Gross Motor Function Measurement- 88 (GMFM-88): GMFM-88 was used to assess gross motor function (8).

Pediatric Evaluation of Disability Inventory (PEDI): PEDI was used to assess the child's activities and participation in daily living (8).

Eating Drinking Ability Classification System (EDACS): EDACS was used to assess the child's eating and drinking level (8).

European Child Environment Questionnaire (ECEQ): The ECEQ was used to assess factors in the child's environment (8).

RESULTS

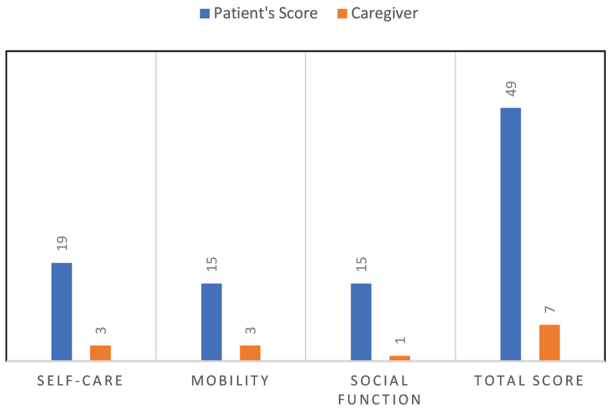
Body Function

The child's pain level was 4 out of 10 according to **VAS,** and it did not affect her daily life. It was also observed that the patient had a severe impairment in intellectual function. However, in general, she is also interacted in the environment. Since the child had severe personal-social effects and autistic findings, her reaction to the environment was limited, and she did not return when called by her name.

Activity and Participation

According to the **VSS** performed to evaluate speech, her level was at level IV. At this level, the child does not have intelligible speech.

In the **GMFM-88** evaluation, only the sitting, standing, walking, running, and jumping sections were evaluated. Scores from these sections were determined and converted to percentages. According to the evaluation, the highest score was in the sitting section, while the lowest score was in standing. However, it



GMFM	Sitting	Standing	Walking, Running, Climbing	Total
Score	36	7	8	18.3
Percentage Score	%60	%17,9	%11,11	%26,703

Figure 1. *The GMFM-88 and PEDI scores of the child*

Table 1. *Assessment tools categorized by ICF-CY major categories*

Body Function	Activity and Participation	Environmental Factors
VAS	**VSS**	ECEQ
Modified Hoehn & Yahr Scale	**GMFM-88**	
	PEDI	
	EDACS	

VAS, Visuel Analog Scale; VSS, Viking Speech Scale; ECEQ, European Child Environment Questionnaire; GMFM-88; Gross Motor Function Measurement-88; PEDI, Pediatric Evaluation of Disability Inventory; EDACS, Eating Drinking Ability Classification System

Table 2. *Codes, qualifiers, and assessment methods of body functions, activities, participation, and environmental factors*

Body Functions (b)	Codes	Qualifiers	Assessment Methods
	b117.3	Intellectual functions	Observational
	b280.2	Sensation of pain	VAS
Activity and Participation (d)	Codes	Qualifiers	Assessment Methods
	d330.4	Speaking	VSS
	d4103.1	Sitting	GMFM-88
	d4104.2	Standing	GMFM-88
	d4158.1	Maintaining the sitting position	GMFM-88
	d4154.2	Maintaining the standing posture	GMFM-88
	d4301.3	Move objects by hand	PEDI
	d4400.3	Holding objects	PEDI
	d4401.3	Grasp	PEDI
	d4403.3	Drop an object	PEDI
	d4450.3	Pushing an object	PEDI
	d4452.3	Reach an object	PEDI
	d4500.2	Walking a short distance	GMFM-88
	d4552.4	Running	GMFM-88
	d4600.3	Getting around the house	PEDI
	d5100.3	Washing body parts	PEDI
	d5201.3	Dental care	PEDI
	d5300.3	Regulation of urination	PEDI
	d5400.3	Wearing clothes	PEDI
	d550.2	Eating	EDACS
	d560.2	Drinking	EDACS
	d7601.2	Child-parent relationship	PEDI
Environmental Factors (s)	Codes	Qualifiers	Assessment Method
	e1150+2	Auxiliary products and technology for personal use in daily life	ECEQ
	e1201+2	Auxiliary products and technology for personal use in mobility and transport inside and outside the home	ECEQ
	e1251+2	Auxiliary products and technology for communication	ECEQ
	e1301+1	Auxiliary products and technology for education	ECEQ
	e1500+2	Design, construction, and construction products, and technology for the entrance and exit of public buildings	ECEQ
	e1501+2	Design, building, and construction products and technology to increase the facilities inside public buildings	ECEQ
	e310+3	Close family	ECEQ
	e340+1	Personal caregivers and personal helpers	ECEQ
	e460.2	Social attitude	ECEQ
	e5880+1	Health service	ECEQ
	e5801+2	Health systems	ECEQ
	e5802+2	Health policies	ECEQ
	e5850+2	Education and training services	ECEQ
	e5851+2	Education and training systems	ECEQ
	e5852+2	Education and training policies	ECEQ

VAS, Visual Analog Scale; VSS, Viking Speech Scale; GMFM-88, Gross Motor Function Measurement-88; PEDI, Pediatric Evaluation of Disability Inventory; EDACS, Eating Drinking Ability Classification System; ECEQ, European Child Environment Questionnaire

was found that the lowest percentage score was in the walking, running, and climbing sections (GMFM-88 and PEDI scores are shown in the figures below).

The total score for **PEDI** including self-care, mobility, and social function was 49, while the total score for caregiver-assisted was 7. According to the results of this scale, we see that the child was insufficient to do her daily activities on her own, and at the same time, she was mostly dependent on her mother to do these activities.

The patients eating and drinking skills were determined as level III according to **EDACS.** This means that the child eats and drinks with limitations in terms of safety, and some limitations in effectiveness might exist.

Environmental Factors

Environmental factors were evaluated as facilitators or barriers. According to **the ECEQ,** education and training services, accessibility of public buildings, income level of family, individual attitudes of immediate family members, auxiliary products, health systems, and policies were facilitators, whereas unfamiliar people, cognitive problems, and social attitudes were barriers.

DISCUSSION

This study aimed to evaluate the child with 16p13.11 microduplication syndrome according to the ICF approach. During this process, not only the patient's body function but also the social function of the person was taken into consideration. It is difficult to be objective and cooperate with the patient in the evaluations because autistic findings, intellectual disability, and personal-social areas are affected in this child. Different assessment tools were applied to the patient considering various factors.

Gross motor skills are an indispensable part of the activity, and motor impairments adversely affect participation in daily life. Considering the child's activity, she could sit and stand on her own but could not walk or run independently and could not go up and down stairs. It was also noticed that she could not communicate effectively and could not eat or drink alone. In studies conducted in children with this syndrome, it has been determined that there are developmental, cognitive, behavioral, and intellectual problems just like in our study (1-7).

Participation is a considerable element and emerges as a result of the interaction between body functions, structures, activities, and environmental factors. Participation in daily activities contributes to the development of children with and without disabilities and has a crucial relationship with health and well-being. In our study, it was observed that the child was highly dependent on her mother for her activities in daily life. Being dependent on family or environment in daily life can be considered the most important problem in front of participation.

The ICF includes environmental factors such as recognition of the important role of the environment in people's functioning. These factors can be from physical factors to social factors. Interaction with environmental factors is an essential aspect of the scientific understanding of 'functioning and disability. In this study, ECEQ was used to evaluate the effectiveness of environmental factors. The social attitude was a barrier for the child, while the accessibility of the structures within the society was a facilitator. Whereas the child's parents were satisfied with the education given to the child at school, they thought the social assistance provided to them was not sufficient.

In conclusion, this child with 16p13.11 microduplication syndrome serves as an example to demonstrate the difficulties in a comprehensive evaluation of patients affected with various symptoms, including autistic features, intellectual disability, seizures, and stereotypical movements in combination under the heading of neurodevelopmental disorders.

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Sažetak

EVALUACIJA DEVOJČICE SA SINDROMOM MIKRODUPLIKACIJE 16p13.11 PREMA MEĐUNARODNOJ KLASIFIKACIJI FUNKCIONISANJA, NESPOSOBNOSTI I ZDRAVLJA

Cilj: Prikaz procene funkcionalnog statusa deteta sa 16p13.11 mikroduplikacionim sindromom prema međunarodnoj klasifikaciji Međunarodnog okvira za funkcionisanje, nesposobnosti i zdravlja (ICF) Svetske zdravstvene organizacije.

Prikaz slučaja: Jedanaestogodišnja devojčica sa sindromom mikroduplikacije 16p13.11 je pregledana korišćenjem instrumenata klasifikovanih prema kategorijama MKF za decu i omladinu (ICF-CI) za procenu funkcije tela, učešća u aktivnostima i faktora okoline. Postojao je širok dijapazon problema, od telesnih funkcija do učešća u aktivnostima i faktora okoline. Pored ovih problema, postojali su i socijalni i kognitivni poremećaji.

Zaključak: Fizički i kognitivni problemi u funkcionisanju i aktivnosti tela zajedno predstavljaju velike prepreke za učešće u svakodnevnom životu.

Ključne reči: 16p13.11 sindrom mikroduplikacije, ICF, aktivnost, učešće, faktori sredine.

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Review article

PRENATAL MONITORING OF PREGNANCIES COMPLICATED BY DIABETES MELLITUS

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Abstract: Preconception and prenatal monitoring evaluate the condition of the mother's underlying disease and possible complications during pregnancy. Before conception, patients with diabetes should be informed that suboptimal glycoregulation is associated with reduced fertility and pregnancy losses. The task of the perinatologist in pregnancies affected by diabetes mellitus is to prevent complications of the underlying disease, such as hypoglycemic crises. Another important component of prenatal care in diabetic pregnancies is the recognition and prevention of pregnancy complications such as preeclampsia, polyhydramnios, congenital malformations, fetal macrosomia, and infections.

Keywords: diabetes mellitus, pregnancy, complications, preeclampsia, polyhydramnios.

INTRODUCTION

There are two main problems in planning a pregnancy in women with diabetes. First is how diabetes will affect the pregnancy and the child's health, and the second is how will the pregnancy affect the course of diabetes. Therefore, proper planning of all available procedures is crucial to minimize perinatal and maternal morbidity and mortality (1).

Preconception and prenatal monitoring evaluate the condition of the mother's underlying disease and possible complications. Most patients, according to the experience of clinicians, do not achieve satisfactory glycoregulation preconceptionally, and a large part of pregnant women has undiagnosed diabetes. Before pregnancy, it is important to:

1. Assess glycoregulation and glycosylated hemoglobin, and train the patient to determine the value 5 to 7 times a day with a glycemic meter.

2. Assess normal values of arterial blood pressure.

3. Assess kidney function by biochemical laboratory findings, determination of creatinine and urea clearance, and determination of proteinuria. If proteinuria is present, examine the urine bacteriologically.

4. Assess the state of the retina with an ophthalmological examination of the state of the retina performed by an ophthalmologist specializing in retinal diseases.

5. ECG should be done for women over 35 years old, those with hypertension, nephropathy or peripheral vascular disease, obese, with hypercholesterolemia, as well as if diabetes lasts longer than 10 years. In the case of pathological ECG findings or suspicious clinical circumstances, a stress test should be performed.

6. Assess peripheral and autonomic neuropathy, i.e. loss of sensorium on the lower extremities, heat intolerance, postural hypotension, and gastroparesis.

7. Assess hypoglycemia frequency, severity, and manifestations.

8. Assess any elements of peripheral vascular disease that may be present.

9. Evaluate the function of the thyroid gland (TSH and free T4) in patients with type I diabetes (1, 2).

After assessing the patient's condition, it should be emphasized that strict glycoregulation is the basis of a good pregnancy outcome and the patient should be provided with information, advice, and support.

Pregnancy planning and contraception

From the adolescent period, education about fertility control is especially important for patients with diabetes. Women who have diabetes and are planning to become pregnant should be offered the information:

- what are the risks of complications in pregnancy with diabetes concerning the duration of the disease;
- contraception use until good glycoregulation is established;
- glycemic goals, glucose monitoring, diabetes medications, and diabetes complications must be reviewed before and during pregnancy;
- more time and effort that is needed to keep diabetes under control during pregnancy

Nutrition, nutritional supplements, body mass, and physical activity

Dietary advice is especially important for these patients. If the body mass index is above 27 kg/m^2, it should be recommended to reduce the body mass according to the established protocol. It is important to highlight the importance of folic acid intake (5 mg per day) until the 12th week of pregnancy to reduce the risk of congenital anomalies of the nervous system (3, 4).

Target preconception glycemic values

Individual glycemic target values should be determined and self-monitoring should be enabled to avoid hypoglycemia. The goal is to maintain HbA1c below 6.1%. It is important to explain the importance of this to the patient (5). If glycosylated hemoglobin is above 10%, pregnancy should be avoided, and reducing this value towards the target of 6.1%, significantly reduces the risk of congenital anomalies. It is preferable that, in the case of planning a pregnancy, the level of HbA1c is determined once a month, and that, if they have not done so by then, they should be trained in self-measurement of blood glucose. If there is a need for more intensive therapy, a more frequent measurement of glycemia is recommended. In patients with type I diabetes, it is necessary to periodically detect ketonemia and ketonuria with test strips (6).

Safety of diabetes medications before and during pregnancy

Metformin can be used safely as sole or adjunctive therapy and can serve as a substitute for insulin. As a rule, other oral medications from the hypoglycemic group are already replaced by insulin in the preconception period. On the other hand, clinical research data indicate the safety of fast-acting insulin analogs (aspart and lispro) for fetuses and neonates. Regarding long-acting insulin analogues, there are insufficient data at this time to make explicit statements (7). Before conception, as well as when pregnancy is confirmed, the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists must be stopped, which must be replaced by alternative antihypertensive drugs that are safe to use. The same applies to statins (8).

The most common questions and dilemmas of patients and questions asked:

Does diabetes affect a woman's ability to conceive?

Various abnormalities of the reproductive function of women with diabetes are described. These include delayed menarche and early menopause, delayed ovulation, and an increased incidence of irregular menstrual cycles that occur twice as often compared to control subjects. A positive relationship between the duration of diabetes and delayed menarche was shown, even when maternal menarche was taken into account (9, 10).

The mechanisms that compromise fertility in women with diabetes are not fully understood. They may originate from a reduced response of luteinizing hormone to gonadotropins, a decrease in basal levels of LH and FSH, a decrease in thyrotropin that leads to a drop in circulating thyroxine and a decrease in the synthesis and release of prolactin, or a decreased synthesis of corticosterone. A decrease in ovarian mass has been proven in animal models, in animals where diabetes may have induced a reduced ovarian response to gonadotropins. Decreased insulin-induced progesterone synthesis in granulosa cells in women with diabetes has also been observed, even in cases of good disease control. Improving glycoregulation should improve fertility (11, 12, 13).

Does diabetes increase the risk of early termination of pregnancy?

The risk of spontaneous abortions (SAB) in diabetes is not fully specified. According to some research, SAB rates in diabetic pregnancies are no different from the SAB rates in the general population (14). Several scientists have found a link between increased HbA1c concentrations (an indicator of poor glycemic control) in the first trimester and SAB. Furthermore, SAB is associated with glycemic control in the immediate pre-pregnancy period, more so than in the immediate post-abortion period (15).

The increased risk of SAB in diabetes is most likely related to the adverse environment to which the developing fetus is exposed. This results in dam-

age to the fertilized ovum or the fetus itself, as well as congenital anomalies incompatible with life. Potential mechanisms of SAB may be due to inadequate placentation and vascularization as a result of poor glycemic control, as well as an increased incidence of chromosomal aberrations (16). Whether there is a threshold of hyperglycemia above which the risk of SAB is increased in women with diabetes is a controversial issue. The Diabetes in Early Pregnancy (DIEP) study (17) showed that higher HbA1c concentrations in the first trimester were associated with increased rates of SAB.

Does diabetes increase the risk of congenital malformations?

Congenital malformations (CM) are the leading cause of perinatal mortality in diabetes, accounting for 50%, compared to 20% to 30% in the general population. Children whose mothers are preconception diabetics (type I and type II) have an increased risk for congenital anomalies (18).

Some authors indicate that elevated HbA1c values in the first trimester are associated with a higher risk for CM. Diabetic vasculopathy has also been linked to an increased risk of CM in some studies (18).

Does pregnancy increase the risk of maternal hypoglycemia?

Intensive insulin therapy can worsen the counterregulatory response to hypoglycemia. Patients with long-term insulin therapy can sometimes tolerate suboptimal plasma glucose levels without any symptoms of hypoglycemia. In such patients, symptoms and a hormonal counterregulatory response become noticeable at significantly lower glucose concentrations (19).

Pregnant women are often on intensive insulin therapy, and hypoglycemia occurs as a common complication. In addition to the previously described mechanism, it has been shown that during pregnancy the counterregulatory response decreases even more (20).

Coustan et al. (21) noticed a rate of moderate hypoglycemia of 72% and severe hypoglycemia of 46% in 22 pregnant women with type I diabetes who were randomized to either an insulin pump or intensive conventional therapy.

Steel and Johnson (22), as well as Hellmuthet al (23).measured hourly nighttime glucose levels in pregnant women during the first trimester and reported that 37% had hypoglycemia, which was asymptomatic in 42 out of 43 patients.

Kitzmiller et al. (24) reported that 58% of 84 women who became pregnant after preconception testing had 1 to 17 episodes of hypoglycemia per week in the first 7 weeks of pregnancy.

Kimmerle et al. (25) also noticed severe hypoglycemia in 41% of 77 women with type I diabetes, especially in the first half of pregnancy. Likewise, Rosenn et al. (26) found that significant hypoglycemia, occurred in 71% with a peak incidence between weeks 10 and 15; 34% of 84 patients had at least one episode of hypoglycemia accompanied by convulsions, loss of consciousness, injury, emergency administration of glucagon or intravenous glucose.

Gabbeet al. (27) demonstrated that women who used an insulin pump during pregnancy had no episodes of significant hypoglycemia, and those who switched to an insulin pump during pregnancy had a reduction in episodes of severe hypoglycemia.

Bjorklundet al. (28) reported an increase in the number of fetal movements and an increased heart rate, while there was no effect on the speed and appearance of blood flow through the umbilical artery during moderate hypoglycemia.

Does diabetes increase the risk of preeclampsia?

The incidence of preeclampsia in women with diabetes is 5% to 7% higher than in the general population. In a prospective study of 491 women with type I diabetes, Hanson and Persson (29) found preeclampsia or pregnancy-induced hypertension in 21%, four times more than in the general population in Sweden. The frequency of preeclampsia increases with the increase in the class of diabetes in pregnancy according to White.

Finally, in women with diabetic nephropathy, most authors found a high incidence of preeclampsia/pregnancy-induced hypertension or threatened preeclampsia of about 30%.

Sidiqqi et al. (30) found a frequency of pregnancy-induced hypertension of 15.4% in 175 women with type I diabetes, closely related to nulliparity, poor glycoregulation, the first and second trimesters of pregnancy, as well as a higher class according to P. White. Kitzmiller et al. (24) showed that the rate of pregnancy-induced hypertension in their diabetic population was 5%, which was not significantly different from 3.8% in the general population. Martinet al. (31) found a frequency of pregnancy-induced hypertension of 20% in diabetics (twice as much as in the general population), but no connection with glycoregulation was found.

Several studies have examined the relationship between microalbuminuria and preeclampsia. Combs et al. (32) found an increase in the risk of preeclampsia

if microalbuminuria increased to 190 mg in 24 hours. Similarly, Ekbom et al. (33) have noted that microalbuminuria before pregnancy is the strongest predictor of preeclampsia in type I diabetes.

It is unclear how diabetes affects the risk of preeclampsia. Although the etiology of preeclampsia is unknown, it appears to be related to impaired adaptation of the maternal vasculature to pregnancy. Poor glycoregulation is associated with a state of compromised vascular adaptation in pregnancy and the induction of preeclampsia in a positive relationship with the severity of the disease in pregnancy.

Does diabetes increase the risk of preterm delivery?

Premature birth is one of the most significant obstetric syndromes having a frequency of about 10%. It is responsible for 75% of perinatal morbidity and mortality. There are different data on the incidence of spontaneous preterm births in diabetes. In the studies published so far, the share of iatrogenic prematurity is especially emphasized, considering that part of the therapy in certain situations is planned preterm birth. Not so long ago, premature birth was undertaken to avoid the risk of intrauterine fetal death, especially after the 37th week of gestation (34).

Green et al. (35) demonstrated that 26.2% of women with type I diabetes had a preterm delivery, in comparison to 9.7% of women without diabetes, and that the most important risk factor associated with giving birth before the 37th week of gestation was preeclampsia. These results are in accordance with those reported by Rosenn et al. (26) which showed that improved glycemic control was associated with a lower risk of preterm birth. Kovilam et al.(36) even proved that an increase in the Hba1c levels by 1% increases the risk of premature birth by 37%.

Sibai et al. (37) reported that women with diabetes had a significantly higher rate of spontaneous (16.1% vs. 10.5%) and induced (21.9% vs. 3.4%) preterm deliveries in comparison to the control group.

Weiss et al. (38) measured umbilical vein insulin levels in infants of diabetic mothers and found that among children who had high insulin levels, the preterm birth rate was 71% compared to 5% among children whose levels were normal.

The association between preterm birth and poor glycemic control requires a rational explanation. Although the etiology of preterm labor is still not clearly defined, different pathophysiological conditions may play an independent role and trigger a common mechanism that leads to preterm labor, such as the local release of prostaglandins in the uterine muscle. Prostaglandin production is increased in the platelets of diabetics, but no data show an increase in prostaglandin production in the uterus or amnion of pregnant women with diabetes. Furthermore, it is impossible to conclude whether lifestyle and other factors may increase the risk of preterm birth in patients with poor glycemic control (39).

Does diabetes increase the risk of polyhydramnios?

Polyhydramnios is common in diabetic pregnancies. Cousins (40) determined a frequency of 17.6% in classes B and C, according to White, and 18.6% in classes D, R, and F. Higher rates of polyhydramnios were also determined by Lufkin et al. (41) (29% compared to 0.9% in the control group), as well as Kitzmiller et al. (24) (31%) and Rosennet al. (26) (26.4% to 0.6%).

Although the diagnosis of polyhydramnios is also related to the subjective assessment of the sonographer, the use of the amniotic fluid index (AFI) improves the objectivity of data on the amniotic fluid volume. The frequency of polyhydramnios in the control population may be underestimated because sonographic examinations are performed less often in healthy pregnant women. Polyhydramnios in diabetes can be a consequence of a higher concentration of glucose in the amniotic fluid, which increases the osmotic pressure, and when the balance is restored, it leads to an increase in the volume of the amniotic fluid. Additionally, maternal hyperglycemia causes fetal hyperglycemia, which further leads to fetal polyuria and increased amniotic fluid.

Does diabetes increase the risk for infections?

Diabetics are known to have an increased risk for infections. Deficiency of the immune system and reduced activity of lymphocytes and leukocytes can explain the tendency to infection. These abnormalities appear to be associated with poor glycemic control. As part of the body's adaptation to pregnancy, immunomodulation occurs, which is necessary for the survival of the fetus's allograft. As part of this, there is a depression of cellular immunity, which in diabetes is an additional risk for infection.

Vejlsgaards (42) found an increase in the frequency of urinary tract infections in pregnant women with diabetes. Diamond et al. (43) reported that wound infections, endometritis, or both, are more common in postpartum diabetic women. Cousins, Pedersen and Molsted-Pedersen (40, 44) found that pyelonephritis

was more common in diabetic pregnancies and was associated with increased perinatal mortality.

Stamleret al. (45) reported that 86% of women with diabetes had at least one infection antenatally, compared with 26% of women without diabetes. During pregnancy, these patients had a five times higher frequency of various infections.

CONCLUSION

Improving glycoregulation should improve fertility. The increased risk of SAB and CM in diabetes is most likely related to the unfavorable environment to which the developing fetus is exposed. Disturbances in fetal growth and the amount of amniotic fluid index are also present in diabetic pregnancies. The same applies to the development of preeclampsia and infections. Prenatal monitoring is of great importance in pregnancies complicated by diabetes mellitus.

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Sažetak

PRENATALNI NADZOR TRUDNOĆA KOMPLIKOVANIH DIJABETES MELITUSOM

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Prekoncepcijski i prenatalni nadzor evaluiraju stanje osnovne bolesti majke i eventualne komplikacije tokom trudnoće. Pre začeća potrebno je pacijentkinjama sa dijabetesom predočiti da je suboptimalna glikoregulacija skopčana sa smanjenim fertilitetom i gubicima trudnoće. Zadatak perinatologa kod trudnoća opterećenih dijabetes melitusom je da predupredi komplikacije osnovne bolesti kao što su hipoglikemijske krize. Druga važna komponenta prenatalnog nadzora u dijabetičnim trudnoćama je prepoznavanje i sprečavanje komplikacija trudnoće kao što su preeklampsija, polihidramnion, kongenitalne malformacije, fetalna makrozomija i infekcije.

Ključne reči:dijabetes melitus, trudnoća, komplikacije, preeklampsija, polihidramnion.

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Review article

"SIX SIGMA" STANDARD AS A LEVEL OF QUALITY OF BIOCHEMICAL LABORATORIES

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Abstract: The principal role of biochemical laboratories is responsibility for reliable, reproducible, accurate, timely, and accurately interpreted analysis results that help in making clinical decisions, while ensuring the desired clinical outcomes. To achieve this goal, the laboratory should introduce and maintain quality control in all phases of work. The importance of applying the Six Sigma quality model has been analyzed in a large number of scientific studies. The purpose of this review is to highlight the importance of using six sigma metrics in biochemical laboratories and the current application of six sigma metrics in all laboratory work procedures. It has been shown that the six sigma model can be very useful in improving all phases of laboratory work, as well as that a detailed assessment of all procedures of the phases of work and improvement of the laboratory's quality control system is crucial for the laboratory to have the highest level of six sigma. Clinical laboratories should use Sigma metrics to monitor their performance, as it makes it easier to identify gaps in their performance, thereby improving their efficiency and patient safety. Medical laboratory quality managers should provide a systematic methodology for analyzing and correcting quality assurance systems to achieve Six Sigma quality-level standards.

Keywords*:* six sigma, biochemical laboratory, quality control.

INTRODUCTION

Six Sigma is a systematic approach that aims to improve work processes through the identification, measurement, and analysis of process problems (1). Sigma (σ) is one in which it is statistically expected that 99.999666% of the manufactured products have no defects. For process control at 6 SD, Six Sigma represents the possibilities of 3.4 DPMO (defects per million opportunities). This means that increasing the Sigma plays a role in increasing the consistency and stability of the test, thus reducing costs for the healthcare facility (2). An average product, regardless of its complexity, generally has a sigma value of approximately 4σ. The best or "world-class" product has an effect of 6σ (3).

The correlations between Sigma metric and defect are:

- 1 σ is equal to 690 000 errors or DPMO reports,
- 2 σ is equal to 308 000 DPMO reports,
- 3 σ is equal to 66 800 DPMO reports,
- 4 σ is equal to 6 210 DPMO reports,
- 5 σ is equal to 230 DPMO reports and
- 6σ is equal to 3.4 DPMO reports (4).

Lean Six Sigma methodology is a new business management strategy in the field of healthcare and is very well incorporated into the process of quality control and patient satisfaction (5).

Healthcare systems are special organizations that face complicated tasks. To overcome these tasks, they should use the DMAIC (define, measure, analyze, improve, control) principle of Lean Six Sigma to provide the best possible service. The use of DMAIC offers rules on how to improve the system of quality services focused on patient satisfaction. These guidelines can improve procedures and steps in the laboratory process (6).

Six Sigma uses two methods to improve the quality: DMAIC and DMADV (define, measure, analyze, design, verify). DMAIC principle is used for process improvement while DMADV is used for product and process design. The DMAIC principle has five stages that lead to the improved work quality. The first four

phases are implemented as management and statistical tools that facilitate the understanding of the process and the problems associated with it, as well as finding the cause of the problem and appropriate solutions. The fifth phase is the phase of finding the cause of the problem and improving the quality of work (7).

The Six Sigma (σ) metric was first applied in the biochemical laboratory by David Nevalainen in 2001. A new field, not without controversy, challenges, and debate. But since 2001, a toolkit has been developed that allows laboratories to harness the power of Six Sigma to assess the quality of work (8).

Although the Six Sigma concept comes from the industrial sector, some of the world's leading medical laboratories are beginning to apply this concept with great success. The main task of the biochemical laboratory is to provide accurate, reliable, reproducible, timely, and correctly interpreted analysis results that support clinical decision-making, while the ultimate goal must be to ensure the desired clinical outcomes. To fulfill the stated task, the laboratory should implement and maintain the quality of all laboratory work phases, concentrating on the economy. In recent years, biochemical laboratories have been struggling with a growing workload with a wider range of analyzes with the same or fewer workers while always needing to provide an accurate result with faster processing time and high quality. The laboratory influences more than 70% of medical decisions, such as admission, treatment, and discharge, and accounts for less than 5% of all healthcare costs. However, there are increasing expectations from the biochemical laboratory to reduce their costs with the same or often higher quality and standard. The way to solve this situation is to simplify all laboratory phases and avoid "defects" not only from the analytical but also from the pre-and post-analytical part. The Six Sigma model enables quality improvement with a focus on providing "value" and improving performance through the complete elimination of errors, and by that, we mean everything that does not add value to our products or services (9).

In the biochemical laboratory, we can define errors as incorrect results that differ from the actual value by more than the total allowable error. The "tolerance limit" and "offset" mentioned in the Sigma industrial formula are the same as the total, allowable, error and the analytical bias in laboratory work JO Westgard adapted this formula and introduced this one that can be applied in the laboratory:

$$\text{Sigma} = (TE_a - |B|) / SD$$

- TE_a - total allowable error,
- B - bias
- SD – standard deviation (9).

This formula can be used to estimate the proportion of incorrect results or the analytical failure rate resulting from the combined effects of bias and inaccuracy. With biases ≥ 1 SD, the one-sided probability is considered, and the area outside the nearest total allowable error generally represents the failure rate (9).

Quality assessment using the Six Sigma model provides evidence of the achieved analytical efficiency in relation to user requirements and is of great importance for identifying and prioritizing important improvements in the quality control of laboratory phases (10). The calculation of the Sigma value is the best risk predictor for laboratory testing but also a parameter used to design the selection of the statistical quality control method needed to detect errors (11). The Six Sigma metric corresponds to 3.4 errors per million determinations (12).

APPLICATION OF SIX SIGMA MODELS IN BIOCHEMICAL LABORATORIES

Pre-analytical phase and Six sigma metrics

The importance of applying the Six Sigma quality models has been analyzed in many scientific studies. Improving the pre-analytical procedure in the laboratory using Six Sigma was the aim of the study by Bayat H et al. This study was conducted over a year. More than 1.4 million samples and more than 54 thousand pre-analytical error reporting forms, such as insufficient patient data, sample data, and hemolyzed, lipemic, and insufficient samples were reported, and the total number of errors was summed and reported as DPM and σ. In 75% of test report forms, the diagnosis wasn't present and $\sigma < 1$ was obtained, and for other errors such as sampling time, sigma values were below 3. For insufficient samples and inappropriate blood-to-anticoagulant ratio, sigma the value was 4.3 (4). In al TC et al. showed how using Lean Six Sigma metrics can improve medical laboratory efficiency and reduce turn-around time (TAT), which belongs to the post-analytical phase. In their longitudinal study, they showed that using Lean Six Sigma the pre-analytical phase, in their case, could be shortened by 3h and 22.5 minutes and that the analytical procedure could be shortened from 68 to 59 minutes. They also showed that error-prone steps and potential biological risks for laboratory staff were reduced by 30% to 3%. (8) The aim of the study by Elbireer et al. was to describe how the quality of entering laboratory data was raised to a higher level by using this model. The Six Sigma Quality Improvement research group examined

Table 1. *Chronological presentation of the application of the six sigma methodology for internal controls of different types of analytes*

	Authors	Year	Study type	Total number of ICQs of all analytes	Sigma value for all ICQs analytes	Collection period
1.	Nanda SK et al. [2]	2013.	Retrospective study	13	5 - ≥ 6 4 – 3-6 4 - ≤ 3	October 2012 – March 2013
2.	Afrifa J et al. [17]	2015.	Retrospective study	12	12 - ≤ 3	January – March 2014
3.	Nar R et al. [21]	2017.	Retrospective study	18	6 - ≥ 6 10 – 3-6 2 - ≤ 3	June – August 2015
4.	Iqbal S et al.[22]	2017.	Cross-sectional study	10	3 - ≥ 6 2 – 3-6 5 - ≤ 3	October 2014 – March 2015
5.	Mao X et al. [19]	2018.	Retrospective study	20	9 - ≥ 6 7 – 3-6 4 - ≤ 3	April – August 2017
6.	Kumar BV et al. [18]	2018.	Retrospective study	16	4 - ≥ 6 7 – 3-6 5 - ≤ 3	July 2015 – June 2016
7.	Xia Y et al. [23]	2018.	Retrospective study	42	13 - ≥ 6 18 – 3-6 11 - ≤ 3	January – December 2016
8.	Mahmood B et al. [26]	2018.	Prospective study	6	3 - ≥ 6 1 – 3-6 2 - ≤ 3	22/5/2017 – 27/7/2017
9.	Liu Q et al. [20]	2019.	Retrospective study	6	6 - ≥ 6 (app.st.) 6 - ≤ 6 (EQA, RCPA, RiliBÄK)	January – June 2017
10.	Sayeed S et al. [27]	2019.	Retrospective study	8	3 – 3-6 5 - ≤ 3	Three months
11.	Đido V et al. [28]	2019.	Prospective study	6	1 - ≥ 6 4 – 3-6 1 - ≤ 3	March – April 2018
12.	Taher J et al. [29]	2019.	Cross-sectional study	18	9 - ≥ 6 9 – 3-6	
13.	Zhou Et al. [11]	2020.	Retrospective study	19	5 - ≥ 6 9 – 3-6 5 - ≤ 3	01/01/2018 – 10/07/2018
14.	Teshome M et al. [16]	2021.	Cross-sectional study	14	1 – 3-6 13 - ≤ 3	10/02/2020 – 10/07/2020
15.	Liu Y et al. [24]	2021.	Retrospective study	13	NCCL: 2 - ≥ 6 9 – 3-6 2 - ≤ 3 EFLM: 5 - ≥ 6 4 – 3-6 4 - ≤ 3	October 2017 – September 2018
16.	Peng S et al. [25]	2021.	Retrospective study	18	5 - ≥ 6 11 – 3-6 2 - ≤ 3	January – June 2018
17.	Goel P et al. [30]	2021.	Cross-sectional study	10	4 - ≥ 6 4 – 3-6 2 - ≤ 3	February – July 2019

Abbreviations: app. st. = "appropriate" quality standards derived from biological variation; EQA = external quality assessment; RCPA = quality requirements of the Royal College of Pathologists of Australasia; RiliBÄK = standards from the 2015 quality guide created by the German medical laboratory quantitative analysis and quality assessment committee; NCCL = National CenterFor Clinical Laboratories; EFLM = European Federation of Clinical Chemistry and Laboratory Medicine.

several factors, such as formulating objectives, recording data entry errors to examine the effectiveness, analyzing all data, and determining the root cause of erroneous laboratory data entry. Ultimately, the team applied control measures to address the main cause and sustain improvement. After launching this project, there was a reduction in errors from 423 errors (σ = 4.34) in a month to approximately 166 per month (σ = 4.65) in a year. The research group found the average cost of identifying and correcting errors to be $16.25 per error. Therefore, reducing errors by approximately 250 errors per month in one year saved approximately $50.000 (13). On the other hand, Vanker et al. analyzed the use of the principles of Six Sigma metrics to determine the degree of errors in the registration of tests in the Laboratory Information System and to determine their potential clinical impact. In this research, the tested samples were compared with the tests registered in the Laboratory Information System. Out of 47,543 tests, 72 errors were recorded, leading to an error rate of 0.15%, which equates to $\sigma = 4.4$. A review of patient records showed that this error could have affected the patient's clinical care. This research has shown that the clinical impact of errors made during the pre-analytical phase of laboratory work is possible. A lower percentage of errors can be ensured by using the Six Sigma program (14). Another study that aimed to examine the frequency and type of preanalytical errors leading to sample rejection was conducted on 19,002 samples. The sample rejection level was unsatisfactory with $\sigma = 3.6$. Their result showed that a higher proportion of errors (73.3%) occurred during sample collection as opposed to errors related to patient identifications (26.6%). The most common pre-analytical error was the hemolyzed sample (64.0%) (15). The research of preanalytical errors during one whole year was the aim of the research of Zorbozan N et al. According to their results, the lowest sigma values were for hemolyzed samples (4.36), samples with inadequate anticoagulant-to-sample ratio (4.68) and coagulated samples (4.78).

Analytical phase and Six sigma metrics

The most common errors that can occur during the analytical process in medical laboratories are non-linear results used without retesting, questionable results that are contradictory, EQC failure, IQC result failure, and failure to perform daily IQC (16). Therefore, Table 1 shows the previous estimates of six sigma metrics for different analytes, where sigma was calculated from internal control I (normal) and II (abnormal/pathological). The results of both I and II internal controls $\sigma \geq 6$ are classified as $\sigma \geq 6$. As shown in Table 1, a large number of studies, based on the analysis of certain biochemical parameters and the assessment of internal control, showed an unsatisfactory level of sigma (< 3) which shows instability and low reliability of results (17, 18, 19). We can say that a more detailed evaluation of analytical performances is needed by strengthening quality control to achieve the highest possible level of six sigma for a medical laboratory, as some studies have shown (2, 12, 20-31). The lowest sigma value was observed for the following parameters: sodium (17, 19), potassium (18), chloride (2, 17, 22), urea (18, 19, 21, 27), creatinine (22, 26, 27), total protein (2, 22), albumin (2, 22, 23, 27), cholesterol (17, 18, 22, 27), total bilirubin (18, 22, 27), glucose (17, 22), some tumor markers (Ca 125, AFP) (20) and some hormones (fT4, prolactin, testosterone, and insulin) (21).

Postanalytical phase and Six sigma metrics

In the already mentioned research by Zorbozan N et al., the research aimed to examine the post-analytical errors of laboratory work. Two indicators of this phase of work were examined, namely: the number of critical values from the validation of the results to the notification of the patients and the clinicians who ordered the test. For both indicators in this research, there were no errors and the sigma value was > 6. The reason for the excellence of their results is explained by the implementation of a system that automatically sends a message to the patient in case of critical values, and such a system is connected to their laboratory information system. In addition, the sigma value was calculated for tests with the exact time interval between the specimens received in the laboratory to the time of reports dispatched with verification (TAT - turn around time) was determined. The lowest sigma values were for the TAT of Potassium 3.84 and TAT of Troponin (I or T) 4.10, while the TAT of INR was > 6 (31).

CONCLUSION

The Six Sigma model is known as the latest principle of quality management and is often used in many fields, such as industry, business, and the healthcare system. It represents a powerful management tool and enables specific rules that can contribute to reducing the occurrence of errors. The Six Sigma methodology uses a particular approach to solving problems that are mainly based on statistical tests.

Clinical laboratories should use Sigma metrics to monitor their performance, as this makes it easier to

identify gaps in their performance, thereby improving their performance and patient safety. Quality managers in medical laboratories should be required to provide a systematic methodology for analyzing and correcting quality assurance systems to achieve Six Sigma quality-level standards.

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Sažetak

"SIX SIGMA" STANDARD KAO NIVO KVALITETA BIOHEMIJSKIH LABORATORIJA

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Glavna uloga biohemijskih laboratorija je odgovornost za pouzdane, ponovljive, tačne, pravovremene i pravilno interpretirane rezultate analiza koji pomažu u donošenju kliničkih odluka, a istovremeno osiguravaju željene kliničke ishode. Za postizanje ovog cilja treba uspostaviti i održavati kontrolu kvaliteta svih faza rada laboratorija. Važnost primene Six Sigma modela kvaliteta analizirana je u velikom broju naučnih istraživanja. Cilj ovog preglednog članka je dati uvid u važnost primene Six Sigma metrike u biohemijskim laboratorijama, kao i u dosadašnju primenu ovog modela u analitičkim postupcima laboratorijskog rada. Pokazalo se da ovaj model može biti vrlo koristan u poboljšanju svih faza laboratorijskog rada, kao i da postoji potreba za detaljnom procenom analitičkih postupaka i jačanjem sistema kontrole kvaliteta laboratorija kako bi se postigao najviši nivo. Kliničke laboratorije trebale bi koristiti Sigma metriku za praćenje svoje produktivnosti, jer se tako olakšava prepoznavanje nedostataka u njihovom radu, čime se poboljšava njihova efikasnost i sigurnost pacijenata. Menadžeri kvaliteta medicinskih laboratorija trebali bi osigurati sistemsku metodologiju za analizu i unapređenje sistema osiguranja kvaliteta kako bi se dostigli najviši standardi nivoa kvaliteta.

***Ključne reči**:* šest sigma, biohemijska laboratorija, kontrola kvaliteta.

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Review article

NUTRITION IN PREGNANCY WITH DIABETES MELLITUS

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Abstract: The nutritional needs of diabetic pregnancies are different from normal pregnancies. Differences in nutritional recommendations can also be seen between pregnant women who are using and who are not using insulin therapy. In this literature review, recommendations for different meal proportions of carbohydrates, proteins, and fats in the diets of pregnant women with diabetes mellitus are listed. Different meal plans were also addressed in this group of patients. The role of exercise in the management of diabetes in pregnancy is undeniable and different approaches found in the literature are presented.

Keywords*:* diabetes mellitus, pregnancy, nutrition.

INTRODUCTION

The main goal of therapy and dietary regime in pregnant women with pregestational and gestational diabetes is to ensure the food needs of the mother and the fetus are in a state of optimal health and euglycemia (1). Educating and encouraging patients in this direction is crucial.

The diet of a pregnant woman with diabetes does not differ significantly compared to the condition before pregnancy. The total daily caloric intake is 7140 - 7560 KJ (1700 - 1800 kcal), assuming that she is not at work, which is a sufficient amount for the good condition of the organism of the mother and the child. Pregnancy should not be a time for losing weight or excessive weight gain (up to 12 kg). Food is divided into 5 - 6 smaller meals according to the principle of proper nutrition in diabetes. Pregnant women who receive insulin according to the scheme of intensive therapy will take meals, as usual, three times a day (2). If insulin therapy was started during pregnancy, the meals are adapted to the type of insulin and its action. This is a group of pregnant women who need extensive nutrition education because it is a new experience for them (3).

According to the National Academy of Sciences 1990 (4) recommendation on nutrition during pregnancy, the caloric intake should be based on the pregnant woman's pre-pregnancy body weight and rate of progress during pregnancy to determine optimal body weight. For a regular-weight woman, caloric needs are estimated at 36 kcal/kg/day (2200 kcal/day) during the first trimester of pregnancy, with an increase of 40 kcal/kg/day (2500 kcal/day) during the second and third trimesters. Jovanovic - Peterson and Peterson (5), as well as the American Diabetes Association (6) later on, recommend an intake of 30 kcal/kg/day for a woman with normal nutrition (80% to 120% of regular weight), 40 kcal/kg/day for an undernourished woman (< 80% of ideal body weight)) and 24 kcal/kg/day for an obese woman (> 120% of ideal body weight), based on the concept of keeping the woman above the threshold for ketonuria while preventing postprandial hyperglycemia.

The caloric needs of obese women with and without diabetes are controversial (7). Although there is caution regarding the potentially harmful effects of maternal ketonemia that occurs with insufficient caloric intake on the fetus, studies in obese pregnant women with diabetes have shown improved pregnancy outcomes with moderate caloric restriction (25 kcal/kg/day or 1800 to 2000 kcal/day). Severe ketosis disrupts the mother's acid-base balance, which is undoubtedly dangerous for both the mother and the fetus. With a

strict restriction of calorie intake (< 1200 kcal/day), ketonemia can occur, and prolonged exposure of the fetus in utero is associated with problems in the neurological development of the newborn. Ketosis can be avoided by feeding smaller and more frequent meals containing slowly absorbing carbohydrates, thereby improving insulin response and delaying lipolysis and ketogenesis between meals.

Carbohydrates, Proteins, and Fats

An intake of 40% to 50% is more appropriate for maintaining glycemia in pregnancy. By using carbohydrates with a lower glycemic index, more than 60% of the total energy needs can be met with them, without a harmful effect on glucose tolerance. Diets with low glycemic indexes are associated with reduced insulin sensitivity. A euglycemic diet designed to alleviate postprandial hyperglycemia is effective. In a pregnancy complicated by diabetes, postprandial hyperglycemia is a major promoter of fetal macrosomia. Women who are insulin resistant may require a reduction in carbohydrate content to 40% of all calories. The diabetic diet is based on the concept that there are two main classes of carbohydrates: simple or refined (glucose, sucrose, and fructose), which are quickly absorbed and cause a relatively large increase in glycemia, and complex or starchy (such as rice, potatoes, vegetables) which are absorbed and digested more slowly and slightly increase glycemia. Complex carbohydrates that contain fiber should replace simple or refined carbohydrates whenever possible (8, 9).

Simple carbohydrates are not recommended in the diet of people suffering from diabetes, except in limited amounts in treating hypoglycemia, acute diseases, and kidney complications, when they serve as energy compensation due to reduced protein intake. Complex carbohydrates are slowly broken down, so blood glucose gradually rises. This is a characteristic of carbohydrates attached to dietary fibers (cellulose, pectin, gum). For people who have enough insulin and eat large amounts of food rich in carbohydrates, the excess energy is converted into fat, which leads to an increase in body weight (10).

In the diet of patients with diabetes, carbohydrates must represent 50 to 60% of the daily energy intake. These must be complex unrefined carbohydrates of vegetable origin.

Fiber is defined as all food components that are resistant to hydrolysis during digestion. They are primarily found in plant foods, including cereals, fruits, and vegetables. There are two types of fiber: water-soluble and water-insoluble. Soluble fibers such as pectin, resin, and polysaccharides affect glycemia and insulin levels through delayed intestinal absorption and gradually increase glycemia. Foods rich in soluble fiber include fruits, oats, barley, and vegetables. Insoluble fibers such as cellulose, lignin, and most hemicelluloses have a greater effect on gastrointestinal emptying and fecal volume than on plasma glucose and insulin levels. A daily intake of 20 to 35 g of soluble and insoluble fiber is recommended (11).

The recommended protein intake is 65g/day. The optimal amount of protein in the diet has not been determined, although in most diets it ranges from 12% to 20%. This amount must be adapted to the physiological needs of the pregnant woman and the growth and development of the fetus and placenta (12). Since most amino acids are gluconeogenic, a high-protein diet in diabetics is believed to help stabilize glycemia by providing a substrate for glucose production.

To achieve normoglycemia fats can make up more than 40% of daily calorie intake. A diet with a lot of fats is not recommended, considering that they can increase insulin resistance and have a toxic effect on β - cells. Saturated fats, found primarily in animal fats, meat, hydrogenated fats, palm oil, coconut oil, coconut butter, whole milk products, and commercial baked goods, should be reduced to a third of calories or less. Mono-unsaturated fatty acids in grape seed, olive, and peanut oil, should make up a third or more of the calories. The rest of the fat should be made up of polyunsaturated fats found in vegetables and fish oil. Supplementation of fish oil and polyunsaturated fatty acids reduces hypertension and serum triglycerides while slightly increasing LDL cholesterol in patients with diabetes (13). The increase in plasma insulin after the ingestion of a mixed meal accelerates the uptake of ingested triglycerides (TG) by tissues and serves to increase fat synthesis and storage in the liver and adipose tissue.

The influence of glucose intake on the metabolism of free fatty acids (FFA) is different compared to normal pregnancy. Normally in pregnancy, the rise in plasma insulin after glucose intake inhibits lipolysis which reduces the amount of FFA available for lipolysis in skeletal muscle. In patients with type II diabetes, despite the availability of insulin, there is much less suppression of lipolysis during glucose intake due to insulin resistance, and FFA accumulation occurs. Similar metabolic changes have been observed in patients with type I diabetes, mainly due to insulin deficiency, although insulin resistance may contribute in these patients.

The concentration of FFA in the blood is often elevated in patients with diabetes. This phenomenon appears to be due to the accelerated mobilization of fat reserves in the body and may be attributed to re-

duced insulin action. In patients with type II diabetes, an increase in FFA occurs in the presence of normal or elevated insulin levels, indicating resistance to the inhibitory effect of insulin on lipolysis. Increased availability of FFA leads to oxidation in skeletal muscles. Although FFAs cannot be directly converted to glucose, they promote hyperglycemia in diabetic patients by providing the liver with energy fuel and cofactors for gluconeogenesis. FFAs affect glucose disposal in skeletal muscle by activating cellular processes that interfere with insulin signaling (14). In patients with diabetes, the postprandial rise in plasma triglycerides may be elevated and/or prolonged, mainly due to defective storage of triglycerides. Fat intake may contribute to further worsening of glycemic control.

Salt and Liquids

Salt is necessary in the daily diet. It is known that taking a large amount of salt (more than 3g) is a risk for high blood pressure. People with high blood pressure, heart disease, and diabetes who have impaired kidney function should reduce their salt intake to 2.4g to 1.4g per day (15). Adequate fluid intake is a health condition for both healthy people and people with diabetes. This is even more important for people with elevated body temperature, increased sweating, and physical exertion. People with heart disease and those with reduced urine output due to kidney disease must be careful and regulate their fluid balance under the supervision of a doctor.

Meal planning

Although the nutritional needs of women with gestational and pregestational diabetes are the same, there are some differences in the approach to meal planning (2). Individual adjustments in meal planning according to lifestyle, physical activity, cultural habits, and preferences are the cornerstone of successful diabetes nutritional therapy. The recommended caloric intake schedule is similar for gestational and pregestational diabetes (16). However, the number of snacks in women with gestational diabetes is controversial. Some recommend three meals, with only an evening snack, in obese women. Others advise smaller meals with adequate snacks between meals.

The composition of calories in a meal is important for maintaining postprandial glycemia in gestational diabetes. Peterson and Jovanovic - Peterson (5) showed that reducing carbohydrates by 33%, 45% and 40% in breakfast, lunch, and dinner is necessary to maintain glycemic control. With the carbohydrates in the snack, total carbohydrates account for 40% to 50% of calories. No study has shown the effect of a particular type of carbohydrate or fat on glycemia and pregnancy outcomes.

Three meals and three snacks are therefore considered optimal. Snacks serve to avoid a rapid drop in glycemia as a result of insulin action.

Implementing a proper diet is the basis of treatment for all people with diabetes, regardless of the type of disease. We use the ADA (American Dietetic Association) system for calculating the needs for macronutrients and energy intake. Food is divided into six groups. Each group contains foods with the same characteristics of composition and energy value. The only differences are in the weight of the foods in the same group. The schedule of meals is important so that the smallest time gap between meals is four hours. The portion of carbohydrates in meals should be balanced. It is important to eat less fat, especially cholesterol. It is recommended to avoid frying, baking, and frying food. Food should be prepared by stewing, boiling, baking in foil, on the grill, and using as little fat as possible (16).

Daily food intake is divided into six meals. In patients who are treated only by changing their diet, i.e. in those in whom it is useful to correct weight, the daily food intake should be divided into three meals of low energy value. Three meals are also recommended for patients who are treated with multiple doses of insulin, even though they are fed a standard or increased food intake. The number of insulin doses necessary during the day depends on the number of meals. An exception can be made if the patient is not allowed to take a large daily meal. Patients treated with two doses of mixed insulin per day should take five to six meals, depending on the combination of insulin they receive. If short-acting insulin is taken in the evening in combination with an intermediate-acting one, the sixth meal should be consumed before going to bed to prevent nocturnal hypoglycemia (16).

Foods that should be avoided except in the treatment of hypoglycemia are sugar, honey, chocolate, sweets, drinks with sugar, and all foods with simple carbohydrates (monosaccharides and disaccharides). These foods are easily resorbed and cause an increase in glycemia after a meal. Other foods to avoid are alcohol and animal fats. Foods that can be taken in smaller quantities are fats of plant origin. Foods that can be taken without restriction if there are no other reasons for restriction are herbal spices, pepper, vinegar, lemon juice, and spices without energy value, drinks without added sugar are coffee, tea, mineral water, tonic, and lemonade (17).

In the Diabetes Control and Complications Study (18), several specific dietary regimens were associated with reductions in hemoglobin A1c levels. Adher-

ing to a prescribed meal schedule and adjusting food and insulin to increase blood sugar levels helps reduce HbA1c. In those who did not regularly take a snack in the evening while following specific guidelines in the treatment of hypoglycemia, lower levels of HbA1c were recorded compared to patients who took an additional snack. More frequent glycemic measurement was associated with statistically significantly better control. All patients, especially women with gestational diabetes who are on insulin therapy, should have meal strategies in case of illness, holidays, celebrations, and dinners away from home. Regardless of the meal planning strategy used, all patients must learn to adjust their insulin dose to their carbohydrate intake. These methods allow active control of blood sugar.

Exercise and diet

Excessive treatment of hypoglycemia can cause hyperglycemia and contribute to poor glycemic control. Glucose tablets or gels work much faster than milk and fruit juice and have a similar and consistent glycemic response without causing rebound hyperglycemia. Food diaries or records that patients make periodically are useful in identifying foods or situations that affect glycemia. Patients and nutritionists can develop a strategy to prevent hyperglycemia and hypoglycemia by choosing more adequate food, portions, or meals during the day (19).

Women should be encouraged to continue physical activity with the consent of a perinatologist. The optimal time for exercise is 60 to 90 minutes after a meal for a patient with gestational diabetes and those with pregestational diabetes. A regular schedule of physical activity can be an integral part of the overall treatment and does not require changes, but additional and occasional exercise may require a higher food intake. As with fasting, during exercise, there is a need to create endogenous fuels to meet the increased needs of the tissues. During exercise, energy primarily comes from the liver, which can increase glucose production by 300 to 500%. Hepatic glucose production is precisely regulated to maintain normal levels of circulating glucose despite increased consumption by skeletal muscle. During exercise, FFAs are also mobilized from adipose tissue to reduce the depletion of limited hepatic glycogen stores. The body stores these glycogen reserves for the needs of the CNS. As physical activity continues, FFA consumption assumes an increasingly important role in meeting the needs of skeletal muscle. This spares the liver further demands for glucose production, which, after prolonged exercise, occurs to a greater extent from gluconeogenic precursors, such as protein-derived amino acids (20).

During exercise, insulin secretion is decreased, the sympathetic nervous system is activated, and several counterregulatory hormones are increased, including glucagon, cortisol, growth hormone, and catecholamines (epinephrine, norepinephrine). These hormones have their highest values during intense physical exertion. This hormonal milieu promotes the mobilization of glucose and FFA from the liver and adipose tissue, providing the necessary fuel for muscle tissue. Non-hormonal mechanisms are also important: increased fuel consumption by the muscle is mediated by local non-hormonal mechanisms, including increased mobilization of glucose transport proteins (eg. GLUT 4) to cell surfaces (21, 22).

Studies using radio-labeled glucosehave helped to clarify the mechanism of the effect of physical activity on lowering glycemia in patients with diabetes. Normally, physical activity leads to a significant increase in glucose uptake by skeletal muscle. Glycemia remains unchanged because hepatic glucose production increases to compensate for increased peripheral glucose consumption. This process is mediated by a drop in insulin levels and activation of the sympathetic nervous system, as well as the release of counter-regulatory hormones. In diabetic patients receiving exogenous insulin, circulating insulin levels may remain inappropriately high during exercise. Exercise can enhance the absorption of insulin from subcutaneous injection sites. Relative hyperinsulinemia prevents compensatory increases in hepatic glucose production and may enhance glucose uptake by exercising muscles. The net effect is potentially dangerous hypoglycemia (23).

The clinical benefit of the acute glycemic-lowering effects of exercise in patients with type I diabetes is limited. Unless exercise is regular and of appropriate intensity and duration, few long-term effects in improving glycemic control can be expected. Hypoglycemia is a common complication of strenuous exercise in patients with type I diabetes. The rapid rise in counterregulatory hormones, together with the diabetic patient's increased response to these hormones and the tendency to overeat when symptoms occur, can lead to hyperglycemia. In clinical practice, intermittent exercise may cause large glycemic fluctuations instead of the desired effects of improving glycemic control (24).

The main difference in gluconeogenesis between subjects without diabetes and patients with type I diabetes is quantitative. During short-term exercise in subjects without diabetes, increased hepatic glucose production is mediated by accelerated glycogenolysis while the rate of gluconeogenesis remains unchanged. Patients with diabetes show a rapid increase in gluconeogenesis during exercise. In healthy people, these changes can only be induced by prolonged periods of

exercise (2 to 4 hours). The effect of exercise in insulin-deficient diabetic patients is to increase the gluconeogenesis that characterizes diabetes. In patients with type II diabetes, there is a more favorable risk-benefit ratio of planned physical activity compared to insulin-dependent patients. In patients with type II diabetes, regular aerobic exercise improves insulin sensitivity and may have beneficial effects on both long-term glycemic control and microangiopathy. Because patients with type II diabetes retain some degree of endogenous insulin regulation, there is a reduced tendency for sudden and extensive changes in glycoregulation during exercise. An aerobic exercise program is routinely recommended for most patients with type II diabetes, and exercise is advised for patients with type I diabetes, mainly to delay cardiovascular complications (25).

CONCLUSION

Food should be divided into 5 - 6 smaller meals according to the principle of proper nutrition in diabetes. If insulin therapy was started during pregnancy, the meals are adapted to the type of insulin and its action. By using carbohydrates with a lower glycemic index, more than 60% of the total energy needs can be met with them, without a harmful effect on glucose tolerance. Diets with low glycemic indices are associated with reduced insulin sensitivity. A euglycemic diet, designed to alleviate postprandial hyperglycemia is effective. A high-protein diet in diabetics helps to stabilize glycemia by providing a substrate for glucose production. A diet with lots of fats is not recommended, considering that they can increase insulin resistance and have a toxic effect on β - cells. Salt intake must be strictly controlled, and alcohol intake must be stopped. Exercise is of great importance in diabetes prevention and management during pregnancy.

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Sažetak

ISHRANA TRUDNICA SA DIJABETESOM

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Nutritivne potrebe kod trudnoća opterećenih dijabetesom razlikuju se od fizioloških trudnoća. Razlike u nutritivnim preporukama se mogu videti i između trudnica koje koriste i koje ne koriste insulinsku terapiju. U ovom pregledu literature navedene su preporuke za različitu zastupljenost ugljenih hidrata, proteina i masti kod trudnica sa dijabetes melitusom. Obrađeni su i različiti planovi obroka u ovoj grupi pacijenata. Uloga vežbanja u kontroli dijabetesa u trudnoći je neosporna i predočeni su različiti pristupi pronađeni u literaturi.

***Ključne reči**:* diabetes melitus, trudnoća, ishrana.

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Review article

OROPHARYNGEAL DYSPHAGIA IN ELDERLY PERSONS - ETIOLOGY, PATHOPHYSIOLOGY AND SYMPTOMATOLOGY

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Abstract: Swallowing disorders can occur at any age, although they occur more often in old age when the physiology of swallowing changes due to aging. Oropharyngeal dysphagia is a very common clinical condition affecting 13% of the total population over 65 years of age and 51% of institutionalized older people. Given that oropharyngeal dysphagia can lead to increased morbidity and mortality in the elderly, it is necessary to prevent the occurrence of dysphagia in this population group as much as possible. In relation to this, the paper aims to provide insight into contemporary research into the etiology, pathophysiology, and symptomatology of oropharyngeal dysphagia in the elderly. In this review study, the electronic databases of Google Scholar Advanced Search and the Consortium of Serbian Libraries for Unified Procurement - KoBSON were searched. The following keywords and phrases were used in the search: swallowing, dysphagia, oropharyngeal dysphagia, aging, age and dysphagia, etiology of oropharyngeal dysphagia, the clinical picture of oropharyngeal dysphagia, pathophysiology of oropharyngeal dysphagia. This systematic review and meta-analysis of papers showed significant progress in the effective diagnostic approach of oropharyngeal dysphagia during the last years but also a significant lack of knowledge about adequate modifications of drugs applied during the treatment of patients with dysphagia. A good understanding of the etiology, pathophysiology, and symptomatology of oropharyngeal dysphagia would eliminate the harmful effects of pharmacological substances on the function of swallowing, given that the elderly, on the advice of a doctor, use them daily.

Keywords: swallowing disorders, oropharyngeal dysphagia, aging.

INTRODUCTION

Swallowing is a set of movements that take place in the initial part of the digestive tract, and their purpose is to bring chewed food from the mouth through the pharynx and esophagus to the stomach. The act of swallowing is divided into three phases: buccal, pharyngeal, and esophageal. The first phase, buccal, takes place under the control of the will, and the other two, pharyngeal and esophageal, are under reflex control (1).

The oral cavity, larynx, and esophagus take part in the act of swallowing. Disturbance at any level of these structures can cause difficulty swallowing, called dysphagia. If there is difficulty passing food from the oropharynx to the esophagus, the patient has oropharyngeal dysphagia. On the other hand, the problems that occur during the passage of food to the esophagus characterize esophageal dysphagia (1).

Swallowing disorders can occur at any age, although they occur more often at an older age, when, due to the aging process, the physiology of swallowing changes, which leads to dysphagia being experienced by 12 - 25% of people over 50 years old (2). With aging, the humidity of the oral cavity decreases, and the sense of smell and taste weakens as a result of weaker sensorimotor integration, which negatively affects the success and safety of swallowing (3).

Oropharyngeal dysphagia is a very common clinical condition affecting 13% of the total population older than 65 years and 51% of the institutionalized elderly (2). The prevalence of oropharyngeal dysfunction among people living independently, aged 70 to 79, is about 16%. With age, this percentage increases, and for people over 80 years old, it amounts to 33%. This percentage is higher among elderly hospitalized patients and is 47% (4). Patients experience difficulty forming a bite, nasal insufficiency, and cough accompanying tracheal aspiration (5). It most often occurs in people with neurological or muscular disorders affecting skeletal muscles. Neurological diseases in which oropharyngeal dysphagia occurs as a symptom are Parkin-

son's disease, stroke, multiple sclerosis, amyotrophic lateral sclerosis, bulbar poliomyelitis, pseudobulbar paralysis, and other central nervous system damage. Oropharyngeal dysphagia occurs in comorbidity with muscle diseases such as dermatomyositis, myasthenia gravis, and muscular dystrophy (6).

Although oropharyngeal dysphagia causes life-threatening complications, it is often not treated because the elderly are preoccupied with other health problems and ignore the difficulties they have during swallowing. Therefore, it is necessary to include dysphagia screening in the elderly to include the person in rehabilitation in time (5).

The goal

Average life expectancy is constantly increasing worldwide. In 2000 it was 66.8 years of age, while according to the latest statistical analysis, it is 73.4 years of age in 2019 (7). This number is expected to increase even more by 2050 when every sixth individual on our planet will be 65 years or older (World Population Aging, 2019). Given that oropharyngeal dysphagia can lead to increased morbidity and mortality in the elderly, it is necessary to prevent the occurrence of dysphagia in this population group as much as possible. In relation to this subject, this paper aims to provide insight into contemporary research into the etiology, pathophysiology, and symptomatology of oropharyngeal dysphagia in the elderly.

Method

In this review study, the electronic databases of Google Scholar Advanced Search and the Consortium of Serbian Libraries for Unified Procurement - KoBSON were searched. The following keywords and phrases were used in the search: swallowing, dysphagia, oropharyngeal dysphagia, aging, age and dysphagia, etiology of oropharyngeal dysphagia, the clinical picture of oropharyngeal dysphagia, pathophysiology of oropharyngeal dysphagia. The literature was searched in Serbian and English. Papers were collected in which the etiology, pathophysiology, and clinical picture of oropharyngeal dysphagia in the elderly were presented. Works published from the beginning of the 21st century until today were taken into account. The analysis included a large number of papers, but for the purposes of this paper, 23 review and research papers and one monograph were selected, which presented the etiology, pathophysiology, and symptomatology of oropharyngeal dysphagia in the elderly.

RESULTS WITH DISCUSSION

Etiology of oropharyngeal dysphagia

Analyzing the anatomical structure of the esophagus and the clinical manifestations of aging in the esophagus, research shows that the aging process is most reflected in the esophageal sphincter of the esophagus (8, 9).

The esophageal muscle leads to relaxation, extensibility, the distraction of the hyolaryngocricoid complex forward, and the creation of appropriate pressure on the muscle wall during swallowing. Disruption of one of its functions will lead to swallowing dysfunction (5).

Oropharyngeal dysphagia is a frequent companion of many neurological diseases and surgical procedures such as total laryngectomy (10). Radiation can reduce saliva and lead to dry mouth, but also limited mobility of oropharyngeal structures. Pain in the mouth and throat can cause a person to eat less (1).

By asking the question, "What happens when you try to swallow? Do you have trouble chewing? Do you have difficulty swallowing solids, liquids, or both solids and liquids? What are the symptoms associated with difficulty swallowing? How long does your act of swallowing last?". Specialists can identify a specific oropharyngeal type of dysphagia in approximately 80% of patients during history taking (11).

Differentiation of esophageal muscle opening abnormalities in oropharyngeal dysphagia is still a clinically complex process. On the other hand, the frequent neglect of swallowing problems in elderly patients further complicates the diagnostic process (12).

Swallowing coordination and the pathophysiology of oropharyngeal dysphagia

The oral phase takes place under the control of the left hemisphere, and the pharyngeal phase is regulated by the activity of neurons in the right hemisphere (13). Due to the onset of a neurological disease, there is a disturbance in the processing of sensory information, which results in reduced efficiency of swallowing. Due to the plasticity of the brain, physiological recovery reactions occur, but this recovery during the swallowing process does not allow for complete recovery. With the progress of the disease, there are more massive interruptions of the neural networks, and therefore more difficult swallowing physiology (14).

By monitoring the neural processing of swallowing with magnetic resonance imaging, the involvement of bilateral and widespread cortical and subcortical networks was observed. That network includes the involvement of the frontal part of the brain and the basal ganglia (15). As a result of a stroke, one of the most common causes of death in old age, the synchronization of these brain parts, is disrupted. Depending on the localization of the stroke, the degree of disturbance

of the swallowing process will also depend, given that bilateral coordination in the swallowing process has been proven (16).

Unlike a unilateral stroke, the brain damage seen in Amyotrophic Lateral Sclerosis makes it difficult to restore neuronal connections. With the progression of this disease, there is a decrease in cortical activation which further worsens the swallowing process (17). Lesions outside the upper motor neuron in Bulbospinal muscular atrophy will lead to more severe damage to the frontal cortex responsible for deglutition synchronization (18). Analyzing the activity of neurons in Parkinson's disease, adaptive changes in the swallowing process are observed (19, 20).

Signs and symptoms of oropharyngeal dysphagia in the elderly

Problems with swallowing occur due to physiological changes in muscle mass, abnormalities in the function of the muscles involved in swallowing, chemical changes in the enzymes that shape the bite, due to taste and smell disorders, due to the appearance of many neurological diseases associated with brain aging (3). Therefore, prevalence rates increase significantly with patient age.

The term "presbyphagia" describes physiological changes in swallowing. These changes caused by aging affect every stage of swallowing. In the oral phase of swallowing, there is a disturbance in the formation of bites due to insufficient saliva production. Disturbance in this phase of swallowing affects prolonged activation of the swallowing reflex, leading to frequent aspiration in the elderly (21).

A large number of accompanying symptoms of oropharyngeal dysphagia are often associated with the effects of aging factors and diseases. Over the years, an increasing number of people have had some form of pharmacotherapy every day. Consuming different drugs intended to control various diseases leads to functional changes in the regions involved in the act of swallowing (22). On the other hand, analyzing the function of the regions involved in the act of swallowing in healthy old people, Rogus and Logeman (23) found no differences in the function of swallowing. This supports the fact that the anatomomorphological characteristics of the regions involved in the act of swallowing change physiologically with age, gradually leading to swallowing disorders.

Several studies have shown that a disturbance in the mass and function of the swallowing muscles can lead to a disturbance in the act of swallowing. Analyzing the differences in function and muscle mass, it was concluded that there is a difference between younger and older subjects. Also, this difference was observed between patients of the same age who suffered from various diseases in favor healthy elderly persons (24, 25). The results of this study raised doubts about the connection between muscle mass and function of the whole body with the mass and function of the swallowing muscles, which has not been scientifically confirmed to date.

CONCLUSION

Oropharyngeal dysphagia is a considerable health problem in the elderly and has recently been classified as a geriatric syndrome. Therefore, it is necessary to include dysphagia screening in the elderly to refer the person to a doctor in time. Bearing these facts in mind, this review aims to analyze current knowledge about the etiology, pathophysiology, and symptomatology of oropharyngeal dysphagia in the elderly.

This systematic review and meta-analysis of papers showed significant progress in the effective diagnostic approach of oropharyngeal dysphagia during the last years but also a significant lack of knowledge about adequate modifications of drugs applied during the treatment of patients with dysphagia.

The results of these studies lead us to the need for more professional training on the etiology, pathophysiology, and symptomatology of oropharyngeal dysphagia for all healthcare workers. A good knowledge of the etiology, pathophysiology, and symptomatology of oropharyngeal dysphagia would eliminate the harmful effects of pharmacological substances on the function of swallowing, considering that the elderly, on the advice of doctors, use drugs daily.

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Licensing

Sažetak

OROFARINGEALNA DISFAGIJA KOD STARIJIH OSOBA - ETIOLOGIJA, PATOFIZIOLOGIJA I SIMPTOMATOLOGIJA

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Poremećaji gutanja mogu se javiti u bilo kom životnom dobu, mada se češće javljaju u starosti kada se fiziologija gutanja menja usled starenja. Orofaringealna disfagija je veoma često kliničko stanje koje pogađa 13% ukupne populacije starije od 65 godina i 51% starijih osoba smeštenih u ustanove. S obzirom na to da orofaringealna disfagija može dovesti do povećanja morbiditeta i mortaliteta kod starijih osoba, neophodno je što je moguće više sprečiti pojavu disfagije u ovoj populacionoj grupi. U vezi s tim, ovaj rad ima za cilj da pruži uvid u savremena istraživanja etiologije, patofiziologije i simptomatologije orofaringealne disfagije kod starijih osoba. Za ovaj rad pretražene su elektronske baze podataka Google Scholar Advanced Search-a i Konzorcijuma biblioteka Srbije za objedinjenu nabavku – KoBSON. U pretrazi su korišćene sledeće ključne reči i fraze: gutanje, disfagija, orofaringealna disfagija, starenje, starost i disfagija, etiologija orofaringealne disfagije, klinička slika orofaringealne disfagije, patofiziologija orofaringealne disfagije. Ovaj sistematski pregled i metaanaliza radova pokazali su značajan napredak u efikasnom dijagnostičkom pristupu orofaringealne disfagije tokom poslednjih godina, ali i značajan nedostatak znanja o adekvatnim modifikacijama lekova koji se primenjuju u lečenju pacijenata sa disfagijom. Dobro poznavanje etiologije, patofiziologije i simptomatologije orofaringealne disfagije eliminisalo bi štetno dejstvo farmakoloških supstanci na funkciju gutanja, s obzirom da ih starije osobe, po savetu lekara, svakodnevno koriste.

Ključne reči: poremećaji gutanja, orofaringealna disfagija, starenje.

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Review article

THEORETICAL BASIS OF PERINATOLOGY THERAPY IN PREGNANT WOMEN WITH DIABETES MELLITUS

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Abstract: Diabetes mellitus is a metabolic disorder that can occur before pregnancy, be detected during pregnancy, or develop during pregnancy. Therapeutic modalities available today significantly facilitate glycoregulation during pregnancy and childbirth. This review presents different insulin regimens, as well as the advantages and disadvantages of oral antidiabetic agents use with a special focus on hypoglycemia. The importance of maintaining optimal glycemic levels and educating patients in blood glucose self-measurement is explained.

Keywords*:* diabetes mellitus, pregnancy, insulin.

INTRODUCTION

Diabetes during pregnancy is complicated by sudden hormonal changes that affect the entire organism (1). During pregnancy, maternal glucose passes through the placenta by facilitated diffusion, while amino acids are actively transported. As pregnancy progresses, its diabetogenic effects are conditioned by the following factors:

1. Increased production of placental hormones that antagonize the effect of insulin
2. Placental enzymes break down the mother's insulin
3. Increased production of glucose in the mother's organism during starvation.

The diabetogenic effect is primarily made by human placental lactogen (hPL). Circulating levels of this hormone increase in parallel with placental growth. hPL increases the production of higher fatty acids by stimulating lipolysis. More fatty acids lead to peripheral insulin resistance through the down-regulation of insulin receptors and thus to compensatory hyperinsulinemia (2).

Frequency of measurement and standard values of glycemia

To achieve a state of euglycemia, frequent measurement of blood glucose is necessary. The introduction of mobile devices for measuring blood glucose levels has made it possible for people with diabetes to control their glycemia several times during the day. The first report on glycemia measurement performed by patients themselves (SMBG - Self-Monitoring of Blood Glucose) confirmed that SMBG is flexible, practical, and affordable for patients; that the glucose values obtained in this way are suitable for clinical analysis; and that glycemic control may be improved if SMBG is used as part of a standard therapeutic protocol. As a result, SMBG has become the main method of ambulatory control of gestational diabetes. However, some metabolic and physiological changes during pregnancy interfere with the accuracy of measurements and affect the results obtained. During pregnancy, glucose and hematocrit values are lower, while triglycerides and cholesterol are increased. These changes can affect the accuracy of the measurement (3).

Langer et al. (4) conducted a large prospective study to determine the optimal glycemia of women with gestational diabetes mellitus (GDM). Their data, collected from 246 women with GDM, show that

women who achieve optimal glycoregulation have a lower incidence of macrosomia and children who are large for gestational age (LGA - Large for Gestational Age). The incidence of LGA babies increases from 9% to 24% if glycemia exceeds 105 mg/dL. In a subsequent study (5) on the same group of women, it was shown that if the average glycemia is below 100 mg/dL, the incidence of LGA and macrosomia is the same as in the general population. Then, average glycemia below 110 mg/dL has a protective effect on the fetus's metabolism and respiratory system, preventing complications. These data suggest that it is possible to compare the glycemia needed to prevent perinatal morbidity between women with pregestational and gestational diabetes.

Postprandial glycemia was found to correlate better with fetal macrosomia compared to fasting glucose values. DeVeciana et al. (6) obtained similar results when they compared the effect of pre-and postprandial glycemia on the incidence of pregnancy complications in women with insulin-dependent diabetes. Macrosomia was more common in the group of women who measured glycemia before meals compared to the other group of women. Then, in the group of women who measured postprandial glycemia, a greater drop in glycosylated hemoglobin was recorded. Therefore, it was concluded that insulin therapy in women with diabetes during pregnancy should be adapted to postprandial glycemia because this achieves better glycemic control and reduces the risk of macrosomia and other complications. It is recommended to measure blood glucose levels after a meal instead of in a fasting state.

Methods of self-measurement of blood glucose

Although self-measurement of glycemia has revolutionized the control of diabetes, it still has certain limitations and does not show the most accurate variations of glycemia that occur during the day. Therefore, devices that constantly measure glycemia have been sought for a long time to ensure better control of diabetes. The Continuous Glucose Monitoring System (CGMS) is marketed by Medtronic. MiniMed was the first meter of this group to become available for use. It is a holter that works with the help of sensors and automatically and continuously measures glucose from the subcutaneous tissue. The monitor is connected to a small sensor (microelectrode) that is implanted under the skin and measures the glucose level. The sensor generates electrical impulses whose strength corresponds to the concentration of glucose in the subcutaneous tissue. The signal travels to the monitor, a pager-sized mobile device that records signals every 5 minutes and converts them to glycemic values, providing 288 readings during the day over three days. Data is entered into the computer; The software then creates graphs and pies that represent glycemic changes. Although CGMS has been proven to be a useful method for normalizing HbA1c levels outside of pregnancy with poorly controlled type 1 diabetes, a large number of unexpected asymptomatic hypoglycemias during the night have been reported (7).

To reduce complications, the executive committee of the American Diabetes Association (8) recommends that the blood pressure of people with diabetes should be up to 130/80 mmHg. Patients with DM type 2 have a lipid metabolism disorder that results in a higher rate of cardiovascular disease. Diabetics usually have increased triglycerides and decreased high-density lipoproteins (HDL). Lipidemia control is aimed at reducing low-density lipoprotein (LDL), cholesterol, and triglycerides and increasing high-density lipoprotein (HDL).

Insulin therapy

During pregnancy, conventional insulin therapy is replaced by intensive therapy to achieve better disease control. Patients are transferred to an appropriate dietary regimen, informed about the action of insulin, and trained to recognize and react to hypoglycemia, then to adjust insulin doses to daily activities and accompanying diseases, as well as to monitor hyperglycemia and the eventual appearance of ketosis.

Insulin is given in a dose that meets basal and mealtime needs, with rapid adjustment to blood glucose levels. The therapeutic regimen includes three or four daily doses of insulin or continuous application using a pump. Regardless of the regimen used, frequent self-monitoring of glycemia is necessary to establish physiological control (9). Patients are trained to dose insulin according to the meals taken, as well as during the night. Meal-adjusted insulin doses depend on its composition, pre-meal glycemia, and physical activity.

In patients with poor disease control, a short hospitalization is often required to initiate therapy. This way, the recommended therapy is adapted to individual needs. For many patients, being able to take control of their disease is of great importance (9, 10).

Therapeutic regimen with multiple daily doses

Insulin is most often given in two to three doses, more often in three doses, although many patients prefer a combination of intermediate-acting and short-acting insulin before dinner and breakfast. The

general rule is that the amount of intermediate-acting insulin exceeds the value of natural insulin by one to two units. Patients usually receive two-thirds of the required dose of insulin before breakfast and the rest in the evening as a combined dose during dinner or divided into two smaller doses. In this case, a combination of short-acting insulin before dinner and intermediate-acting insulin at bedtime is given to prevent nocturnal hypoglycemia. These episodes of hypoglycemia occur when the mother is in a state of starvation, so the placenta continues to use glucose (9, 10).

Continuous subcutaneous insulin infusion

Literature data (9, 11) show that the use of a pump for CSII (Continuous Subcutaneous Insulin Infusion) during pregnancy is still very significant today. This pump is battery operated and attached to the anterior abdominal wall, and can be worn during normal daily activities. This system provides a constant supply of short-acting insulin that is administered subcutaneously. Doses covering basal needs, as well as boluses given before meals, are determined based on blood glucose values. Pregnant women often have to be hospitalized before starting therapy. They are trained on standard continuous insulin therapies and manage to stabilize glycemia within a few days. This means that numerous measures must be taken to prevent episodes of hypoglycemia and hyperglycemia.

Insulin requirements

It is well known that the need for insulin increases significantly during pregnancy due to the increase in the concentration of antagonistic hormones. Several studies (12) have attempted to document the changes in insulin doses required to maintain glycemic control during pregnancy. As these data provide insight into the characteristics of certain populations, control must be carried out at the individual level because insulin dosing is based on the algorithm of glycemic values reported by each patient individually.

An increase in the need for insulin is expected during the second trimester of pregnancy, and it depends in part on the current body weight as well as the pre-pregnancy weight. The significant reduction in insulin requirements remains unexplained and may not be associated with fetal death. Also, it is considered that this phenomenon does not affect the outcome of the pregnancy (13).

Insulin-induced hypoglycemia

Hypoglycemia is a limiting factor for intensive insulin therapy in patients with type 1 diabetes. Most patients with DM type 1 are left without any reserve of β - cells within a few years, with a simultaneously weakened response of α - cells (glucagon) to hypoglycemia, which leads to serious hypoglycemic episodes (13). Women with longstanding diabetes may be deficient in epinephrine, cortisol, and growth hormone in response to insulin-induced hypoglycemia. These individuals typically experience 1-2 symptomatic hypoglycemia episodes each week. Transient hypoglycemia progressing to coma or EPI attacks develops in more than 25% of patients with type 1 DM, while the mortality rate exceeds 4% per year. The fear of severe hypoglycemia can cause psychological instability in patients, and the doctor must search within different regimens of insulin therapy until finding the optimal one so that the patient is under control (14).

Cryer and Gerich (15) defined three categories of physiological conditions that can seriously compromise glycoregulation and lead to hyperinsulinemia, i.e. hypoglycemia: (a) unawareness of hypoglycemia: absence of neurogenic (autonomic) symptoms of hypoglycemia; (b) defective counterregulation due to a combined defect of glucagon and the adrenal response to falling glycemia (c) reduced glucose threshold - lower glycemic values are required for symptoms to appear and counterregulatory mechanisms to be triggered; this happens during intensive therapy and reduction of the total amount of circulating glucose. Although hypoglycemia-related conditions have a similar pathophysiological basis including a reduced response of the autonomic nervous system to hypoglycemia, they are still considered separate entities from diabetic autonomic neuropathy.

Research (16, 17) suggests that hypoglycemia lowers the glucose threshold required to elicit a symptomatic and autonomic response in nondiabetic patients. These findings were also confirmed in patients with DM type 1, so it became clear how previous hypoglycemia leads to the “circulus vitisus”, that is, it reduces awareness of the event, as well as the autonomic response to it. It is believed that avoiding hypoglycemic episodes in patients with DM type 1 who are unable to recognize it leads to improvement, primarily by increasing the sensitivity of β-receptors.

The risk of hypoglycemia during pregnancy is increased because the placenta continues to use glucose while the mother is in a state of starvation, and exogenous insulin, on the other hand, limits the use of other substances. There is no clear evidence that hypoglycemia has teratogenic potential during human pregnancy, but caution is advised, given that the results of studies investigating subtle effects on neurobehavioral development are suspect. Notably, the results of a large study, the California Gestational Diabetes Project (18),

failed to show a link between maternal hypoglycemia and neonatal malformations.

Control during childbirth

The goal of diabetes control during labor is to maintain euglycemia. Hyperglycemia during labor significantly increases the risk of neonatal hypoglycemia. This condition may be present at birth despite excellent glycemic control before delivery. Monitoring a pregnant woman with diabetes during childbirth requires special attention to the mother's glycemia value, then the value of the ingested glucose and the dose of insulin. In general, glucose measurement is performed every 1-2 hours with a mobile glucose meter standing next to the bed (19).

There are several approaches used to maintain maternal euglycemia during labor. An infusion solution containing glucose and insulin is most often used. Ten units of natural insulin are added to 1000 ml of 5% dextrose solution. The infusion is given at a dose of 100 – 125 ml/h and usually results in good control. Insulin can also be given in a syringe in a dose that normalizes glucose values. In women who use an insulin pump, insulin can also be administered in this way. If hyperglycemia persists for a long time, the pump can be switched to intravenous administration (20).

Several studies (21, 22) show that the administration of oxytocin did not affect glycemic control. This decrease in the need for insulin can be explained by a decrease in the level of antagonistic hormones produced by the placenta. Well-controlled studies by Jovanovic and Peterson (23) showed a reduced need for insulin and constant glucose monitoring in the first stage of labor. They used a glycemic-controlled insulin infusion system, the Biostator, showing that insulin requirements dropped to zero during the first stage of labor while glucose was administered at a dose of 2.55 mg/kg/min to maintain a glycemia of 70 - 90 mg/dL.

In patients who deliver by caesarean section, the operation is planned for the morning hours to ensure optimal glycemic control. Patients were trained to take their usual evening dose of insulin the day before delivery. They do not take food in the morning, and they keep the usual morning dose of insulin. Before epidural anesthesia, the intravenous line should ensure volemia to prevent hypotension, and intravenous fluids do not contain glucose. Epidural anesthesia is convenient because it allows the anesthesiologist to monitor the mental status of the patient, as well as the development of possible hypoglycemia. After the operation, glucose levels are measured every 2 hours, and a dextrose infusion solution is given (24).

After childbirth, the need for insulin decreases significantly. The requirement to ensure strict glycemic control before delivery is no longer so strict. Patients who gave birth vaginally can eat and receive, under the control of an endocrinologist, half of the prenatal dose of NPH insulin on the first day after delivery in the morning hours. If the insulin doses from the period before pregnancy are not known, usually after delivery, 1/2 or 1/3 of the dose given before delivery is given. A similar reduction in insulin dose is applied to women using an insulin pump. Frequent blood glucose measurements help with insulin dosing. Insulin should be prescribed based on previous and current glucose values, and the same applies to diet. If subsequent natural insulin is given with the morning dose of NPH insulin, the amount of NPH insulin given the next morning is increased by 2/3 of the natural insulin given. In this way, most patients stabilize a few days after giving birth (25).

Patients who have had a caesarean section receive regular doses of insulin over the next 24-48 hours to maintain glycemia. If the diet they follow is successful, NPH insulin is given in a dose that corresponds to their needs during the previous day. For women using an insulin pump, the insulin dose is approximately half of the dose at the end of pregnancy. Similarly, boluses are reduced by a third or half of the dose at the end of pregnancy. All women can breastfeed their children after giving birth. Insulin requirements may be lower in lactating women (26).

Oral antidiabetic therapy

The drugs available today are divided into three groups: insulin secretagogues, drugs that increase the sensitivity of insulin receptors, and α-glucosidase inhibitors (27). Available drugs from the group of insulin secretagogues include sulfonylurea derivatives (glyburide, glipizide, glimepiride) and newer meglitinide preparations (nateglinide, repaglinide). Both groups of drugs act on the potassium channels of β-cells by performing depolarization and thereby stimulating the secretion of insulin, which is independent of glucose intake. The difference between these two classes of drugs is initially the duration of their action, although the latest research shows that these substances have a certain affinity for cardiac receptors (SUR2), which may change the current recommendations on their use. Meglitinides are non-sulfonic drugs with a rapid onset and short duration faction and must be taken before each meal, and their short action results in mild postprandial hypoglycemia (28).

Drugs that increase the sensitivity of insulin receptors include biguanides (metformin) and thiazoli-

dinediones (pioglitazone, rosiglitazone). Biguanides increase the action of insulin by increasing the release of glucose from the liver, while thiazolidinediones act on peripheral tissues by increasing their sensitivity to insulin (29).The good side of both of these groups of drugs is that they do not cause hypoglycemia, since they do not increase the release of insulin. However, gastrointestinal complaints such as diarrhea and dyspepsia can limit its use, as can lactic acidosis, a rare but potentially fatal complication. To reduce the risk of lactic acidosis, metformin should not be given to patients with impaired liver and kidney function, congestive heart failure, and patients who consume large amounts of alcohol (30).

CONCLUSIONS

Diabetes mellitus is characterized by insufficient insulin secretion and/or peripheral insensitivity to insulin. Achieving optimal glycemic control in pregnant women with diabetes mellitus is necessary to avoid adverse pregnancy outcomes. This is usually achieved with a specifically targeted insulin regimen and close monitoring of glucose blood levels. Two main insulin regimens: Basal and meal-dependent secretion are mimicked by either continuous or interval insulin use. Frequent measurement of glycemia can be bypassed by insulin pump use. Hypoglycemia is one of the main concerns of insulin and oral antidiabetic agents, and patients should be advised on how to recognize it. The prevention of micro- and macrovascular complications requires a joint approach that, in addition to normalizing glycemia, includes strict control of lipid status and blood pressure.

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Sažetak

TEORETSKE OSNOVE PRIMENE TERAPIJE U PERINATOLOŠKOM PERIODU KOD TRUDNICA SA DIJABETES MELITUSOM

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Dijabetes melitus je metabolički poremećaj koji se može javiti pre trudnoće, otkriti u trudnoći ili razviti tokom trudnoće. Terapijski modaliteti koji su danas dostupni značajno olakšavaju glikoregulaciju tokom trudnoće i porođaja. U ovom pregledu prikazani su različiti insulinski režimi, kao i prednosti i mane oralne antidijabetične terapije sa posebnim osvrtom na hipoglikemiju. Objašnjen je značaj održavanja optimalnih nivoa glikemije i važnost edukacije pacijentkinja da same mere nivo ešećera u krvi.

***Ključne reči**:* dijabetes melitus, trudnoća, insulin.

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RETRACTION NOTE

RETRACTED ARTICLE: THE EFFECT AND IMPORTANCE OF EXTRAHEPATIC BILE DUCT ANATOMY VARIATIONS IN THE ETIOLOGY OF HOLEDOCHOLITHIASIS

Sönmez Süleyman, Bozdağ Emre, Cingöz Mehmet, Cingöz Eda, Samadli Vugar

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This paper is retracted at the request of the authors due to the potential existence of a conflict of interest and disagreements between the authors and the head of the department where the research was conducted, regarding the holder of the authorship.

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ERRATUM

ERRATUM FOR ARTICLE: COMPARISON OF CARDIAC MAGNETIC RESONANCE AND CARDIAC ULTRASOUND IMAGING FINDINGS IN CONGENITAL AND ACQUIRED HEART DISEASES

Serdar Serinsoz, Remzi Akturk, Sibel Bayramoglu

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The authors of this paper informed us about the existence of an error. Remzi Akturk has been listed as a co-author in this article. In order to prevent ethical issues, all authors of this article agreed that he should be listed as a guest author instead of co-author because he did not contribute in data collecting. Because of that, the name Remzi Akturk is removed from the author's list in this article.

All authors send a signed agreement that the name of Remzi Akturk must be removed from the author's list.

According to this, the list of the authors on pages 115 and 119

"Serdar Serinsoz, Remzi Akturk, Sibel Bayramoglu"

should be replaced with:

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Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 350 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada.

U izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

Ako je uveličanje značajno (fotomikrografije) ono treba da bude naznačeno kalibracionom linijom na samoj slici. Dužina kalibracione linije se unosi u legendu slike.

Uz fotografije na kojima se bolesnici mogu prepoznati treba poslati pismenu saglasnost bolesnika da se one objave.

Za slike koje su ranije već objavljivane treba navesti tačan izvor, treba se zahvaliti autoru, i treba priložiti pismeni pristanak nosioca izdavačkog prava da se slike ponovo objave.

Pisma uredniku. Mogu se publikovali pisma uredniku koja se odnose na radove koji su objavljeni u SANAMEDU, ali i druga pisma. Ona mogu sadržati i jednu tabelu ili sliku, i do pet referenci.

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The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page.

References in the text are designated with Arabic numerals in parentheses, and the order in which they appear in the text.

Manuscript volume. The complete manuscript, which includes title page, short abstract, text of the article, literature, all figures and permisions for them and legends (tables, images, graphs, diagrams, drawings), title page and abstract in English, can have the length up to 5000 words for original paper, report, paper on the history of medicine and literature overview, while for patient presentation, practice paper, educative article it can be up to 3000 words, and other papers can be up to 1500 words.

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A short title of less than 50 spaces, for use as a running head, is included.

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A list of abbreviations used in the paper, if any, is included. List abbreviations alphabetically followed by an explanation of what they stand for. In general, the use of abbreviations is discouraged unless they are essential for improving the readabillity of the text.

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Review of the literature include: an introduction, subheadings, conclusion, references.

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Methods are described in sufficient detail to permit evaluation and duplication of the work by other investigators.

When reporting experiments on human subjects, it should be indicated whether the procedures followed were in accordance with ethical standards of the Committee on human experimentation of the institution in which they were done and in accordance with the Declaration of Helsinki. Hazardous procedures or chemicals, if used, are described in detail, including the safety precautions observed. When appropriate, a statement is included verifying that the care of laboratory animals followed the accepted standards.

Statistical methods used, are outlined.

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References. References are identified in the text by Arabic numerals in parentheses. They are numbered consecutively in the order in which they appear in the text. Number of references should not exceed 30, except in the literature review, which is allowed to be to 50.

Avoid using abstracts as references and abstract older than two years are not cited.

References are cited by the so-called Vancouver rules, which are based on formats that use the National Library of Medicine and Index Medicus. The following are examples:

1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

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