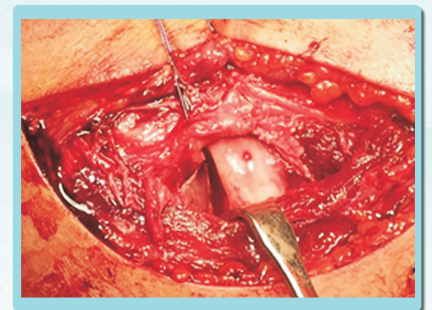
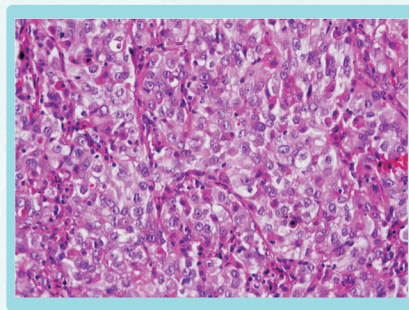
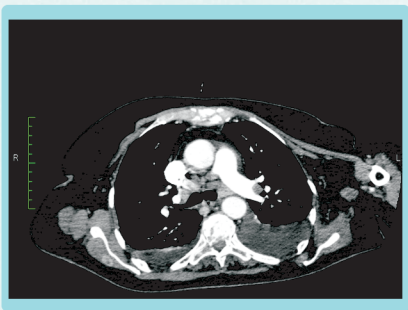




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The European Research Journal is the product of several friends who have merged their dreams, talents, and experiences in order to carry them forward to a meaningful hope. It has been dreamed, designed and brought into reality within months. It has aimed to challenge the idea of “we cannot do serious things”; which has been in our minds for a very long period of time.

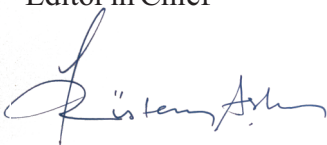
The European Research Journal has a very powerful goal and it reflects an intense labor; it is the product of a dedicated teamwork which has been reviewed many times from the start of its web-design to every single word within the journal and the publishing council. Right after the back-cover of the journal, we have headed to the doors of a new university with its sky-blue colors.

As we greet our readers in our first issue, we did our part in regards to the necessities of becoming an international journal. We are aware of the fact that publishing a journal requires hard-work, serious team harmony and time. Instead of sitting in the back with competent brains, we have decided to be present in the front line. We have hit the road not to be dragged by others, but to do the best we can. We have started with this belief, our determination and discipline will provide us the result.

Our journal is also designed to say “no” to those who work hard but stay away from academics, thinking they are lacking skills in regards to statistics and foreign-language. Our aim in evaluating article is to build an educational platform which offers suggestions that would allow the article to get published no matter the level of the submitted work.

This journal is an invitation letter to sing new songs for those of you who refuse to go back and forth between home, work and entertainment and who would not wait things to happen. It has been sent to those people who wish to contribute to the joint heritage of humanity. February 2015 is the date it has been delivered to the address.

Best Regards,  
Prof. Dr. Rustem Askin  
Editor in Chief



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Starting from the date of EuRJ was founded, which is a two months period; EuRJ has already 11 editorial staffs, 124 registered authors, and 94 reviewers. Eighteen manuscripts have been submitted to our journal. Nine of them were accepted, 2 rejected, and the others are on evaluating process by our advisors. After the release of the first issue, in a short time period, ISSN application process will also be completed by the Ministry of Culture. The European Research Journal is fulfilling the requirements for being an international journal from the first issue. EuRJ has a strong advisory board with eminent scientists in the field and carries a stringent peer review process. The Journal has 18 international and 86 national advisory board members.

The aim of our journal is to represent our country in the international scientific community. Applications for international indexing such as PubMed and SCI-Expanded will begin and hopefully process quickly after the publication of the first issue.

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## The Role of Metformin on Serum Vitamin B12 Levels in Patients with Type 2 Diabetes Mellitus

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### ABSTRACT

**Objectives.** To evaluate the vitamin B12 (VB12) deficiency in patients with type 2 diabetes mellitus (DM-2) using metformin or other hypoglycemic agents. **Methods.** 400 patients with DM-2 were divided into two arms (N = 200/group); 1) those receiving metformin (MET) for at least six months and 2) those receiving hypoglycemic agents other than metformin (OHA). Serum VB12 concentrations were measured. Data were analyzed by using two-sample t-test for numerical data and chi-square with logistic regression analysis for categorical data. Numerical values were expressed as means ± standard deviations. Null hypotheses were rejected at P < 0.05. **Results.** Definite biochemical VB12 deficiency (<148 pmol/L) was found in 29/200 (14.5%) of the MET group while it was observed in 4/200 (2%) in the OHA group (P < 0.001). Similarly, possible VB12 deficiency (serum concentrations <185 pmol/L) was found in 39 (19.2%) of the MET group and 12 (6%) in the OHA group (P < 0.001). There was positive correlation between low VB12 level and metformin administration (R<sup>2</sup> = 0.26, P < 0.001). **Conclusions.** Patients with DM-2 on metformin had lower VB12 levels than those on other hypoglycemic drugs. The relation between VB12 deficiency and metformin therapy indicates the need for periodic measurement of serum VB12 levels in patients treated with metformin.

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**Keywords:** Oral medications, type-2 diabetes, metabolic syndrome, HbA1C, diabetic neuropathy

### Introduction

The care for diabetic patients is a complex process and involves managing disease complications, drug related side effects in

addition to glycemic control. There is supporting evidence that various interventions improve clinical outcome in patients with this disabling

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disease [1]. Metformin is increasingly considered as an important component of the therapeutic standards in patients with type-2 diabetes mellitus (DM-2) [2]. It is usually well tolerated, although it may be associated with some gastrointestinal discomfort [2]. The American Diabetes Association (ADA) recommends metformin and lifestyle modification as the first line therapies for DM-2 [1]. Metformin is one of the few oral hypoglycemic agents that have been shown to improve cardiovascular morbidity and mortality among diabetic patients [3,4]. The unique effect of metformin on restoring sensitivity to insulin has greatly improved the prognosis of diabetic patients and provided added protection against vascular complications [5]. Previous studies suggest a higher prevalence of vitamin B12 (VB12) deficiency in diabetic patients treated with metformin [6, 8]. Although the association between metformin and VB12 deficiency has been widely described, little is known about its underlying pathophysiology. VB12, aka cobalamin, is a water-soluble vitamin that is essential for the normal function of the nervous system and erythropoiesis, through its required role in DNA synthesis. VB12 is essential for three enzymatic processes including the conversion of: a) homocysteine to methionine, b) methylmalonic acid to succinyl coenzyme A, and c) 5-methyltetrahydrofolate to tetrahydrofolate [9,10]. VB12 deficiency manifest itself with hematologic findings in the form of, macrocytic (megaloblastic) anemia and, in advanced cases, pancytopenia. Clinical signs and symptoms are divergent and go beyond the hematologic system. Nervous system is commonly affected in VB12 deficiency and causes varying degrees of sensory neuropathy progressing to combined sclerosis of the spinal cord in severe cases [11,13]. From a clinical standpoint, identification and prevention of metformin-related VB12 deficiency is the key to providing better care for diabetic patients [14].

In this study our primary aim was to define the prevalence of VB12 deficiency in DM-2 patients treated with metformin, and compare them to those patients receiving other hypoglycemic agents. Our primary endpoint was the occurrence

of serum VB12 concentrations below 148 pmol/L. We hypothesized that the prevalence of cobalamin deficiency is higher in patients receiving metformin as a part of their oral hypoglycemic regimen. The secondary aim of this study was to assess for confounding factors that may contribute to this vitamin deficiency.

## Materials and methods

The protocol and study design were reviewed and approved by the institutional review board of Tabriz University of Medical Sciences and its affiliated hospitals for its scientific merit and ethical consideration. The study design was cross-sectional and descriptive in nature. All study subjects were recruited from the pool of DM-2 patients presented to Tabriz University Endocrinology Clinic from January 2011 to March 2013. Following a careful screening for inclusion and exclusion criteria, the subjects were approached by one of the study team members and an informed consent was obtained. The enrolled patients were divided in two groups: 1) those receiving metformin for at least the past six months (MET; N=200); and 2) those receiving hypoglycemic agents other than metformin (OHA; N=200). Out of 200 patients in OHA group, 153 patients were on insulin alone; 12 were on insulin plus pioglitazone hydrochloride; 17 were on glibenclamide and 18 patients were on combination therapy with glibenclamide and pioglitazone hydrochloride.

Subject number and the related power was calculated by MedCalc Software® (Ostend, Belgium) based on the previously published serum VB12 concentrations in DM-2 patients on metformin. Considering a 7% difference in the prevalence of VB12 deficiency reported previously and accepting an alpha error of 0.05, inclusion of 400 patients yielded a power of 80% for this study.

Inclusion criteria were all type-2 diabetic patients within the age range of 18 to 65 years old who were on metformin minimum daily dose of 1 gram for past 6 months for the MET group, and no history of metformin use in the past five years

**Table 1.** Basic parameters between two studied groups

	<b>MET N=200</b>	<b>OHA N=200</b>	<b>P-Value</b>
Age (years)	52.2 ± 7.3	51.6 ± 10.0	0,78
Gender Male/Female	63/137 (31.5%)	68/132 (34%)	0,67
Weight (kg)	77.7 ± 13.1	76.3 ± 8.0	0,3
Height (m)	1.62 ± 1.09	1.62 ± 0.08	0,3
Body Mass Index (kg/m <sup>2</sup> )	29.7 ± 4.7	28.9 ± 3.7	0,11
Duration of the disease (years)	7 77 ± 5 56	8 12 ± 7 57	0 12

MET: metformin, OHA: oral hypoglycemic agent

for the OHA group.

Exclusion criteria were patients older than 65 years, alcoholism or drug abuse, known cases of malabsorption (gastrointestinal surgery, inflammatory bowel diseases and gluten allergy), chronic kidney disease with eGFR<30 mL/min (Stages IV and V), pernicious anemia, history of thyroid disease and thyroxin treatment and/or a history of other organ-specific autoimmune conditions (vitiligo, Addison's, primary ovarian failure, hypoparathyroidism), consumption of VB12 supplementation during the last three months, and receiving antibiotics or any medications known to influence gastrointestinal motility.

The demographic and related clinical data were collected by a study team member and recorded in Microsoft Excel worksheet. Comprehensive medication history was also documented. Fasting venous blood was obtained and blood samples were analyzed for complete blood cell count, comprehensive metabolic panel by the reference laboratory. Serum samples were then analyzed for VB12 concentrations by the same reference laboratory. This laboratory utilizes the Siemens Dimension Vista® system for VB12 assays. This system is based on a competitive immunoassay using direct chemiluminescent technology in which VB12 from the patient sample competes with VB12 labeled with acridinium ester. The system reports Vb12 results in pg/mL (mass units) and then converted to pmol/L (SI units). The conversion formula is 1 pg/mL = 0.74 pmol/L. The reportable range of this assay is 45 pg/mL (33 pmol/L) to 2000 pg/mL (1476 pmol/L). There is no definite consensus about the cut-off point of

VB12 deficiency, mainly because of diversity in studied populations and applied assay kits [15]. In this study, we defined deficiency as serum VB12 level of less than 148 pmol/L (200 pg/mL) [16]. Statistical analysis was performed using SPSS software package version 16.0 for windows. Numerical data were presented as mean ± standard deviation, while categorical variables were demonstrated as frequency and percentage (%). Categorical variables were compared by chi square test with Fisher's exact test while numerical variables were compared using independent samples t test. The correlations between variables were assessed by logistic regression analysis and the correlation coefficient values were reported. Null hypotheses were rejected when the P values were less than 0.05.

## Results

Out of 400 patients 131 (32.8%) were male and 269 (67.2%) were female. The average age for all patients was 51.9 ± 7.1 years old (range: 26-65 years). The average duration of disease in our series was 7.9 ± 5.2 years. There was no difference in age, body mass index and gender distribution between the MET and the OHA groups (Table 1). The average dose for metformin was 1255 ± 21 mg/day in the MET group. Serum concentrations of VB12 were 320 ± 18 pmol/L in the MET group, which were significantly lower than those of 410 ± 24 pmol/L in the OHA group (P<0.001). VB12 deficiency as defined by serum concentrations below 148 pmol/L was recognized in 33 out 400 patients (8.2%). VB12 deficiency

**Table 2.** Comparison of blood sugar, lipid profile, and blood markers between two studied groups

	<b>MET</b> <b>N=200</b>	<b>OHA</b> <b>N=200</b>	<b>P-Value</b>
Fasting Blood Sugar (mg/dL)	151.5 ± 50.5	159.2 ± 69.2	0.76
Hemoglobin A <sub>1</sub> C (%)	7.8 ± 1.3	8.2 ± 1.6	0.18
Triglycerides (mg/dL)	166 ± 73	154 ± 68	0.12
Cholesterol (mg/dL)	176 ± 64	178 ± 40	0.26
High Density Lipoproteins (mg/dL)	45.8 ± 11.6	43.8 ± 10.2	0.17
Low Density Lipoproteins (mg/dL)	98.2 ± 29.4	101.2 ± 28.7	0.12
Hemoglobin (g/dL)	14.5 ± 6.5	14.3 ± 5.9	0.69
Hematocrit (%)	42.1 ± 5.6	42.4 ± 4.5	0.57
Mean corpuscular volume (fL/RBC)	88.2 ± 5.2	88.9 ± 5.2	0.09
Serum Creatinine (mg/dL)	0.98 ± 0.20	1.06 ± 0.30	0.32

MET: metformin, OHA: oral hypoglycemic agent

## Discussion

was found in 29 patients (14.5%) of the MET group and 4 patients (2%) in the OHA group ( $P < 0.001$ ). There is a positive correlation between low VB12 levels and the use of metformin ( $R^2 = 0.26$ ,  $P = 0.001$ ). However, there was no significant correlation between VB12 levels and metformin dose ( $P = 0.711$ ).

Fasting serum glucose concentrations, as well as an indicator of long-term glucose control, hemoglobin A1c (HbA1C), was similar in the MET group compared to the OHA group (Table II). Similarly, there was no significant difference between the two treatment groups in their lipid profile, serum creatinine concentrations and hematologic profile (Table 2).

Additionally, there was no correlation between serum concentrations of VB12 and blood percentages of HbA1C in either study population. Spearman rank coefficient for this correlation was 0.091. Serum level for HbA1c was  $7.8 \pm 1.1$  % in patients with definite VB12 deficiency, which was comparable to  $8.3 \pm 2.0$  % in patients with possible VB12 deficiency and to  $8.0 \pm 1.5$  % in patients with normal serum VB12 ( $P = 0.45$ ).

In this study, we evaluated and compared the prevalence of VB12 deficiency in 400 patients with DM-2 using metformin or other hypoglycemic agents. Our study confirmed the finding of previous studies that metformin decreased serum VB12 levels and was associated with VB12 deficiency [14, 17-19]. Similarly, a randomized placebo-controlled trial of metformin for a period of 4 months on 390 patients with DM-2, reduced serum folate and VB12 level [19]. Therefore, the measurement of serum VB12 level may offer clinical guidance in managing diabetic patients on metformin therapy.

A study in a military primary care clinic estimated the prevalence of VB12 deficiency of 22% of the type 2 diabetic populations. They concluded that VB12 deficiency should be considered in DM-2 patients taking metformin, and recommended daily multivitamin in take to prevent VB12 deficiency [20]. VB12 deficiency has been defined by low serum levels of this vitamin ( $< 148$  pmol/L) in our series [16]. This is widely accepted serum concentration that is

considered as VB12 deficiency although its clinical presentation and severity vary from one patient to another [20]. Despite of lower serum concentrations of VB12, we did not encounter any clinical manifestations of vitamin deficiency in our series. Although we were not able to screen the patients for every subtle and non typical symptom of VB12 deficiency such as fatigue, memory loss, the question whether serum VB12 is an appropriate surrogate for the clinical diagnosis is still debatable. Additionally, there is significant overlap in neurologic symptoms of VB12 deficiency and diabetes that limits the specificity of these symptoms. Most of the studies previously have reported a 14-30% decrease in serum VB12 concentrations by oral metformin in diabetic patients. These authors have proposed a reduction in VB12 absorption in patients taking metformin for 6 months as the cause of VB12 deficiency [19, 21]. VB12 is released from animal proteins after being exposed to gastric acidity. After combining with intrinsic factor (IF) produced by gastric parietal cells, IF-B12 complex is absorbed in the terminal ileum [10].

Metformin induces VB12 malabsorption, which may increase the risk of developing VB12 deficiency [14, 17]. It is speculated that metformin may deteriorate cobalamin absorption by decreasing the reabsorption of bile salts in the ileum [22]. Interestingly, these authors and others report a reversal in VB12 malabsorption by increasing oral calcium intake that hastens the absorption of IF-B12 complex from the ileal mucosa [21, 23]. This discovery may be considered in treating diabetic patients on metformin who presents with drops in serum VB12 concentrations.

Additionally, metformin alters bacterial flora through an effect on gastrointestinal motility resulting in bacterial overgrowth similar to blind loop syndrome, which will further lead to VB12 malabsorption [21]. States of vitamin B12 deficiency and malabsorption were reported with increasing age > 70 years, [24, 26] and severe cases hypothyroidism [27]. However, in our case mix, we excluded those older than 65 years and clinical cases of hypothyroidism. Exclusion of

these patients is the most probable explanation for lack of association of vitamin B12 deficiency with age in our data series. It has been reported that higher doses and longer treatment with metformin are risk factors for B12 deficiency [14, 20]. Ting et al compared 155 DM-2 patients with metformin-related VB12 deficiency as defined in this study (< 140 pmol/L) with 310 matched controls. The dose of metformin was the strongest independent predictor of VB12 deficiency. In this case control study of metformin-related VB12 deficiency, metformin dose and duration of treatment emerged as the most consistent risk factors of VB12 deficiency within a diabetic population [14]. In a cross-sectional study in DM-2 patients treated with metformin, the mean time on metformin treatment was 43.5 months and mean drug dose was 1779 mg/day. Patients taking metformin had significantly lower VB12, but no correlation was found between VB12 plasma levels and metformin treatment time or dosage [28]. Liu et al examined the records of 56 geriatric patients with DM-2 treated with metformin and compared to those of 78 patients who were treated by other means [29]. The mean serum VB12 level was lower in the metformin group by 100 pmol/L. Eight patients in the metformin group and only 3 patients in the nonmetformin group had severe VB12 deficiency (<100 pmol/L). These authors while established a dose dependent pattern for serum VB12 concentrations, they were unable to demonstrate that serum VB12 levels further decrease as the duration of metformin increases. In the study by Nervo et al, serum VB12 level were inversely associated with age and the duration of metformin therapy, and directly associated with the estimated VB12 intake [17]. However, the association of metformin dose with serum VB12 level was not significant. In current study, serum VB12 levels were not associated with the dose of metformin. However, we could not make any comment about the duration of metformin therapy, as this variable was not recorded. Epidemiological studies have shown that the risks of both DM-2 and VB12 deficiency increase with age [18, 30]. The prevalence [ of VB12 deficiency has been reported to range from 20% to 60% in



the elderly population which is significantly higher than that in younger individuals [31]. Again, in our series we did not find any correlation between age and serum VB12. This disagreement between our findings and those previously published might have been due to the inclusion criteria, which limited our patient population up to 65 years old. The strengths of this study include its population based sampling. Moreover, the presence of a control group makes it possible to compare prevalence of VB12 deficiency in a similar diabetic patients not taking metformin. However, this study has important limitations. We have used only the serum VB12 level to define vitamin deficiency and we have not measured serum methylmalonic acid and homocysteine levels, which are more sensitive indicators of VB12 status than serum VB12 levels. Additionally, we have not recorded the amount of non-supplemental VB12 ingestion and therefore the daily intake of the VB12 from food resources has been ignored prior to blood sampling.

## Conclusions

Metformin therapy is associated with a higher prevalence of VB12 deficiency. This finding has implications for planning screening or prevention strategies in patients treated with metformin. As diabetic patients are prone to cardiovascular complication due to the microvascular nature of

their disease, VB12 deficiency adds to this risk by increasing serum homocysteine levels and accelerating the atherosclerotic processes. Although there is no evidence whether VB12 deficiency enhances the severity and the extent of diabetic neuropathy, it is conceivable to eliminate preventable factor as a possible cause of newly diagnosed neuropathies in these chronically ill patients.

The potential risk for developing VB12 deficiency highlights the necessity of checking serum VB12 concentrations during metformin therapy. We recommended using daily multivitamin to prevent VB12 deficiency in diabetic patients taking metformin. Among the patients with established VB12 deficiency (serum VB12 <150 pmol/L), supplemental VB12 should be administered either in the form of injection or orally. The role of daily calcium intake to reverse VB12 malabsorption needs to be further reinvestigated prior to its clinical use.

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## Conflict of Interest Statement

None of the authors has any conflicts of interest

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## The Effect of Perimenopausal Estrogen Levels on Depression and Anxiety: A Pilot Study

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### ABSTRACT

**Objectives.** Among women in the perimenopausal period, rapid hormonal changes can be seen. In the present study, we aimed to investigate the relationship between depression, anxiety and changing estrogen hormone levels at menopause. **Materials and Methods.** The research group was composed of 30 perimenopausal women who had FSH levels higher than 20 IU and irregular menses. Anxiety and depression status was assessed with the Hospital Anxiety and Depression Scale. Patients with or without depression or serious anxiety were compared in terms of age, body mass index (BMI), hot flushes, smoking, premenstrual syndrome (PMS) and estrogen levels. **Results.** There were no statistically significant differences in terms of hot flushes, BMI, smoking, age, and PMS in patients with or without depression/anxiety. Estrogen levels were statistically significantly lower in the group with depression compared to the group without depression ( $p=0.026$ ). **Conclusion.** We believe that falling levels of estrogen in the perimenopausal period can be considered to be a risk factor for depression. The possible role of estrogen replacement in the treatment of depression and anxiety should be investigated in further studies.

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**Keywords:** Perimenopause, depression, anxiety, FSH, estrogen.

### Introduction

The perimenopausal period usually begins in the late 40s. Menstrual irregularity is the most objective indicator used in the diagnosis of this period. Studies indicate that menopause can occur in one to two years with cycles exceeding 42 days.

The average age for perimenopause is 47.5, and 51 for menopause. It is reported that passage from regular menstruation cycles to amenorrhea can exceed eight years [1].

In the premenopausal period, an increase in

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follicular stimulating hormone level (FSH), a decrease in inhibition level, a slight increase in estradiol level, as well as a change in luteinizing hormone (LH) level are observed. In the last year before menopause, in the late perimenopausal period, reduction begins in estradiol levels to below 40 pg/mL. The perimenopausal years are the period in which FSH climbs to postmenopausal levels (above 20 IU/L) and LH stays within normal limits although menstruation continues [2]. 70% of peri- and postmenopausal patients show symptoms and indications related to estrogen deficiency. Apart from vasomotor symptoms, psychological symptoms and indications such as depression, anxiety, irritability, sleep disturbances, and decrease in libido are also prevalent [2]. It is reported that starting from the perimenopausal period there is an increase in risk of depression, including women without a past depression history [3]. It is stated that compared with the premenopausal period, there are persistent symptoms of mood in women in the perimenopausal period, a significant increase in depressive indications in the menopausal period through follow-up studies during this period, and that this risk minimizes significantly in the early postmenopausal period [4]. A five-year follow-up study states that there is a significant mood change in the perimenopausal period, and a 14 fold increase in risk of depression compared with the premenopausal period [5]. It is affirmed that psychological symptoms seen in the menopausal period may be related to changes in levels of estrogen, androgen or both, as well as to psychosocial and dynamic processes [6].

It is reported that changes in estrogen level in the perimenopausal period cause cognitive and mood changes by affecting acetylcholine and serotonin levels in the central nervous system [7]. Estrogen, as a steroid hormone, acts by increasing gene expression in the cell nucleus. There are two important estrogen receptors. The alpha-receptor is responsible for estrogen effects on cognitive functions, whereas the beta-receptor is responsible for the serotonergic system and emotional processes [8]. Mood, cognition and neuronal health are associated with the effect of estrogen on the central nervous system [9]. Estrogen increases

serotonin levels by reducing monoamine oxidase, which catabolizes serotonin, by separating tryptophan bound to albumin essential for serotonin synthesis, and by increasing serotonin transport [10].

While depression in women is more frequent starting from puberty, it is rather rare after the sixth and seventh decades of life. Depression peaks in women in the menarche to menopause period and premenstrual, postpartum and menopause periods, in which hormonal changes occur [11, 12]. It is believed that hormonal changes in the reproductive period may increase depression risk [13].

Premenstrual dysphoric syndrome, postpartum depression and perimenopausal depression triad are designated as the hormone-related depressive disorders [14]. While 20-40% of women have premenstrual syndrome (PMS), 3-5% of them show severe symptoms that can be diagnosed as premenstrual dysphoric disorder [15]. It is observed that although there is no menstruation after hysterectomy protecting the ovaries, PMS symptoms continue. This situation is called 'ovarian cycles syndrome' [16]. In this case, suppression of ovarian activity causes regression in PMS complaints [14]. Depressive symptoms decline following estrogen application in premenstrual syndrome [17]. By applying estrogen or estrogen and androgen together for women with surgical menopause a recovery in mood is reported. A significant decrease in the severity of depression and anxiety and in vasomotor symptoms has been shown in menopausal women who were given tibolone with estrogenic effects and transdermal estrogen [18].

There are rapid hormonal changes in women who are in the premenopausal period. In this study, we aimed to investigate if there was a relationship of estrogen levels, as one of these hormones with changing levels, with depression and anxiety.

## Materials and Methods

This study was carried out over two months. In this period, thirty perimenopausal women were included in the study following their written approval, who were admitted to the Sevket Yilmaz

**Table 1.** Comparison of groups with and without depression in terms of sociodemographic data, clinical variables and estrogen levels.

	With depression min-max (n=15)	Without depression min-max (n=15)	P
Age	45.6-50	46-50.5	0.367*
BMI	22.9-30.2	22.6± 30.1	0.512*
Hot flushes +/-	11/4	11/4	1.00**
Smoking +/-	6/9	5/10	0.705**
PMS +/-	2/13	1/14	0.543**
Estrogen	19.7-32.3	72.4-74	<b>0.026*</b>

SD : Standard Deviation, \*Mann Whitney U, \*\*chi-square

Training and Research Hospital Obstetrics and Gynecology Clinic with menstrual irregularity and with a level of FSH higher than 20 IU. Those having a psychiatric disorder apart from anxiety and depression in their past psychiatric history and those already receiving hormonal replacement treatment were excluded from the study. Data was obtained from the patients for age, body mass index (BMI), hot flushes, smoking, and premenstrual syndrome (PMS). Anxiety and depression were assessed with the Hospital

Anxiety and Depression Scale [19]. This is a self-report scale with 14 articles, composed of 7 symptoms of anxiety and 7 of depression. As a result of a study executed in Turkey, the cut-off point for the anxiety subscale was 10/11 and for the depression subscale was 7/8 [20]. In statistical assessment of age and estrogen levels, which are continuous variables in the groups with/without depression and with/without evident anxiety, we compared the results by Mann Whitney U test. Qualitative variables were compared by chi-square test. Ethical approval was obtained from The Ethical Committee of the Hospital.

## Results

When the 15 patients with depression were compared with the 15 without depression, there was no significant statistical difference between

the groups in terms of age, BMI, smoking, PMS, and hot flushes. Estrogen level in the group with depression was significantly lower than that in the group without depression ( $p=0.026$ ) (Table 1). The same patient group was divided according to the presence of an evident anxiety or not, and when 11 patients with an evident anxiety were compared with 19 patients without anxiety, it was found that there was no statistically significant difference between them in terms of age, BMI, smoking, PMS, hot flushes and estrogen levels (Table 2). PMS was more frequent in smoking patients than non-smoking patients. All of the patients with PMS were smokers and only 29.6% of patients without PMS were smokers ( $p=0.016$ ).

## Discussion

Although the perimenopausal period was found to be associated with depression, no relationship between hormone levels and intensity of mood disorder has been shown [21]. In our study investigating the relationship between estrogen levels and depression and anxiety in women in the perimenopausal period, we found that there was no significant relation between estrogen level and anxiety, while on the other hand the estrogen level of the group with depression was significantly lower than those without depression. In a previous

**Table 2.** Comparison of groups with and without evident anxiety in terms of socio-demographic data, clinical variables and estrogen levels.

	<b>With evident anxiety min-max (n=11)</b>	<b>Without evident anxiety min-max (n=19)</b>	<b>Correlation (9 value)</b>
Age	45.6-50.1	45.4-49.5	0.611*
BMI	25.8-30.4	21.5-28.4	0.372*
Hot flushes +/-	9/2	13/6	0.672**
Smoking +/-	6/5	5/14	0.238**
PMS +/-	2/9	1/18	0.256**
Estrogen	34-39.3	67.8-69.2	0.250*

SD: Standard Deviation, \*Mann Whitney U, \*\*chi-square

study analyzing this relation in postmenopausal patients, high anxiety and depression ratios were found with low estradiol levels [22]. In a study performed in Turkey, depression was more common among menopausal women with low E2 levels, and on the other hand anxiety was more common among women with both low E2 and FSH [23]. In our study, lower estradiol levels were observed in the group with anxiety, although this was not statistically significant. We think that the limited number of patients was not sufficient to show this relation. Nonetheless, the relation between high estrogen levels and reduction in depression ratio that was identified in our study was also seen in other research [24]. In contrast to the results of our study, there are also some studies indicating that there is no relation between estrogen level and depression in the perimenopausal period [25].

According to our study, there is no important relation between body mass index (BMI) and depression. In a study analyzing depression and estrogen in postmenopausal patients, it was affirmed that BMI may be an independent factor with a relation between depression and BMI [22]. We have also not found a significant relation between hot flushes and depression and anxiety in our study. Hot flushes occur due to a disorder of hypothalamus regulation, which is the thermoregulatory center, as a result of estrogen deficiency [26]. Hot flushes are usually seen in advanced stages of menopause and in the early years of the postmenopausal period [27]. A study investigating the relationship between

hot flushes and depression states that there is a strong relation between these two, and both depression and hot flushes occur due to sensitivity to changes in estrogen [28]. It is also reported that women with depression in the perimenopausal period complain more frequently about hot flushes with high severity and so are admitted more frequently for treatment [29]. In a study in which women who did not receive premenopausal psychiatric treatment or hormonal replacement treatment (HRT) were followed for six years, a strong relation between anxiety and hot flush symptoms was found [30].

In our study, we did not find a significant relation between PMS history and depression and anxiety. Depression risk increases in women with premenstrual dysphoric disorder diagnosis, and it is reported that 40-78% of these individuals have a mood and anxiety disorder history [31]. It is stated that the existence of PMS history is predictive for depression in the menopausal period [4].

In our study, we did not find a significant relation between smoking and perimenopausal depression and hot flushes. Smoking is more related to early menopause; this situation is associated with the anti-estrogenic effect of cigarettes [32]. In addition, more hot flush complaints are reported with depressive symptoms with smoking in the reproductive period before menopause [33] and smoking patients with depression in the perimenopausal period [34].

The small number of cases is one of the

limitations of this study. The fact that we have not determined a significant relation between perimenopausal depression and BMI, PMS, hot flushes, and smoking and the incompatibility of this finding with the literature may be because the number of patients was not sufficient to show this relation.

Giving transdermal estradiol to perimenopausal women has an antidepressant effect [35]. Although estrogen treatment was not effective in postmenopausal women, its effectiveness was proven for patients with perimenopausal depression [36]. After perimenopausal women with major depression diagnosis were given 17 $\beta$  estradiol, it was found that the antidepressant effect of hormone treatment was independent from physical effects [37]. In a meta-analysis in which thirty-eight studies were evaluated, it was seen that hormone therapy provides a reduction in the depressive mood [38]. Following depressive disorder diagnosis, the first treatment option in the menopausal period is with selective serotonin reuptake inhibitors. If estrogen deficiency in the perimenopausal period is treated as an independent risk factor, it can be assumed that estrogen can

have a place in the treatment of depression and anxiety disorders during the perimenopausal period [39]. Estrogen treatment has a wide range of uses in menopausal complaints; it is especially effective for hot flushes. It may be a treatment option for women with depression in the perimenopausal period who do not have breast cancer, thromboembolism risk or any other contraindications. It is also assumed that use of estrogen in women with depression in the perimenopausal period may provide additional benefit in terms of disease with increasing risk. Short-term estrogen treatment is reported to have positive effects on mood by reducing vasomotor symptoms and sleeping problems [39]. In a randomized controlled study it was found that an application of estrogen over 3-6 weeks is effective for perimenopausal depressive patients [40].

In conclusion, we believe that decreasing estrogen in the perimenopausal period can be evaluated as an independent risk factor for depression and anxiety. The probable role of estrogen in depression and anxiety treatment in the perimenopausal period should be examined in further studies.

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## The Effect of Endoscopic Sinus Surgery on Quality of Life: A Prospective Clinical Study

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### ABSTRACT

**Objective.** Chronic rhinosinusitis has a negative effect on the quality of life of millions of involved patients. The aim of this study was to assess the effect of endoscopic sinus surgery on the quality of life in patients with chronic rhinosinusitis. **Materials and Methods.** Twenty-five cases with chronic rhinosinusitis, which were resistant to 12 weeks of medical treatment, underwent Endoscopic Sinus Surgery. Two kinds of health related quality of life (HRQoL) surveys (the Chronic Sinusitis Survey and the Rhinosinusitis Disability Index) were applied to all cases before and at least 6 months after the operation. The Lund-Kennedy endoscopic scoring system was used as an objective evaluation. All analysis was performed using SPSS statistical software. **Results.** Statistically significant improvements were computed for cases before and after surgery for the Chronic Sinusitis Survey symptom scores ( $p < 0.05$ ). Also, statistically significant improvements were found for cases using the Rhinosinusitis Disability Index. However, mean changes in endoscopic scores did not statistically correlate with changes in quality of life ( $p > 0.05$ ). **Conclusions.** Our results showed that endoscopic sinus surgery improves the quality of life in cases with chronic rhinosinusitis. But this improvement did not correlate with the endoscopic scores of the paranasal sinuses.

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**Keywords:** Chronic rhinosinusitis; endoscopic sinus surgery; chronic sinusitis survey, rhinosinusitis disability index, quality of life

### Introduction

Rhinosinusitis is one of the most common health problems around the world. The prevalence and incidence of this disease have recently been increasing. Statistical data show that rhinosinusitis is more common than diabetes mellitus, arthritis,

heart disease and headache. It brings significant economic burden in both treatment costs and loss of labor [1].

Rhinosinusitis is defined as inflammation of the nose and paranasal sinuses characterized by two or

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more of the following symptoms, one of which should be nasal obstruction (blockage, congestion) or nasal discharge (anterior/posterior), along with either facial pressure/pain or reduction or loss of smell. Sinus-nasal mucosal inflammation should be confirmed via either endoscopic inspection or imaging. Chronicity is arbitrarily defined as the persistence of symptoms beyond 12 weeks. Currently, chronic rhinosinusitis (CRS) is sub-classified into two distinct subtypes, termed CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP) [2].

Sinusitis has a negative impact on the quality of life that can be compared with diabetes mellitus and congestive heart failure. Besides its physical symptoms, CRS may also cause functional and emotional disorders [3]. Especially CRSwNP has a more negative impact on the quality of life and economic cost than CRSsNP [4]. Endoscopic sinus surgery (ESS) was defined for the treatment of CRS and nasal polyposis by Messenklinger and Wigand in the 1960s. This technique was popularized by Stammberger in Europe and by Kennedy in North America in the 1970s [5]. In many studies, the success rate of ESS has been reported to be between 73-97.5 %. But in those studies, patients were only questioned whether or not they were cured [6]. On the other hand, the final goal in the treatment process of a benign disease like sinusitis should be an increase in the quality of life. There are limited numbers of papers about the impact of ESS on quality of life in the literature. It is important to use disease specific health related quality of life (HRQoL) surveys when determining the success of ESS [7]. The reliability of this survey must be proven.

The aim of this study was to investigate the impact of ESS on the Chronic Sinusitis Survey (CSS) symptoms and quality of life. The second purpose of this study was to investigate the relationship between change in endoscopy score and change in HRQoL following ESS in cases with CRS.

## Materials and Methods

The study included 25 patients (15 males, 10 females; age range 18-65 years) who had

undergone ESS with CRS diagnosis between January 2009- December 2010 and who were followed for at least 6 months after surgery.

The institutional review board of our (blind) hospital provided approval for consent/authorization forms and all research protocols. The diagnosis of CRS was based on clinical symptoms and diagnostic criteria as suggested by the American Academy of Otolaryngology and the Head and Neck Surgery Task Force on Rhinosinusitis [8]. All patients were informed about the study protocol and written informed consent was obtained before their enrollment. After 12 weeks of medical treatment, the patients who still had CRS symptoms underwent ESS. Exclusion criteria were the presence of positive allergy tests, acetylsalicylic intolerance, asthma and history of previous sinus surgery. Cases having nasal pathologies such as septal deviation and concha bullosa accompanying CRSsNP and CRSwNP were not excluded from the study.

Postoperatively, all cases were prescribed antibiotic (amoxicillin+clavulanic acid) and nasal saline irrigation for one week. Nasal steroids were initiated one week after the operation and continued for two months only in the CRSwNP group. All cases in this study were discharged from the hospital within 3 days postoperatively after the removal of nasal packages.

Preoperatively, bilateral assessment of the sinuses was performed by reviewing paranasal computerized tomography (CT) scans in the coronal plane and conducting sinonasal endoscopy with the use of 0o, 2.7mm or 4.0mm diameter rigid endoscopes. Endoscopy procedures were repeated at the 6 month postoperative appointments. CT scans and endoscopic findings were quantified using the Lund-Mackay (score range: 0–24) and Lund-Kennedy (score range: 0–20) scoring systems, respectively. The Lund-Mackay CT scoring system quantifies the severity of image opacification in the maxillary, ethmoidal, sphenoidal frontal sinuses and ostiomeatal complex regions [9]. The Lund-Kennedy endoscopy scoring system grades visual pathologic states within the nose and paranasal sinuses

**Table 1.** The CSS scores for total CRS cases, CRSwNP and CRSsNP subgroups before and after the surgery

	Preoperative mean±SD	Postoperative* mean ±SD	Change mean ±SD	P value
<b>CSS symptom subscale</b>				
In all patients (CRS )(n:25)	4.15±8.72	41.50±12.78	29.05±12.28	0.000
In CRSsNP subgroup(n:14)	2.07±7.76	41.50±9.84	31.12±10.27	0.001
In CRSwNP subgroup(n:11)	12.45±9.96	49.80±16.17	29.05±14.35	0.003
<b>CSS medication subscale</b>				
In all patients (CRS )(n:25)	12.45±10.62	49.80±10.18	24.90±14.01	0.000
In CRSsNP subgroup(n:14)	12.45±9.59	47.72±11.15	24.90±15.24	0.001
In CRSwNP subgroup(n:11)	12.45±12.28	49.80±9.16	29.05±12.76	0.003
<b>CSS total</b>				
In all patients (CRS )(n:25)	16.66±17.78	87.15±20.11	53.95±23.14	0.000
In CRSsNP subgroup(n:14)	18.67±15.73	83.00±17.42	53.95±22.87	0.001
In CRSwNP subgroup(n:11)	16.60±20.85	95.45±24.01	58.10±24.53	0.003

\*At least 6 months after the operation, CSS: chronic sinusitis survey; CRS: chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyposis; CRSsNP: chronic rhinosinusitis without nasal polyposis

including: polyps, discharge, edema, scarring, and crusting [10].

A total of 25 cases met the inclusion criteria and could be followed for at least 6 months. Patients were sub-grouped as chronic rhinosinusitis with nasal polyps (CRSwNP) (n.11) and chronic rhinosinusitis without nasal polyps (CRSsNP) (n:14). A single otolaryngologist performed

all the ESS as defined by Messerklinger and Stammberger.

Two HRQoL surveys, the Rhinosinusitis Disability Index (RSDI) and the Chronic Sinusitis Survey (CSS) were used in this study. Patients were asked to complete each HRQoL instrument at both of the preoperative and at least the 6 month postoperative clinical visits. The RSDI contains 30

**Table 2.** RSDI scores for total CRS cases, CRSwNP and CRSsNP subgroups before and after the surgery

	Preoperative mean±SD	Postoperative* mean ±SD	Change mean ±SD	P value
<b>RSDI physical subscale</b>				
In all patients (CRS )(n:25)	27.00±7.61	9.00±8.94	-18.00±8.95	0.000
In CRSsNP group(n:14)	27.00±7.58	9.00±7.86	-18.00±8.39	0.001
In CRSwNP group(n:11)	27.00±7.96	8.00±10.01	-18.00±8.39	0.004
<b>RSDI functional subscale</b>				
In all patients (CRS )(n:25)	31.00±9.28	6.00±7.61	-22.00±8.67	0.000
In CRSsNP group(n:14)	31.00±8.26	6.00±6.45	-22.00±8.69	0.001
In CRSwNP group(n:11)	31.00±10.83	5.00±8.90	-22.00±8.92	0.003
<b>RSDI total subscale</b>				
In all patients (CRS )(n:25)	24.00±7.55	7.00±7.48	-17.00±6.56	0.000
In CRSsNP group(n:14)	21.00±6.65	6.00±5.65	-17.00±7.05	0.001
In CRSwNP group(n:11)	27.00±8.55	6.00±5.65	-20.00±7.45	0.003
<b>RSDI emotional subscale</b>				
In all patients (CRS )(n:25)	82.00±23.11	23.00±21.91	-18.00±8.95	0.000
In CRSsNP group(n:14)	76.50±21.43	20.50±18.07	-59.00±21.32	0.001
In CRSwNP group(n:11)	83.00±25.84	23.00±25.57	-56.00±20.91	0.003

\*At least 6 months after the operation, RSDI: Rhinosinusitis Disability Index CRS: chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyposis; CRSsNP: chronic rhinosinusitis without nasal polyposis

**Table 3.** Endoscopic scores for total CRS cases, CRSwNP and CRSsNP subgroups before and after the surgery

	Preoperative mean±SD	Postoperative* mean ±SD	Change mean ±SD	P value
Endoscopic scores				
In all patients (CRS )(n:25)	4.00±3.61	0.00±2.09	-4.00±1.52	0.000
In CRSsNP subgroup(n:14)	4.00±2.20	0.00±1.22	-4.00±2.55	0.001
In CRSwNP subgroup(n:11)	6.00±4.30	0.00±2.80	-6.00±3.16	0.003

\*At least 6 months after the operation, CRS: chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyposis; CRSsNP: chronic rhinosinusitis without nasal polyposis

questions (score range: 0-120) and consists of three subscales that measure disease-specific patient status in the physical, functional, and emotional domains. The physical subscale contains 11 questions (score range: 0-44), the functional subscale contains 9 questions (score range: 0-36), and the emotional subscale contains 10 questions (score range: 0-40). Lower RSDI total and subscale scores represent a lower impact of the sinus disease. The CSS is a six-item HRQoL monitor used to measure sinusitis-specific symptoms and medication use during the preceding 8-week period. The aggregate and subscale scores each range from 0 to 100 with lower scores representing a greater impact of sinus disease.

All analysis was performed using SPSS statistical software (version 16.0; SPSS Inc., Chicago, IL).

## Results

The CSS symptom scores for total CRS cases and for CRSwNP and CRSsNP subgroups are shown in Table 1 before and after ESS. Statistically significant improvements were computed for the subgroups before and after surgery. (p<0.05) RSDI scores are shown in Table 2 for before and after ESS. Statistically significant improvements were found for the subgroups. (p<0.05)

Changes in endoscopic scores are shown in Table 3 before and after ESS. Statistically significant improvements were found for all cases and subgroups. (p<0.05)

The CRSsNP subgroup was compared to the CRSwNP subgroup regarding the survey scores that were applied before and after sinus surgery. Comparison of mean changes in survey scores between both subgroups are shown in Table 4. Statistical significant differences were not found between the subgroups. In Table 5, the mean change in endoscopic scores were compared to the mean change in HRQoL measures for all cases. No statistically significant correlation was found between these variables.

No major intraoperative or post-operative complications occurred in any cases.

## Discussion

Sinusitis is one of the most common health problems around the world. The prevalence and incidence of this disease have recently been increasing [1]. The main goal in the treatment of a patient with CRS should be to decrease nasal blockage and nasal discharge complaints, which have a significant correlation with the life quality of the patient [11]. Objective and subjective methods can be used in the evaluation of treatment

**Table 4.** Comparison of mean change scores between both subgroups.

	Endoscopic Change mean	RSDI emotional change mean	RSDI functional change mean	RSDI physical change mean	RSDI total change mean	CSS total change mean	CSS medical change mean	CSS symptom change mean
Z =	-1,820	-0,414	-0,413	-0,441	-0,412	-0,914	-0,363	-0,330
P=	0,069	0,679	0,680	0,659	0,681	0,361	0,717	0,741

RSDI: Rhinosinusitis Disability Index; CSS: chronic sinusitis survey

**Table 5.** The comparison between endoscopic scores and HRQoL measures

		RSDI emotional change mean	RSDI functional change mean	RSDI physical change mean	RSDI total change mean	CSS symptom change mean	CSS medical change mean	CSS total change mean
Endoscopic	r=	-0,091	0,163	0,290	0.130	-0.218	-0.129	-0,215
Change mean	p=	0,666	0,436	0,380	0,534	0,296	0.539	0.302

HRQoL; Health related quality of life; RSDI: Rhinosinusitis Disability Index; CSS: chronic sinusitis survey

achievements. The objective methods are endoscopic scores, CT scores, rhinomanometry and acoustic rhinometry. The subjective methods are HRQoL and disease specific HRQoL [7]. Although medical and surgical reduction of polyps, discharge, edema and crusting significantly improves the inflammatory process and the corresponding endoscopy score, these improvements can explain only a small percentage of the association with patient based HRQoL and sinonasal symptom burden. These results are somewhat surprising since we intuitively expected that reducing mucosal inflammation, infection, and obstruction in the sinuses would result in a greater degree of improvement in the HRQoL domains. One plausible explanation is that disease-specific HRQoL is a complex, multidimensional construct that cannot be measured by endoscopic exams alone in this population [7].

A few previous studies have addressed consistent correlations between measures of endoscopic examination and survey responses in patients undergoing sinus surgery. However, the number of studies is not sufficient.

According to our study and also some analogous studies in the literature, ESS shows significant positive improvements in endoscopic and HRQoL scores for CRS patients. [12] This improvement was observed in both CRSwNP and CRSsNP subgroups. In our study, there were no significant differences between the success of ESS in CRSwNP and CRSsNP subgroups. Mehanna *et al* [13] reported that the greatest benefit was derived by patients undergoing surgery for polyps since nasal blockage and nasal discharge symptoms, which are more related to quality of life, recovered more dramatically after ESS. They also suggested that the subjective recovery of patients who had

undergone anterior ethmoidectomy was greater than for patients who received a posterior ethmoidectomy. Co-existent asthma, allergic rhinitis or aspirin intolerance appeared not to result in a significant decrease in benefit after surgery, except in patients with non-polyp disease who also have both aspirin intolerance and asthma [13]. In the literature, one other study that was similar to our study was reported by Smith *et al.* [14]. They studied 119 patients and found that surgical management of CRS was associated with significant improvements in objective findings and quality of life measures, however, specific patient factors, in particular aspirin use and depression, predicted poorer outcomes.

Lund and Kennedy defended the use of objective materials for evaluation of patients. Kennedy followed up 120 patients for 18 months by endoscopic examination and surveys [15]. A significant improvement was determined in 85% of patients, whereas 2.5% of patients had regression. 49% of patients were observed to have residual disease endoscopically. Lund followed up patients by acoustic rhinometry and olfactometry. Although subjective symptoms were significantly improved, acoustic rhinometry did not correlate with this improvement [16].

Senior *et al* [17] evaluated after 8 years 120 patients who had been included in the study by Kennedy in 1992. Results were obtained by questionnaires that were sent to the patients. They reported that 18% of patients had undergone revision surgery. In our study, the follow-up period was short so that patients could not be followed up for revision surgery.

Our study demonstrated that ESS has improvement effect on the quality of the life from the point of patient's perception. But this

improvement was not correlated significantly with Lund-Kennedy endoscopic scores. Similar to our results Wright and Agrawal [18] reported that there were not significant correlations between endoscopic scores and subjective measures. But, Mace et al [7] reported that there were statistically significant improvement between endoscopic score and all total and subscale HRQoL measures.

Toros et al [19] found a significant correlation between endoscopy score and total patient reported symptoms (on a visual analog scale: 0–10cm) preoperatively and 12 months postoperatively in 86 patients with and without polyps. Likewise, Giger et al [20] reported that the percentage of subjective symptom improvement correlated significantly with postoperative endoscopy findings in the ethmoidal cavities of 77 patients with CRS who did not have nasal polyposis.

Although the studies are similar, most of them used HRQoL surveys as clinical outcomes of interest in smaller populations with varied regard for nasal polyposis. However, they did not assess postoperative trends with the use of validated, disease-specific HRQoL survey instruments. In addition, Birch et al [21] reported finding a lack of correlation between endoscopy scores and self-related symptom scores or RSDI total scores in a nonsurgical population of 53 patients with CRS but without regard for polyp status. Although that study used a disease-specific HRQoL outcome measure, the study was limited to a cross sectional analysis of a smaller, non-surgical population.

Studies in literature supported that ESS for CRS patients who did not respond medical treatment has positive affect on quality of life. But controversial

results that is 'the improvement in quality of life is not always correlated with improvement in the endoscopic scores' can be found in papers. That means; healing from the point of patient's perception may not be parallel to objective endoscopic scores. Technological development both in imaging modalities and ESC instruments will increase surgical success. But still diagnosis of depression, aspirin intolerance and maybe the polyposis can reduce success of ESS. In our study non-correlation between the objective endoscopic finding and disease-specific HRQoL outcome was a surprising result. Treatment of the endoscopic findings may not improve the quality of life. All of those similar and controversial results in literature may promote the researcher for further studies to find the answer of that question. As a physician, what do we focus on in the surgical treatment of CRS? Do we treat the patient complaints or findings on endoscopy and CT?

This study has the limitations of being a relatively small number of cases and short term follow-up. However, since we used HRQoL validated surveys instead of patient reported symptom scale to demonstrate the ESS on quality of the life, our results may be more reliable.

## Conclusion

ESS improves the quality of life in patients with CRSwNP and CRSsNP. But the improvement may not be correlated with objective endoscopy scores.

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## Chondral Lesion of the Capitellum Humeri Accompanying a Radial Head Fracture: A Case Report

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### ABSTRACT

In this case report we present a case of a full thickness chondral lesion of the anterior-distal surface of the capitellum humeri, accompanying an intraarticular radial head fracture. The importance of this case is the resemblance of the chondral injury to a Lorenz-Kocher lesion of the humerus and atypical displacement of chondral fragments. A 32-year-old man was admitted to the emergency room after a fall on his right upper extremity. X-ray and Computed Tomography (CT) scan of the elbow revealed a minimally displaced radial head fracture (Mason type 2), with a 4 mm step (depression) at the joint surface. During the operation, at the anterior surface of the distal humerus, a full thickness chondral lesion was encountered. After removal of chondral fragments from the fractured radial head surface, it was seen that these fragments were of capitellar origin. Following radial head fixation, early active assistive motion was started. At the 6 month visit, the patient was painfree with full participation in activities of daily living with a DASH score of 12.5. This injury is important due to demonstration of such an extensile injury in spite of benign looking radiology. Although radial head fractures were described, these type of occult injuries may be responsible for unexplainable and unfavorable outcomes following low energy radial head fractures treated conservatively.

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**Keywords:** Cartilage lesion, radial head fracture

### Introduction

In this case report, we present a case of a full thickness chondral lesion of the anterior-distal surface of the capitellum humeri, accompanying an intraarticular radial head fracture. The importance of this case is the resemblance of the chondral injury to a Lorenz-Kocher lesion of the

humerus and the atypical displacement of chondral fragments. Since no abnormality regarding capitellum humeri was distinguished preoperatively, the chondral lesion was observed intraoperatively during surgical treatment of the displaced radial head fracture. A full-thickness

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sleeve type chondral defect of approximately 1.5x2.0 cm dimension was encountered on the anterior distal surface of the humerus, face-to-face with the radial head fracture fragment. On exploration, a detached chondral sleeve was found trapped between fracture fragments of the radial head fracture. Theoretically, at the time of injury, the fracture end of the radial head scraped the joint surface of the humerus and trapped the chondral fragment between fracture fragments, like a “carpenter's plane”. Following reduction and internal fixation of the radial head fracture, the patient recovered with +5° to +135° of pain free ROM, with full participation in activities of daily living at 6 months post-operatively. The described mechanism of injury is a rare type with a unique pattern. Since the patient recovered with fixation of the radial head fracture alone, treatment options of such acute chondral injuries are still under debate.

## Case Presentation

A 32-year-old man was admitted to the emergency room after a fall on his right upper extremity. Initial examination revealed tenderness on the lateral aspect of the elbow, swelling without skin compromise, painful range-of-motion of the elbow as well as forearm supination-pronation without any sign of neurovascular deficit. X-ray of the elbow revealed a minimally displaced radial head fracture (Mason type 2) involving the articular surface (Figure 1). Since the fracture was intra-articular, a CT scan with multiplanar

reformatations was done, revealing a 4 mm step (depression) at the joint surface with a 2 mm separation of the main fragment (Figure 2). Operative treatment was therefore decided upon. Under tourniquet with the patient positioned in the supine position, using a posterolateral approach (Kocher), the radial head was exposed. Upon inspection of the fracture line and chondral surfaces, at the anterior surface of the distal humerus a full thickness chondral lesion of 1.5x2.0 cm dimension was encountered with bleeding, non-sclerotic subchondral bone, as well as crushed and scratched periphery. On inspection of the fracture, two pieces of chondral tissue were found to be trapped between fracture fragments (Figure 3-4). After removal of the chondral fragments, it was obvious that these fragments were of capitellar origin. Theoretically, at the time of the initial trauma on the extended elbow, a split fracture of the radial head may have occurred by axial compression. As the elbow was flexed together with axial compression, the fracture end of the intact radial head scraped the capitellum humeri from distal to proximal, behaving just like a “carpenter's plane”. and trapped the chondral tissue between the fracture ends. The fracture was reduced and fixed with three 15 mm screws, with the screw heads countersunk with the radial head (Figure 5-6). Early active assistive motion was started as swelling subsided, followed by full ROM exercises. At the end of the 6th week, the patient had regained 0-130° motion. At the 6 month visit, the patient was painfree with full participation in activities of daily living with a DASH score of 12.5.



Figure 1. X-Ray showing radial head fracture

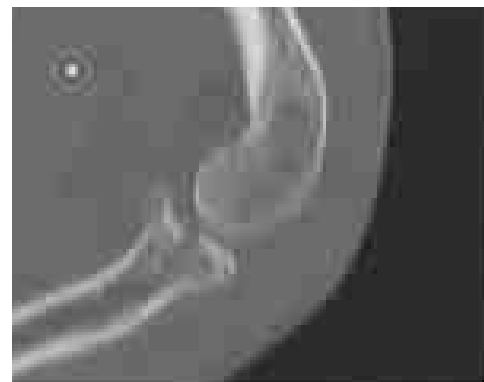


Figure 2. Sagittal CT image reveal a displaced radial head fracture

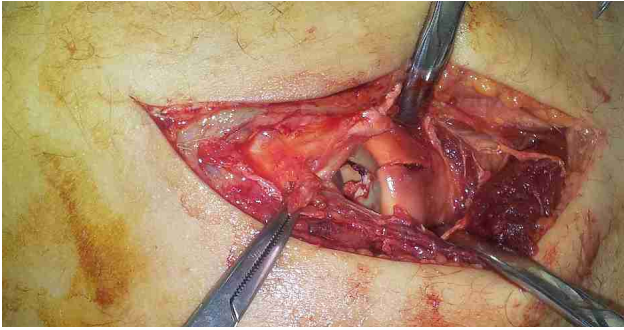


Figure 3. Intraoperative image showing chondral fragments



Figure 4. Entrapped chondral fragments

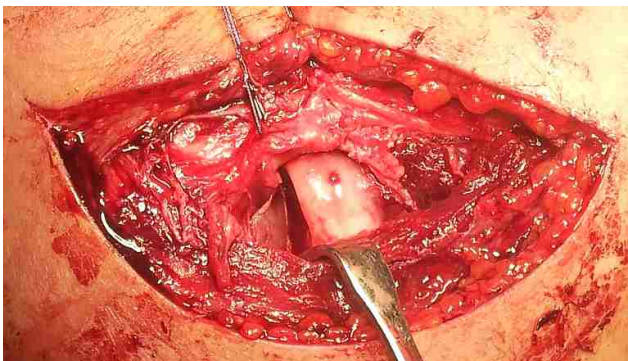


Figure 5. Intraoperative image of capitellum

## Discussion

The Mason classification is widely used to describe radial head and neck fractures. Type II fractures have more than 2 mm of displacement, involving at least 30% of the radial head, type III fractures are significantly comminuted and a type IV fracture is a radial head or neck fracture associated with an elbow dislocation [1]. Capitellar fractures have been classified according to the size of the detached fragment as types I and II. Type I involves a large portion of the capitellum and may be associated with the olecranon, radial head, coronoid process and supracondylar fractures [2]. The Kocher-Lorenz, or type II fracture involves a superficial osteochondral fragment of the capitellum, such as the osteochondritis dissecans of the elbow [3, 4].

As in our observation, only a few cases of Kocher-Lorenz fractures of the capitellum are reported in the literature and also there is little data available regarding chondral lesions accompanying radial head fracture Mason type II [5, 6]. Also, there is no optimal treatment available regarding evidence based me.

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## Renal Angiosarcoma: A Rare Case Report

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### ABSTRACT

Angiosarcomas constitute about 2% of all sarcomas and generally are the worst prognostic subtype of soft tissue sarcomas. Angiosarcomas are very aggressive tumors and one year after diagnosis half of the patients die with metastasis of lung, lymph nodes, bone and soft tissue. Diagnosis can be accurate with immunochemistry stain, such as for factor 8 related antigen, CD 31, CD 34 and von Villebrand factor. Our patient was A 61-year-old woman who died four months after symptoms appeared with extensive metastasis. She was able to receive chemotherapy for only one course and after that treatment was changed to palliative.

*Eur Res J 2015;1(1):24-28*

**Keywords:** Angiosarcoma, renal, metastasis.

### Introduction

Angiosarcomas are very rare malignancies, constituting about 2% of all sarcomas [1]. Skin and superficial tissue are the most involved areas, and unlike other sarcomas, other involvement areas are the uterus, ovaries, small intestine, lung, heart, oral cavity, orbita and thyroid [2]. Angiosarcomas are the worst prognostic subtype of soft tissue sarcomas. Angiosarcomas are very aggressive tumors and after successful treatment, local recurrence is seen in 1/5 of patients and half of the patients die with metastasis of lung, lymph

nodes, bone and soft tissue [3]. Immunochemistry stains can help to confirm the diagnosis, such as for factor 8 related antigens, CD 31, CD 34 and von Villebrand factor [4]. In this report we present a case of a rare renal angiosarcoma.

### Case Presentation

A 61-year-old woman presented with shoulder pain that began 3 months before diagnosis. During

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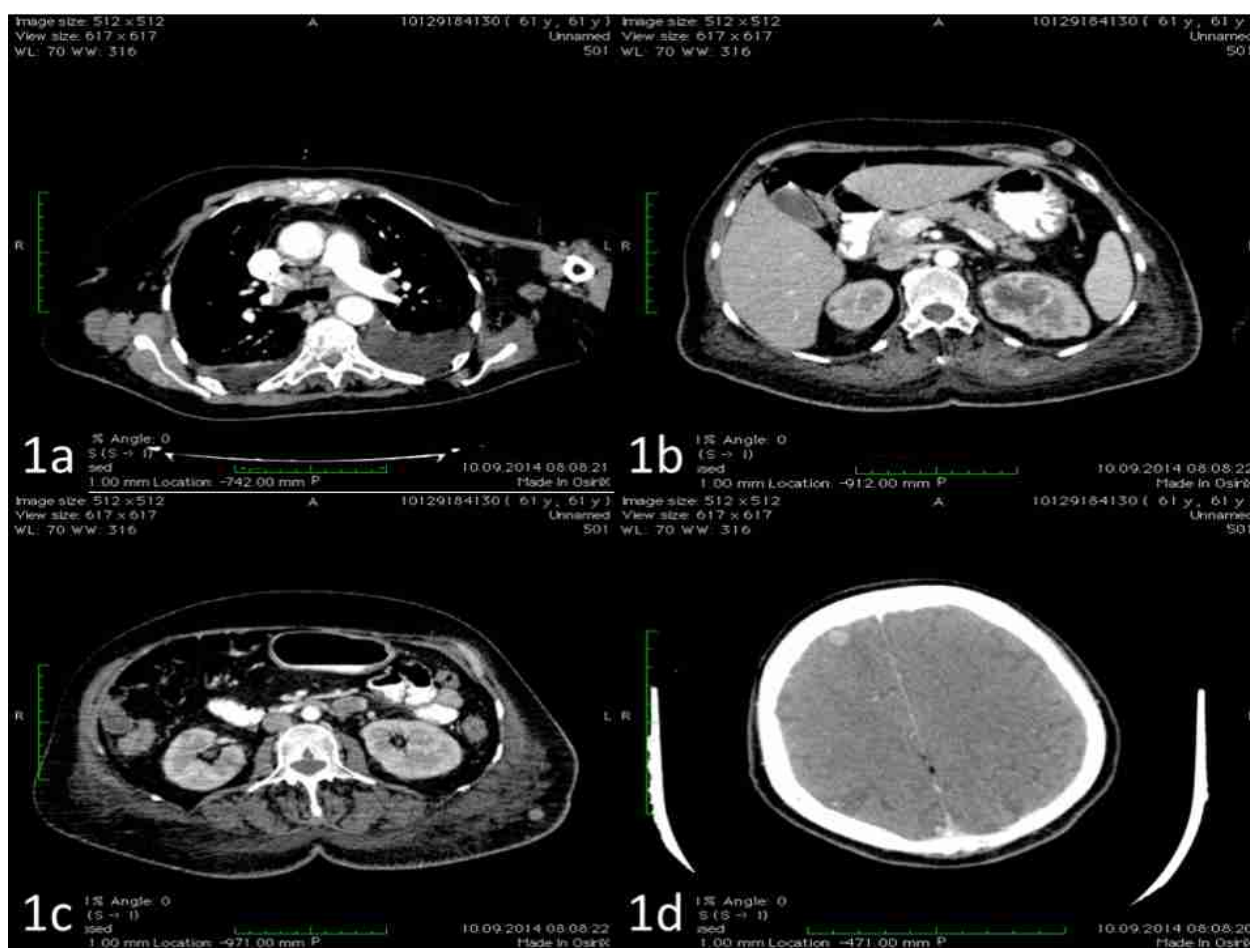
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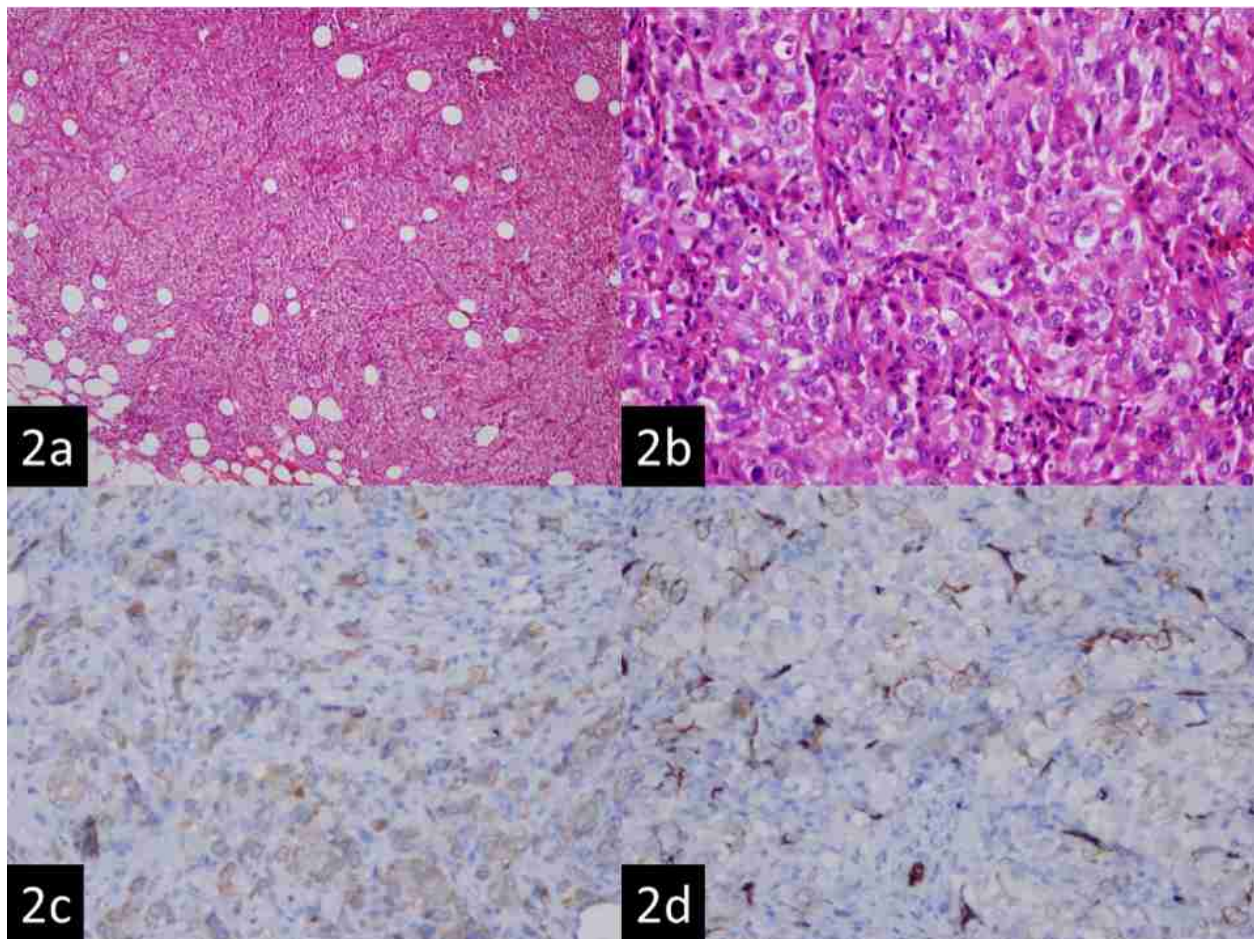
this period she had lost 9 kg. On magnetic resonance imaging (MRI), there was only tendinosis of the supraspinatus and infraspinatus muscle and only symptomatic treatment had been given for her pain. Because of continuing pain, blood tests were performed and calcium was detected at 13 mg/dl. The patient was then evaluated with mammography, breast ultrasonography, cranial, thoracic and abdominal computed tomography (CT). There was a 50x52mm significantly contrasted, hypodense left renal mass on CT evaluation. Additionally, there were frontal brain and cerebellar metastases, multiple lymphadenopathy (the largest thoracic, paratracheal 30x24 mm; the largest abdominal, pelvic mesenteric 20x15 mm), lymphangitis carcinomatosa of the lung, skin and soft tissue metastasis, bilateral surrenal gland mass(right 31x18 mm, left 15x10 mm) and multiple bone metastases on CT evaluation

(Figure 1). Bone metastasis was confirmed by bone scintigraphy. There were multiple breast masses on mammography and ultrasonography, the largest mass was 12x9 mm with malignant features. Trucut biopsy was performed from the left renal mass. Atypical cells with small nucleoli, large vesicular nuclei, and large pale eosinophilic cytoplasm were observed and s100, CD31, actin and desmin stain negativity and CD34 positivity were detected with immunochemistry stains (Figure 2).

The patient was assumed to have renal angiosarcoma, and was started with cisplatin and docetaxel treatment and zoledronic acid for bone metastasis. Only one course of chemotherapy was given after which the patient worsened and the treatment plan was changed to palliative. The patient died one month after diagnosis.



**Figure 1. (a)** Bilateral pleural effusion with mediastinal LAPs, **(b)** Left renal mass, **(c)** Intraabdominal enlarged lymph nodes, **(d)** Frontal brain metastasis.



**Figure 2.** (a) Malignant epithelial cells infiltrating fibroadipose tissue, (b) Pleomorphic epithelioid cells with large eosinophilic cytoplasm, (c) Pan-CK-antibody staining against membranes in some cells, (d) CD 34 positivity of malignant cells.

## Discussion

Angiosarcomas are a very rare malignancy and constitute about 2% of all sarcomas. They have an aggressive nature, progress in a short time, and most patients die generally within one year of diagnosis [1-3]. There is no standard treatment because of its rarity [5]. There are many hypotheses concerning the mechanism of tumor formation. According to Mc Carthy and Park's hypothesis, angiosarcomas originate from vascular structures in traumatized granulation areas. They showed that benign angiomas transformed to malignant angiosarcomas after radiotherapy in three cases [6]. Duck described 30 angiosarcomas related to vinyl chloride in 1975 [7]. Smoking and androgens may explain the male predominance of angiosarcoma [8]. Angiosarcomas may frequently develop from

benign vascular lesions but less often they develop after benign and malignant nerve sheath tumors, neurofibromas, leiomyoma, spindle cell hemangioma, retinoblastoma, Klippel-Trenaunay syndrome, Xeroderma pigmentosum, malignant germ cell tumors, herpes zoster lesions and Aicardi syndrome [3]. Despite these possibilities, there was no risk factor in our case. Till today, the cause of angiosarcoma is still unknown.

Angiosarcoma may be seen at any age, however, the disease is more common in older and male patients. Unlike other sarcomas, angiosarcomas generally occur in superficial tissue [9]. Renal angiosarcoma symptoms generally mimic renal cell carcinoma, such as hematuria and flank pain, so that patients are treated as for renal cell

carcinomas until pathological diagnosis. (5). Our case is the 61-year-old woman with primary kidney tumor, and there is no symptom of renal mass, only had shoulder pain. Our case had an atypical presentation without symptom of renal mass and risk factor

In a recent article, angiosarcoma cases evaluated in England, Germany, France and Spain until March 2013. Only 42 cases had reported in this region before March 2013. Renal angiosarcomas generally rapidly progress with hematological so that they were known generally poor prognostic tumors. Half of metastatic patients have two or more metastatic sites, lung and liver 46%, bone 39% and abdominal lymph node 11%, respectively (5). Aggressive nature of disease was seen in our case. There was only 3 months between symptoms and diagnosis but multiple metastatic sites detected such as brain, lung, lymph node, skin, bone and adrenal gland (Figure-1).

On pathological evaluation, unlike superficial angiosarcomas, deep tissue angiosarcomas present nested and clustered round cells with high nuclear grade and epithelioid appearance (2). For a definite diagnosis requires evaluation of immunohistochemistry stains such as factor 8 related antigen, CD 31, CD 34 and von Willebrand factor. CD 34 positivity is important for diagnosis of angiosarcomas (4). In our case, assessment of pathologic features, we detected malignant epithelial cells infiltrating fibroadipose tissue, pleomorphic epithelioid cells with large eosinophilic cytoplasm, Pan-CK-antibody formation against the membranous in some cells and CD 34 positivity in malignant cells (Figure-2). There is no standard treatment for angiosarcomas and most of the time patients couldn't take any treatment

because of rapid progression and late diagnosis. Surgery is the best option if patients are eligible for curative surgery (5). When compared surgery with or without chemotherapy and radiotherapy, combined modalities have superior overall survival, 13 months ( $P > 0.05$ ) compared to 7 months in patients, respectively (10). In a series, radiation-induced breast angiosarcomas treated with doxorubicin and paclitaxel, patients had higher response rates and longer progression-free survival (11). We started our patient with cisplatin and docetaxel treatment and zoledronic acid despite this she died one month after diagnosis. Angiogenic drugs may be hopeful but preliminary clinical experiences reported modest and conflicting results (11). Some phase II trials investigated the effect of anti-VEGF (such as bevacizumab) and tyrosine kinase inhibitors (such as pazopanib, sunitinib and sorafenib) however there is no superiority for progression-free survival and response rate, both of them still low (12).

## Conclusion

Renal angiosarcomas are rare, aggressive and treatment-resistant malignant tumors. Early diagnosis for curative surgery is important for the patient, and chemotherapy is generally not effective, so that a new approach is needed. Targeted therapies may be successful for angiosarcomas due to vascular effects. Multicenter prospective studies are needed to understand and develop the correct treatment choice.

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## Late Onset of Facial Nerve Palsy After Tympanomastoidectomy: HSV-1 Activation?

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### ABSTRACT

We present a case of a right peripheral facial palsy occurring 7 days after an operation. A 42-year-old female patient had an uneventful right tympanomastoidectomy in our clinic. She developed right House-Brackmann Grade II peripheral facial palsy postoperatively at the 7th day. A viral screen was performed using an Enzyme Immunoassay. Herpes Simplex Virus-1 specific antibody titer was determined on the 2nd day of facial palsy, confirming the viral etiology. She was commenced on steroid therapy. Her facial nerve functions recovered completely after one week.

*Eur Res J 2015;1(1):29-32*

**Keywords:** HSV-1, facial nerve palsy, tympanomastoidectomy

### Introduction

Facial palsy is an uncommon complication of middle ear surgery. Its onset is usually immediate due to a trauma during surgery but there are a few cases in the literature of delayed facial palsy (DFP) following tympano-mastoid surgery [1-3]. In these cases, the etiology is not clear. However, in some papers, surgical stress is suspected to reactivate latent Herpes Simplex Virus Type-1 (HSV-1) in the geniculate ganglion [2].

Here we present a case with DFP on the 7th day after surgery, in which facial function recovered completely over a period of one week by medical treatment alone with methylprednisolone. We

would like to emphasize that facial nerve dysfunction after ear surgery is not only due to direct surgical trauma to the nerve but also due to secondary effects of the operation (surgical stress) that can cause viral reactivation resulting in DFP.

### Case Presentation

A 42-year-old female patient presented with a 2-day history of weakness on the right side of her face, inability to close her right eye and asymmetrical appearance of the mouth while smiling, which was assessed as House-Brackmann

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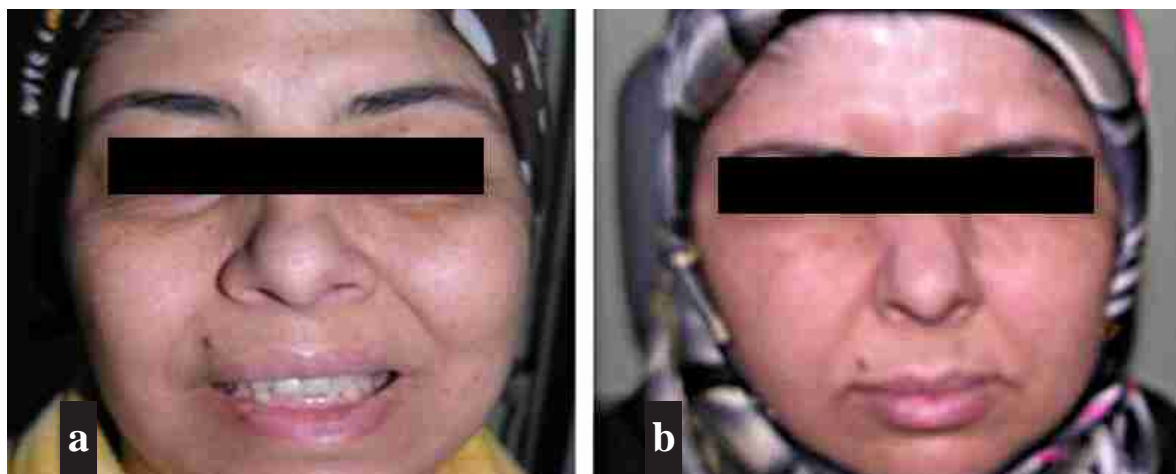
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Grade II Peripheral Facial palsy (Figure 1a). She had a right tympanomastoidectomy in our clinic nine days previously, and her symptoms developed on the 7th day after surgery. In the operation, the facial canal and chorda tympani were intact. Epitympanic recess and protubarium were invaded

with polypoid mucosa. There was no postoperative visible problem with facial nerve function immediately after surgery and during seven days postoperatively. The patient had an uneventful recovery following the procedure.



**Figure 1. (a)** She presented with a 2-days history of House-Brackmann Grade II Peripheral facial nerve palsy on the 9th day postoperatively. **(b)** The facial nerve functions recovered completely after one week, with high dose intravenous methylprednisolone for two days and 1mg/kg/day methylprednisolone by tapering per 3 days. (The informed consent was obtained and pictures were used by the permission of patient)

Her past medical history was not significant for any systemic chronic disease or recent upper airway infection. But she had great emotional stress before and after the surgery. Medications at the time of admission were ciprofloxacin 750 mg/dose BID and naproxen sodium 500 mg/dose BID per oral.

She had a good general condition. On examination her temperature was 36.0°C, heart rate was 80 beats per minute, and blood pressure was 110/80 mm Hg. Her face had a normal tone and symmetry at rest. There was complete closure of the right eye with minimum effort and a slight asymmetry of the mouth. Her facial nerve function was assessed to be House Brackmann grade II. There were no visible vesicles to suggest a herpetic infection. The patient did not have otalgia, vertigo or dizziness. Therefore, the mastoid dressing was not removed.

Complete blood count and serum biochemistry, including creatinine, urea, glucose and electrolytes, were normal. A viral screen was performed using an Enzyme Immunoassay. HSV-1 specific antibody titer was determined during the acute phase on the

2nd day of facial palsy, confirming the viral etiology.

The patient was started on a high dose (250 mg/day) of intravenous methylprednisolone sodium succinate for two days. She was then prescribed 1 mg/kg methylprednisolone (60 mg) for 3 days, followed by a taper to 10 mg per three days, for a total of 20 days. Also, acyclovir therapy was recommended but she rejected this after being informed about the side effects of the drug. Her facial nerve functions recovered completely after one week (Figure 1b).

## Discussion

Delayed facial palsy (DFP) is defined as dysfunction occurring more than 72 hours postoperatively. JT Wrabec reported 7 cases of DFP after tympanomastoid surgery, which represents 1.4% of all cases (n,486) and 1.9% in revision cases (n,155) [1]. Viral reactivation may be an important etiological factor in the development of delayed onset facial nerve palsy.

Any factors causing neural inflammation, e.g. direct thermal or mechanical injury to the facial nerve, local effects of blood breakdown products or any mediators causing vasospasm, can be encountered in the etiology of DFP [4].

Shea and Ge reported DFP in 0.22- 0.51% of patients after stapedectomy. They reported 11 cases of DFP. Six of them were evaluated serologically. Anti-HSV antibody titers were elevated in 5 of 6 patients. They focused on viral reactivation as heading the list for the most probable cause. Serologic investigations are suggested for diagnosis of the activation of latent herpes virus [5,6]. Murakami et al suggest that herpes simplex HSV-1 is active in idiopathic facial paralysis [7]. They suggested steroids and antiviral medication as the appropriate management strategy for the acute phase of the disease and propose that the majority of patients will completely resolve their paralysis with no residual deficits. A new study in rats by Turner MT et al. provides evidence supporting the use of prophylactic antivirals for otologic surgeries associated with high rates of DFP [8].

Since we did not have an opportunity to test for viral DNA, we evaluated the patient serologically. De Diego et al reported a lesser degree of neural degeneration in Bell's palsy patients treated with low-dose prednisone (1 mg/kg body weight) within the first 96 hours, using acyclovir in controls [9]. Furthermore, an added beneficial effect of starting high dose steroid therapy early after palsy onset was suggested [10]. The dosage of prednisolone employed in different studies ranged between 216-760 mg/day. In this study, facial function recovered

completely over a period of one week by medical treatment, consistent with the literature.

Regarding the reports of DFP in stapedectomy operations, the cause of viral reactivation is attributed to the mechanical irritation of the facial or chorda nerve [5,11]. Since tympanomastoid surgery is a relatively more aggressive operation than stapedectomy, the surgical stress during tympanomastoidectomy may also play a role in triggering viral reactivation.

"Is DFP after surgery coincidental?" is another question. If the association was coincidental, then the incidence of DFP would be expected to be the same as Bell's palsy, which was reported to be approximately 1:5000 persons per year [12]. As mentioned earlier, DFP is reported in 1.4% of cases after tympanomastoid surgery, which is well above the rate of Bell's palsy [1].

## Conclusion

Any person undergoing ear surgery is a potential candidate for facial nerve dysfunction. This unfortunate event requires the physician to decide whether a second operation is needed or to give medical treatment. DFP, as the name implies, is noticed more than 72 hours after surgery since facial nerve function is normal during this postoperative period. Thus it indicates that the facial nerve is anatomically intact in DFP, but that secondary events cause nerve palsy. Consequently, medical treatment (as with Bell's palsy) will be sufficient for DFP.

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