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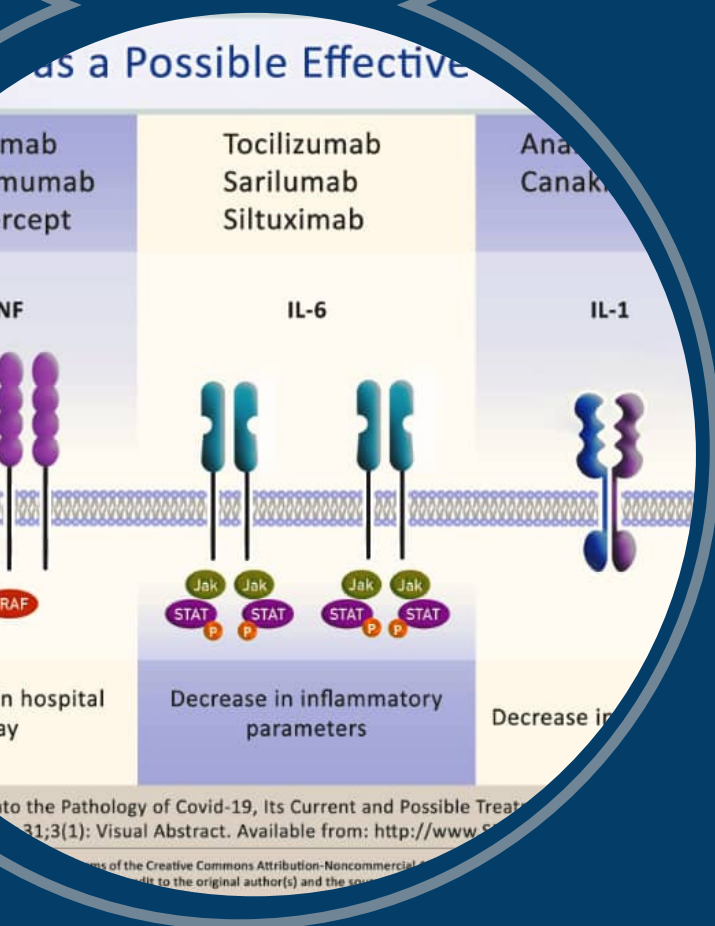
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Low serum vitamin D is associated with failure of Helicobacter pylori treatment

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ABSTRACT

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Background and Aims: *Helicobacter pylori* are the most common gastrointestinal infection worldwide. Determination of contributing factors for successful eradication of *Helicobacter pylori* is important for better infection control. Therefore, this study was conducted to investigate the association between serum vitamin D deficiency and *Helicobacter pylori* eradication rate.

Materials and Methods: In this nested case control study in Loghman Hospital in Tehran in 2018 and 2019, 200 consecutive patients with *Helicobacter pylori* infection using amoxicillin, pantoprazole, bismuth, and metronidazole for 4 weeks were enrolled. The serum vitamin D level was compared across the groups with successful (n=153) versus unsuccessful (n=47) eradication of infection. Finally, data analysis was performed using SPSS statistical software version 25 and the mean, standard deviation, frequency, percentage and statistical test of Chi-square were used to describe and analyze the data and the significance level in this study was less than 0.05.

Results: The results of this study demonstrated that before-treatment vitamin D level was between 10 and 20 ng/dL in majority of unsuccessful cases (40.4%) and it was more than 30 ng/dL in majority of successful cases (83.7%) showing statistically significant difference ($P < 0.001$).

Conclusion: This study showed a significant association between vitamin D deficiency and *Helicobacter pylori* eradication and low vitamin D level resulted in failure of treatment; Hence in unsuccessful cases, assessment of vitamin D level and possible supplementation in those with hypovitaminosis D is recommended.

INTRODUCTION

Helicobacter pylori (Hp) is a gram-negative, microaerophilic, and spiral bacterium that colonizes the stomach of humans. The prevalence of this bacterium is very high, from 25% in developed countries to 90% in developing countries [1, 2]. The bacterium causes some diseases involving the gastrointestinal tract, including chronic gastritis, peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer [3]. Concerning ulcers, 76%–95% of gastric ulcers and 90% of duodenal ulcers are associated with Hp infection [4]. Hp infection treatment and eradication is significantly effective in the treatment of gastric ul-

cer and gastric lymphoma, so successful eradication of this pathogen can prevent gastric cancer [5, 6]. According to previous studies, factors influencing the eradication failure of Hp include low drug compliance, antibiotic resistance, microbial virulence factors, genetic factors in the host, smoking, alcohol consumption, and diabetes [7-9]. Besides, it is clear that, like other infections, host immunity plays an essential role against Hp infection. Many of recent studies have shown that vitamin D, in addition to its known role in calcium and phosphorus metabolism, acts as an anti-inflammatory agent and immune system regulator. This vitamin plays a role in reducing the risk of chronic diseases such as some common cancers, autoimmune, cardiovascu-



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lar, and infectious diseases. Infections of the urinary tract, respiratory tract and tuberculosis and deficiency of vitamin D can lead to an increase in immune system disorders and be risk factors for the development of infectious diseases, including urinary tract and respiratory infections and tuberculosis [10-14]. Laboratory studies have shown that vitamin D binds to its receptor (vitamin D Receptor: VDR), activating a signal pathway that triggers several immune responses. This vitamin is involved in the regulation of the immune response in many infectious diseases by regulating the expression of a number of endogenous antimicrobial peptides [15-17]. Laboratory studies have also shown that vitamin D and its decomposition products have an antimicrobial effect, specifically against *Hp* bacterium, and play a role in homeostasis of gastric mucosa and protection of host against this pathogen. Also, VDR is up regulated in the gastric epithelium in the presence of *Hp* [18-20]. However, there are few clinical studies on the effect of vitamin D on *Hp* eradication treatment, some of which have been performed on specific populations such as the elderly or diabetic people, and the presence of intervening factors that are effective on the results is not fully known [21, 22]. Considering the high prevalence of *Hp* infection and the importance of its eradication, it is important to eliminate the factors that increase the likelihood of treatment failure. Also, according to laboratory studies, it seems not only Vitamin D deficiency (VDD) may have an effect in increasing the eradication failure rate, but also treatment of such deficiency and supplementation may have direct antimicrobial or protective effects on the gastric mucosa against *Hp* infection. Therefore, considering the importance of the subject matter, the present nested case-control study investigated the association of VDD with *Hp* eradication therapy.

MATERIALS and METHODS

The present study was performed on 200 patients aged 18-80 years who underwent endoscopy at Lohman Hospital from June to March 2019, and the presence of *Hp* infection was confirmed based on histopathological samples. Patients with previous history of *Hp* eradication, renal and hepatic failure, systemic inflammatory or autoimmune disease, antacid or anti-inflammatory drug, and corticosteroid / immunosuppressive therapy in the previous two months have been excluded from the study. Prior to treatment, serum vitamin D levels were determined in all patients, and they were divided into four categories, including vitamin D<10, 10-20, 21-30, and > 30 ng /dL. All patients underwent four-week bismuth-based quadruple *Hp* eradication treatment (two amoxicillin 500 mg b.d, two metronidazole 250 mg b.d, two bismuth 250 mg b.d, and pantoprazole 40 mg b.d.) To confirm the eradication of *HP*, the urea breath test was performed for all patients for four weeks after the treatment. Accordingly, patients were divided into two groups: failed treatment and successful treatment, and vitamin D levels were compared between two groups. All participants gave informed written consent prior to the study. All the

patients in study have not taken vitamin D in the past year. This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1398.197).

Data analysis method

Finally, data analysis was performed using SPSS ver. 25. The mean and standard deviations were used to describe quantitative variables and the number and percentage were used to describe qualitative variables. The inter-group comparison was carried out using chi-square test and P-value < 0.05 was considered as the significance level.

RESULTS

In this study, 200 patients with *Hp* infection who underwent *Hp* eradication therapy using amoxicillin, metronidazole, bismuth, and pantoprazole for four weeks were divided into following groups based on the urea breath test: optimal therapeutic response (n=153 people) and treatment failure (n=47 people).

In the group with positive urea breath test, 18, 13, and 16 people, and in the group with negative urea breath test, 51, 64, and 38 people were in the <35, 35-55, and >55 age groups, respectively. There was no significant difference between the two groups in terms of age group distribution (P = 0.2).

There were 33 (2.70%) and 95 females (1.62%), respectively, in the groups with and without treatment failure, and the rest were male. There was no significant difference between the two groups in terms of sex distribution (P = 0.4). Table 1 shows the distribution of the two groups with and without treatment failure based on body mass index (BMI). There was also no significant difference between the two groups in terms of this variable (P = 0.6).

Table 1. Distribution of two groups with and without treatment failure based on body mass index.(BMI= Body Mass Index)

BMI	Urea Test		P-value
	Positive N=47 (%)	Negative N=153 (%)	
18.5< (Underweight)	16(34.0)	47(30.7)	0.6
18.5-25 (Normal)	17(36.2)	55(35.9)	
25-30 (Overweight)	13(27.7)	39(25.5)	
30≤ (Obese)	1(2.1)	12(7.8)	

Table 2. Distribution of two groups with and without treatment failure based on vitamin D levels.

Serum Vitamin D	Urea Test		P-value
	Positive N=47 (%)	Negative N=153 (%)	
<10 ng/dL	8 (17.0)	6 (3.9)	<0.001
10-20 ng/dL	19 (40.4)	15 (9.8)	
21-30 ng/dL	4 (8.5)	4 (2.6)	
30 ng/dL <	16 (34.0)	128 (83.7)	

At the beginning of the treatment, vitamin D levels in the majority of patients (40.4%) of the treatment failure group was 10-20 ng/dL, but it was more than 30ng/dL in the majority of patients (83.7%) of the group with optimal therapeutic response. Such a difference was statistically significant ($P < 0.001$) (Table 2).

DISCUSSION

Considering the high prevalence of *H. pylori* infection (HP) and the importance of its eradication, it is important to eliminate the factors that increase the likelihood of treatment failure. Laboratory studies suggest the role of vitamin D in host immunity against Hp infection as well as the specific antibacterial effects of this vitamin against Hp pathogen. Therefore, the present study investigated the effect of VDD on the success rate of eradication treatment in Hp-positive patients. The results showed that vitamin D level was 10-20 ng/dL in the majority of patients (40.4%) in the treatment failure group at the beginning of treatment, but it was more than 30 ng/dL in the majority of patients (83.7%) in the group with optimal therapeutic response at the beginning of treatment, which was statistically different.

A retrospective study (2018) was carried out on 160 patients with type 2 diabetes who underwent Hp eradication treatment from 2015 to 2017 and had their baseline vitamin D levels checked. Patients were divided into two groups: successful eradication therapy (n=124 people) and failed eradication treatment (n=36 people). The statistical analysis showed that the mean vitamin D level in the treatment failure group was significantly lower than the successful eradication group, which is consistent with the results of the present research [16].

A study was carried out on 220 patients diagnosed with Hp gastritis using endoscopic biopsy in 2017, and vitamin D levels were measured in all of them before the eradication treatment. Patients were treated with bismuth-based quadruple Hp eradication treatment for 14 days and were then divided into two groups based on vitamin D levels: vitamin D <10 ng / dL and vitamin D $\geq$ 10 ng / dL. Hp eradication was successful in 77.2% of cases. VDD was prevalent among 30.5% of the studied population. The mean vitamin D levels in the eradication failure group were significantly lower. Also, the number of patients with VDD in the treatment failure group was significantly higher than the successful treatment group, and the results of the mentioned study, similar to the present research, showed that VDD is a risk factor for the failure of Hp eradication therapy [15].

A case-control study (2018) was carried out on 150 patients diagnosed with Hp gastritis using endoscopy and confirmed by stool antigen tests (SATs). Patients were divided into two groups based on their vitamin D levels: <20 ng/dL (VDD) and $\geq$ 20 ng/dL. Results showed that vitamin D levels in the treatment failure group were significantly lower than in the successful treatment group. Besides, the number of patients with VDD was significantly higher in the treatment failure group, which is consistent with the results of the present research [17].

A cross-sectional study (2018) was conducted on 254 patients aged above 65 years who underwent endoscopy between the years 2010 and 2017 and were examined for Hp infection. Of the total patients, 23 were Hp-positive and 211 were Hp-negative. Most patients with VDD were in Hp-positive group. Also, multivariate regression analysis showed that VDD was significantly associated with an increased risk of Hp infection after the removal of age, sex, variables and Charlson comorbidity index (CCI). This suggests that VDD has an effect on increasing both the risk of Hp infection and treatment failure [18].

In a study in 2012, the mean vitamin D level in 36384 outpatients was measured and determined, and the results of statistical analysis showed the role of hypovitaminosis D (VDD) as a risk factor for autoimmune diseases. It was also found that lower vitamin D levels in Hp patients can be influential factors for more severe invasion of gastric mucosa, which can be the main justification for the results obtained in the present study [20].

In a cross-sectional study on 208 patients with upper gastrointestinal symptoms in 2018, they were genotyped for VDR polymorphism and the results were compared between Hp-positive and Hp-negative individuals. Results showed a significant relationship between VDR gene polymorphism and Hp infection, which justifies our research findings at the molecular level [22].

A case-control study (2014) investigated the role of VDR in intrinsic immunity against Hp infection. A total of 17 Hp-positive patients and 16 controls were included in the study, and the results showed overexpression of VDR and Cyclic Adenosine Monophosphate in the gastric mucosa in cases of Hp infection. The results also showed that VDR plays an important role in the gastric mucosal hemostasis and protection against Hp infection, which is consistent with the findings of the present research [23].

A laboratory study in 2015 showed that the combination of vitamin D decomposition products had antibacterial effects only against Hp, but not other bacteria. Therefore, the results of the present research cannot be generalized to other bacteria. A laboratory study in 2018 showed that some compounds derived from vitamin D, including VDP1 [(1R,3aR,7aR)-1-[(1R)-1,5-dimethylhexyl]octahydro-7a-methyl-4H-inden-4-one], have completely specific and very strong antibacterial effects against Hp and they can be used to produce medicine against this bacterium in the future, and the results of the present research also support this theory [24].

CONCLUSION

Overall, the results of the present case-control study revealed a significant statistical relationship between serum vitamin D deficiency level and *H. pylori* eradication rate. Vitamin D deficiency increases *H. pylori* treatment failure, so measuring serum vitamin D levels in cases of treatment failure and the use of vitamin D supplements are recommended in people with vitamin D deficiency to improve the eradication

treatments of *H. pylori*.

CONFLICT OF INTERESTS

We do not have conflict of interests.

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Evaluation of correlation of serum vitamin B12 with proteinuria in type 2 Diabetes Mellitus patients

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Background and Aims: Diabetic nephropathy is one of the leading causes of end stage renal disease (ESRD) in the world. This study was conducted to investigate the correlation of B12 deficiency with presence of proteinuria in patients with Diabetes Mellitus.

Materials and Methods: This study was performed on patients with type 2 Diabetes Mellitus. The inclusion criteria were: HbA1C $\leq 8\%$, absence of hypertension or controlled blood pressure (BP $<140/90$) in hypertensive patients, no smoking, absence of any recent stressful illness such as MI, CVA and causes of proteinuria other than diabetic nephropathy. The serum level of B12 and the amount of urine protein-to-creatinine ratio (UPCR) were measured, and correlation between b12 deficiency and presence of proteinuria was assessed using Spearman correlation test.

Results: In this study 78 patients (44.87% women and 55.13% men) were examined. There was an inverse and weak correlation between the serum B12 deficiency and presence of proteinuria ($r=-0.104$), which was not statistically significant ($p=0.254$). Due to the statistically significant difference between two groups with and without proteinuria in antiproteinuric drugs, as well as Metformin use and chronic kidney disease (CKD) stage, a subgroup analysis was performed in each of these subgroups. There was no correlation between the B12 deficiency and presence of proteinuria.

Conclusion: The findings revealed no statistically significant correlation between the serum B12 deficiency and presence of proteinuria.

INTRODUCTION

Diabetes is known as a common non-communicable disease in various societies. This disease affects various organs. One of the complications of diabetes is nephropathy [1]. Diabetic nephropathy is the cause of 30-50% of the ESRD cases in the United States. The clinical presentation of diabetic nephropathy is defined as proteinuria, hypertension, and progressive decline in renal function. The growth factors, hemodynamic and hormonal changes cause the release of inflammatory factors and reactive oxygen species which

cause glomerular hyperfiltration, renal hypertrophy and altered glomerular composition that presents clinically with albuminuria and hypertension [1]. The care and treatment suggested so far (including controlling blood sugar, lipids, blood pressure, and prescribing drugs such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) were inadequate to treat diabetic nephropathy and other unknown factors seem to be effective in causing diabetic nephropathy [1, 2].

In diabetic patients, the serum level of B vitamins is re



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duced, but the mechanism of reduction is not entirely clear; nevertheless, one reason for the decrease can be long-term use of Metformin that reduces the absorption of vitamin B12 and folic acid from the gastrointestinal tract [3, 4]. In a cross-sectional study, 22% of patients with diabetes lacked B12 [2]. However, in another study of diabetic patients with or without nephropathy, vitamin B1 and B6 deficiency were common and vitamin B12 deficiency was rare [5]. Many patients with type 2 diabetes are treated with Metformin and the association between long-term use of Metformin and the B12 deficiency has been established. Although, there have been differences in the extent of this relationship in different studies; in one study, nearly 30% of diabetic patients treated with Metformin were deficient in vitamin B12 [6]. The decrease in the level of B vitamins, including B12, causes hyperhomocysteinemia, consequently, it causes increasing oxidative stress and decreasing antioxidant function [7-9]. Therefore, considering the importance of recognizing the causes of diabetic nephropathy other than the known factors for the prevention of ESRD, we decided to investigate the link between vitamin B12 deficiency and proteinuria in patients with Diabetes Mellitus.

MATERIALS and METHODS

This study was approved by the ethical committee of Shahid Beheshti medical university (IR.SBMU.RETECH.REC.1398.424). This study was performed as a descriptive correlation study in patients with type 2 Diabetes Mellitus referred to Loghman Hakim Hospital. The patients were first explained about the study and its goals; the patients were included in the study with personal consent. The inclusion criteria were: HbA1C $\leq$ 8%, absence of hypertension or controlled blood pressure (BP < 140/90) in hypertensive patients, no smoking, absence of any recent stressful illness such as MI, CVA and causes of proteinuria other than diabetic nephropathy such as acute febrile illness and kidney disease (glomerular or tubular). At first, a complete history of the patients was taken and a physical examination was performed. After 12 hours of fasting, 7 cc of blood was taken from the patients on an outpatient basis and collected in three test tubes. 1 cc in test tube containing EDTA anticoagulant for blood cell count, 1 cc in test tube containing EDTA anticoagulant for HbA1C, 5 cc in third test tube that was centrifuged and the serum was removed. 0.5 cc of the serum was frozen at minus 20 ° C and was maintained to measure the serum B12 level and the remaining 4.5 cc was used to measure triglycerides, cholesterol, HDL, LDL, fasting blood sugar (FBS) urea and creatinine. Biochemical assays were used to measure triglycerides, cholesterol, HDL, LDL, FBS, urea, creatinine. The B12 level was measured by COBAS E411 and Electrochemi-

luminescence (ECL) method. The patients were instructed not to do too much physical activity before preparing a urine sample and rest for 10 minutes in a supine position. Random urine was taken from a patient to measure the level of creatinine and protein in the urine, urine protein, and creatinine were measured by biochemical tests. The amount of proteinuria was calculated by measuring the ratio of protein to creatinine in random urine. GFR was calculated using the MDRD formula.

The data were analyzed utilizing SPSS software version 24 by spearman correlation coefficient, independent t and chi-square tests. $p < 0.05$ is considered as a statistically significant level in this study.

RESULTS

In this study, 300 patients with type 2 Diabetes Mellitus were studied, of which 78 patients were eligible for the study. The data of these 78 patients (35 females and 43 males) with a mean age of $8/14 \pm 59$ years (minimum 26 and maximum 87 years) were analyzed. 33 (42.3%) patients had proteinuria and 45 (57.7%) patients had no proteinuria. There were 48 (61.5%) patients with hypertension, but all of them had controlled blood pressure at the time of the study. 51 (65.4%) patients were treated with ACEI and ARB. 61 (78.2%) patients also took other protein-lowering drugs including Pentoxifylline, Atorvastatin, Glucilazide, Allopurinol, Indapamide, Dipyridamole, and Spironolactone.

Table 1. Demographic and clinical characteristics of patients (BMI= Body mass index, ARB= Angiotensin receptor blockers, ACEI= Angiotensin-converting enzyme inhibitors, GFR= Estimated glomerular filtration rate)

Characteristics	All patients	Subgroups		p-value
		With proteinuria N=33	No proteinuria N=45	
Age (mean $\pm$ SD)	78	62.82 $\pm$ 10.9	56.20 $\pm$ 16.6	0.038
Male	43 (55.1)	22 (66.7)	21 (46.7)	0.110
BMI (kg/m²) (mean $\pm$ SD)	78	28.78 $\pm$ 5.65	34.26 $\pm$ 9.35	0.002
Hypertension	48 (61.5)	22 (66.7)	26 (57.8)	0.480
ARB/ACEI Consumption	51 (65.4)	27 (81.8)	24 (53.3)	0.015
Taking proteinuria lowering drugs	61 (78.2)	30 (90.9)	31 (68.9)	0.026
Taking multivitamins	14 (17.9)	7 (21.2)	7 (15.6)	0.561
Metformin consumption	36 (46.2)	9 (27.3)	27 (60)	0.006
eGFR				
90 $\leq$	2 (2.6)	0 (0)	2 (4.4)	
60-89	22 (28.2)	4 (12.1)	18 (40)	
30-59	40 (51.3)	18 (54.4)	22 (48.9)	0.002
15-29	9 (11.5)	6 (18.2)	3 (7/6)	
<15	5 (6.4)	5 (15.2)	0 (0)	
B12 deficiency	24 (30.77)	12 (36.4)	12 (26.7)	0.254

Table 2. Laboratory findings of patients (FBS= Fasting blood sugar, eGFR= Estimated glomerular filtration rate)

Variables	Subgroups		p-value
	With proteinuria N=33 (Mean±SD)	No proteinuria N=45 (Mean±SD)	
Serum Vitamin B12 (pg/ml)	377.12±332.53	294.63±283.082	0.254
Hemoglobin (g/dl)	12.712±1.965	13.309±1.44	0.333
Triglyceride (mg/dl)	139.06±111.85	141.49±59.14	0.910
Cholesterol (mg/dl)	135.52±33.46	150.27±36.84	0.069
HDL (mg/dl)	41.69±10.77	40.08±8.87	0.483
LDL (mg/dl)	73.78±26.67	85.84±31.45	0.071
Creatinin (mg/dl)	2.25±1.62	1.25±0.415	0.001
FBS (mg/dl)	118.27±45.08	131.3±34.75	0.172
eGFR (ml/min/1.73 m ²)	37.74±18.47	57.12±17.23	0.000

The percentage of ACEI, ARB and other proteinuria-lowering drugs were higher in patients with proteinuria. There were 36(46.2%) patients treated with Metformin, of which 15 (41.7%) patients had B12 deficiency ($P = 0.054$). Most patients had stage 2 (28.2%) and 3 (51.3%) CKD. More details about the demographic and clinical information of patients with comparison between the two groups with and without proteinuria are given in Table 1.

55.1% of patients ($n = 43$) had HbA1C below 7% and 44.9% ($n = 35$) had 7-8 HbA1C. There was no significant difference between taking multivitamins containing B vitamins and the serum lipid level of the two groups with and without proteinuria ($P > 0.05$).

In this study, the serum B12 level was measured by ECL method with a normal level of 197-771 pg/ml. The values below 197 were considered as B12 deficiency. 30.8% of patients ($n = 24$) had B12 deficiency. 36.4% of patients with proteinuria and 26.7% of patients without proteinuria had B12 deficiency. The mean serum B12 level in patients with proteinuria was 377.2 ± 332.53 and in patients without proteinuria was $282/283 \pm 63/294$. Using Spearman correlation test, it was found that there is a weak inverse correlation between the serum B12 level and proteinuria ($r = -0.104$) which was not statistically significant ($p = 0.254$). Due to the statistically significant difference between the two groups with and without proteinuria in the use of ACEI and ARB and other proteinuria reducing drugs as well as the use of metformin and CKD stage, subgroup analysis was performed and Spearman test indicated that the correlation between proteinuria and the B12 level in each of the above subgroups was not statistically significant.

Other laboratory information of patients is given in detail in Table 2.

DISCUSSION

Diabetic nephropathy is one of the leading causes of ESRD in the world [1]. B12 deficiency has been suggested as one of the possible effective causes in the development and acceleration of diabetic nephropathy [10]. Therefore, considering the importance of recognizing the factors affecting di-

abetic nephropathy for prevention and treatment, the aim of this study was to determine the correlation between the serum B12 level and proteinuria in patients with Diabetes Mellitus which according to the results of this study, the correlation between the two was inverse, weak, and was not statistically significant. The consideration for the role of vitamin B12 stems from the fact that the lack of this vitamin can increase oxidative stress by increasing homocysteine and cause toxic effects [7,8]. But the question that needs to be answered first is whether there is a correlation between the serum B12 level and proteinuria that in the next step, if this correlation is proven, the effects of this vitamin in the prevention and treatment of diabetic nephropathy should be investigated. In a study of 100 Indian patients with type 2 diabetes, the B12

level was significantly lower in the group with nephropathy than in the group without nephropathy [10], yet in a study conducted in the United States on 2965 patients, there was no correlation between the serum B12 level and albuminuria or decreased renal function [11]. However, this study has not been performed on diabetic patients; also, in another study performed on diabetic patients in Germany, there was no significant relationship between the serum B12 level and albuminuria [5]. A study was conducted in 2010 to evaluate the effect of high doses of B vitamins (including folic acid, B6, and B12) on patients with nephropathy that at the end of treatment, not only proteinuria did not change significantly, but these patients had a greater decrease in GFR and a greater increase in MI and stroke than the control group [12]. Therefore, lowering homocysteine by administering high doses of vitamin B12 was not necessarily associated with reducing the effects of hyperhomocysteinemia [13]. Therefore, there is currently no strong evidence to support the administration of vitamin B12, to reduce diabetic nephropathy.

One of the significant results in this study is the rate of B12 deficiency in patients treated with Metformin (41.7%), which is higher than similar previous studies [2, 4]. This indicates the need to pay more attention to the evaluation of patients treated with metformin for B12 deficiency.

LIMITATIONS and SUGGESTIONS

One of the limitations of this study is the small number of samples and another limitation is the lack of measurement of the serum levels of methylmalonic acid and homocysteine. Thus, our suggestion is to conduct a study with a large number of sample volumes in this field, and in addition to the serum B12 level, the serum level of Methylmalonic Acid and homocysteine should also be measured.

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CONFLICT OF INTERESTS

The authors declared no competing interests.

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Role of Diffusion Weighted MRI in Differentiation of Malignant from Benign Ovarian Tumors

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ABSTRACT

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Background and Aims: Ovarian masses are common and due to the risk of dissemination, biopsy is not recommended before surgery; thus, imaging techniques can play a crucial role in differentiating benign from malignant lesions. Diffusion weighted magnetic resonance imaging (DW-MRI) is now considered a part of the standard evaluation of pelvis. The aim of this study was to investigate the role of DW-MRI in distinguishing between benign and malignant ovarian tumors and its comparison with pathology results.

Materials and Methods: In this diagnostic study, 85 non-pregnant women of childbearing age with an ovarian mass who were referred to Imam Hossein hospital in 2018 were evaluated. All patients underwent MRI before surgery and apparent diffusion coefficient (ADC) value was calculated for each. In addition, demographic data and postoperative pathology results were recorded. The acquired data were then entered into the SPSS software for statistical analysis.

Results: The mean age of the participants was 39.01 ± 6.98 years. Mean ADC value was calculated as $1.14 \pm 0.67 \times 10^{-3} \text{ mm}^2/\text{s}$. Mean ADC value was significantly lower in malignant lesions compared to borderline and benign ones ($P < 0.001$). Mean ADC value was the highest in cysts and the lowest in metastatic lesions (with the exception of serous cystadenocarcinoma ($P = 0.267$) compared to other types of lesions ($P < 0.05$). The optimal cutoff point for ADC to differentiate between benign and malignant ovarian lesions was $1.16 \times 10^{-3} \text{ mm}^2/\text{s}$ with 95% sensitivity, 100% specificity, 100% positive predictive value (PPV), 98% negative predictive value (NPV), and 99% accuracy.

Conclusion: ADC value in DW-MRI is highly sensitive and specific in differentiation between benign and malignant ovarian tumors.

INTRODUCTION

Ovarian masses are a common clinical finding and may be symptomatic or asymptomatic with incidental detection. In addition, ovarian cancer, as one of the most common types of cancer, is found in 3.6% of women worldwide [1]. Therapeutic procedures differ when ovarian lesions are benign or malignant and this is challenging since many lesions are only found to be malignant during or after surgery based on pathology and not preoperatively. On the other hand, due to the risk of dissemination, biopsy is not recommended before surgery; therefore, imaging techniques can play a significant role in differentiating benign from malignant

lesions preoperatively [2]. Many diagnostic imaging techniques have been used to determine the characteristics of malignant ovarian masses, namely ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) [3]. CT is now considered to be the preferred method due to its efficacy in the assessment of the benignity or malignancy of ovarian masses; however, it involves radiation exposure [4, 5].

MRI can be used to locate the origin of a pelvic lesion and determine the characteristics of an adnexal mass, especially when the lesion is undetermined with regard to malignancy [6, 7]. One of the major advantages of MRI is lack of expo



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sure to radiation, which is of great importance in women of childbearing age [2]. Furthermore, MRI is 76 % sensitive, and 97 % specific in the diagnosis of ovarian cancer, especially when indeterminate ovarian masses on US are concerned [8]. DWI is also thought to be a helpful technique in the evaluation of ovarian masses. This method basically evaluates the extent of water diffusion in tissues and it can quantitatively measure the random motion of water molecules by ADC values [9, 10]. DW-MRI and ADC have been shown to be effective in differentiating benign from malignant ovarian tumors in multiple studies [11-13]; however, the efficacy of DW-MRI remains controversial, whereas some other studies have found this technique ineffectual in distinguishing between malignant and benign lesions of ovary [14, 15]. Further studies are required to determine the true value of DW-MRI and ADC in this regard; therefore, in this study we have investigated the role of DW-MRI in differentiation of benign from malignant ovarian tumors and appointed a cutoff point for ADC, while calculating its sensitivity and specificity.

MATERIALS and METHODS

Participants

This diagnostic study was conducted in Imam Hossein Hospital, Tehran, in 2018. The study sample consisted of 85 non-pregnant women of childbearing age (15-45 years) in whom an ovarian mass was diagnosed using US or other diagnostic methods. The exclusion criteria were pregnancy and unavailability of postoperative pathology results.

Study Design

This study was performed according to the Declaration of Helsinki issued by the World Medical Association. After obtaining written informed consent and recording demographic data, before surgery, participants underwent conventional MRI using a 1.5 tesla MRI scanner (Avanto, manufactured by Siemens) and DWI sequence was used to calculate ADC. During surgery, a specimen was collected from the lesion and the pathology finding regarding type

and malignancy of the lesion was reported postoperatively. The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU. MSP. REC.1397.27).

Data analysis method

Statistical analysis of data was performed using SPSS software version 25 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to report frequencies, percentages, and mean values. Since age and ADC values were not normally distributed (evaluated by Kolmogorov-Smirnov test), comparison was made using non-parametric tests such as Kruskal-Wallis and Mann-Whitney; however, mean values were used as measures of central tendency in tables. A receiver operating characteristic (ROC) curve was created to calculate sensitivity and specificity.

RESULTS

Sixty-five non-pregnant women of childbearing age with an ovarian mass were evaluated in this study. The mean age of the participants was 39.01 ± 6.98 years. Mean ADC value was calculated as $1.14 \pm 0.67 \times 10^{-3} \text{mm}^2/\text{s}$. Most of the ovarian masses/tumors were malignant (61.2%), followed by benign (23.5%) and borderline (15.3%) lesions. Teratomas were the most common type of ovarian masses (17.6%), followed by mucinous cystadenocarcinomas (16.5%), endometriomas (15.3%), and cysts (15.3%), while serous cystadenocarcinomas were the least common (2.4%) (Table 1). Malignant lesions had the lowest mean ADC ($0.70 \pm 0.17 \times 10^{-3} \text{mm}^2/\text{s}$), followed by borderline ($1.61 \pm 0.54 \times 10^{-3} \text{mm}^2/\text{s}$), and benign ovarian masses ($1.98 \pm 0.52 \times 10^{-3} \text{mm}^2/\text{s}$) ($P < 0.001$). Furthermore, patients with malignant lesion were the oldest (41.25 ± 5.50 years), followed by patients with borderline (37 ± 7.74 years), and benign lesions (34.5 ± 7.65 years) ($P < 0.001$); however, in a two-by-two comparison, the age difference between patients with benign and borderline lesions was not statisti

Table 1. Frequency of ovarian masses with respect to malignancy and type of lesion

BMI		Number (%)
Malignancy of the tumor	Benign	20 (23.5%)
	Borderline	13 (15.3%)
	Malignant	52 (61.2%)
Types of lesions	Teratoma	15 (17.5%)
	Mucinous cystadenocarcinoma	14 (16.5%)
	Endometrioma	13 (15.3%)
	Cyst	13 (15.3%)
	Adenoma	7 (8.2%)
	Adenocarcinoma	7 (8.2%)
	Germ cell tumor	7 (8.2%)
	Metastatic tumor	4 (4.7%)
	Clear cell carcinoma	3 (3.5%)
	Serous cystadenocarcinoma	2 (2.4%)

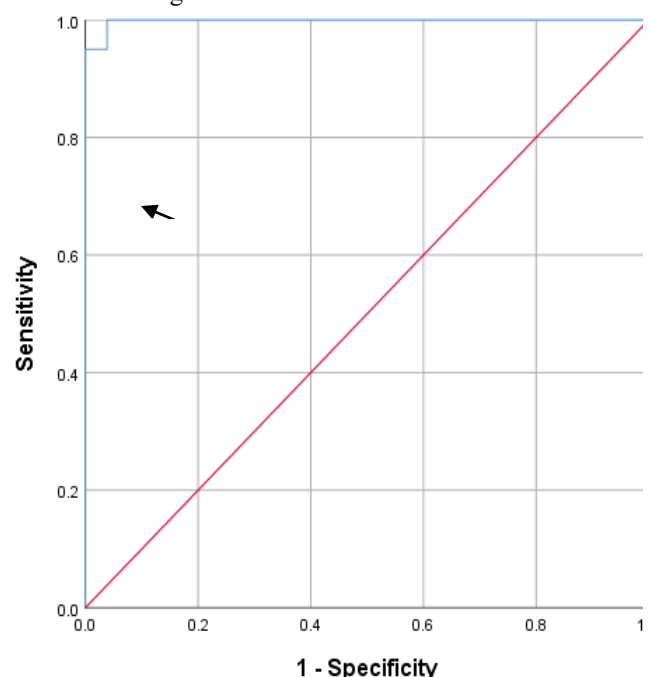


Figure 1. ROC curve of sensitivity and specificity of ADC

Table 2. Comparison of age and ADC values among malignant, borderline, and benign ovarian tumors (SD= Standard deviation)

Malignancy of the tumor	Age (Years)	P-value*	ADC ($\times 10^{-3} \text{ mm}^2/\text{s}$)	P-value*
	Mean $\pm$ SD		Mean $\pm$ SD	
Benign	34.50 $\pm$ 7.65	<0.001	1.98 $\pm$ 0.52	<0.001
Borderline	37.00 $\pm$ 7.74		1.61 $\pm$ 0.54	
Malignant	41.25 $\pm$ 5.50		0.70 $\pm$ 0.17	

* Analyzed by Kruskal-Wallis test

Table 3. Comparison of ADC values among different types of ovarian masses (SD= Standard deviation)

Types of lesions	ADC ($\times 10^{-3} \text{ mm}^2/\text{s}$)	P-value*
	Mean $\pm$ SD	
Cyst	2.25 $\pm$ 0.40	<0.001
Endometrioma	1.61 $\pm$ 0.54	
Adenoma	1.49 $\pm$ 0.31	
Teratoma	0.84 $\pm$ 0.81	
Mucinous cystadenocarcinoma	0.71 $\pm$ 0.16	
Germ cell tumor	0.68 $\pm$ 0.12	
Clear cell carcinoma	0.63 $\pm$ 0.15	
Adenocarcinoma	0.61 $\pm$ 0.13	
Serous cystadenocarcinoma	0.56 $\pm$ 0.08	
Metastatic tumor	0.43 $\pm$ 0.06	

* Analyzed by Kruskal-Wallis test

cally significant ($P=0.250$) (Table 2). Table 3 shows the comparison of mean ADC values among different types of ovarian masses; cysts had the highest, and metastatic tumors the lowest ADC values ($P<0.001$). Figure 1 shows the ROC curve for the cutoff point of ADC that best differentiates malignant from benign ovarian tumors. The optimal cutoff point for ADC was $1.16 \times 10^{-3} \text{ mm}^2/\text{s}$ with 95% sensitivity, 100% specificity, 100% PPV, 98% NPV, and 99% accuracy.

DISCUSSION

Much effort has been made to find a suitable and harmless diagnostic tool to evaluate ovarian masses regarding benignity or malignancy, because this can guide therapeutic procedures and patients' management. DW-MRI has been used in multiple studies for the differentiation of malignant from benign ovarian lesions; however, results have been controversial. Furthermore, different ADC cutoff point have been suggested. The differential value of ADC to distinguish between benign and malignant lesions has also been investigated in various organs and it has been shown to be beneficial to differentiate between benign and malignant lesions in several organs such as liver, uterus, and breast while ineffective in other organs such as thyroid, pancreas, and salivary glands [16]. The results of our study showed that the optimal cutoff point for ADC was $1.16 \times 10^{-3} \text{ mm}^2/\text{s}$ which was 95% sensitive and 100% specific for the diagnosis of malignant ovarian masses, in addition to 100% PPV, 98% NPV, and 99% accuracy.

US is usually the first diagnostic imaging tool when an

ovarian lesion is suspected, mostly due to its availability [17]. Sensitivity and specificity of Doppler US has been reported as 84% and 82%, respectively for the diagnosis of ovarian cancer [8].

CT after contrast administration is mostly beneficial when spread of malignancy and response to therapy are concerned; however, its value is limited in the primary diagnosis of ovarian masses. Furthermore, its limitation regarding exposure to radiation and use of contrast media in patients with renal dysfunction should be taken into consideration. In case of undetermined adnexal masses, CT has shown 81% sensitivity and 87% specificity in the diagnosis of ovarian malignancy [8]. In a case-control study by Fan et al. the sensitivity, specificity, PPV, NPV, and accuracy of CT for diagnosis of ovarian cancer were 84.48%, 76.67%, 87.50%, 71.88%, and 81.82% respectively, while those in DW-MRI were 93.10%, 83.33%, 91.53%, 86.21%, and 89.77%, respectively; thus DW-MRI was superior to CT regarding sensitivity, specificity, and accuracy [18]. In addition, the combined sensitivity and specificity of DW-MRI in the diagnosis of malignant versus benign ovarian tumors in 10 studies has been reported as 93% and 88%, respectively [9, 10, 19-26]. However, in some studies DWI was not proven effective in distinguishing between malignant and benign ovarian masses [14, 15, 27].

The results of our study showed significantly lower ADC values in malignant ovarian lesions compared to benign or borderline lesions. Contrarily, in a meta-analysis conducted by Kim et al., ADC values measured in DWI were not significantly different between malignant and benign ovarian lesions [28]. The difference between studies may be due to different stages of malignant tumors, the accuracy of the MRI device, and the sample size. On the other hand, consistent with the findings of our study, Kovac et al. found that lower ADC values were highly suggestive of endometrioid adenocarcinomas compared to other malignant ovarian lesions [29]. Additionally, Li et al. showed that the mean ADC value of benign ovarian lesions was significantly higher than malignant masses. In the same study, an ADC cutoff of $1.25 \times 10^{-3} \text{ mm}^2/\text{s}$ was associated with sensitivity of 90.1% and specificity of 89.9% for differentiation between malignant and benign ovarian surface epithelial tumors [9]. Since the lower ADC cutoff in our study has higher sensitivity and specificity, ours appears to be more appropriate in this regard. In another study which was performed by Oh et al., an ADC value of $1.09 \times 10^{-3} \text{ mm}^2/\text{s}$ was 94.4% sensitive and 85.7% specific for distinguishing between grade I and grade II or III ovarian cancer [30]. The cutoff point suggested by this study is slightly lower than ours and it has similar sensitivity; however, its specificity is much lower than ours. Although the application of the ADC cutoff point in this study is quite different compared to ours, the ADC cutoff in our study seems to be superior regarding specificity.

Besides, Davarpanah et al. found that ovarian lesions with

ADC values of higher than $1.55 \times 10^{-3} \text{mm}^2/\text{s}$ have a more than 99.9% chance of being benign [31]. Obviously, the $1.16 \times 10^{-3} \text{mm}^2/\text{s}$ ADC cutoff in our study for benign lesions covers the cutoff suggested in this study.

In comparison with other studies, the ADC cutoff suggested by our study appears to be the most sensitive, specific, and accurate to distinguish between malignant and benign ovarian tumors, while maintaining the highest PPV and NPV.

CONCLUSION

Our results showed that DW-MRI together with ADC measurements are beneficial in the diagnosis of malignant ovarian lesions and their differentiation from benign masses. Moreover, ADC values of lower than $1.16 \times 10^{-3} \text{mm}^2/\text{s}$ are highly suggestive of malignancy. DW-MRI and ADC measurements should be included in the assessment protocol of ovarian lesions preoperatively.

CONFLICT OF INTERESTS

None declared.

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Surgical Technique for Femoral Intramedullary Bent Nail Removal: A Case Report and Review of the Literature

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ABSTRACT

A 21-year-old male patient was admitted with a severe right thigh deformity following a car accident. He had experienced a previous history of intramedullary interlocking femoral nail 3 years ago.

The neurovascular examination was normal. The radiologic evaluation revealed a bent nail with 105° angular deformity in the sagittal plane.

With a lateral approach to the apex of the fracture site, the bent nail was cut by an 8mm cobalt drill, two parts of the nail were extracted; then fixation was performed by a new intramedullary interlocking nail and autogenous cancellous graft.

The fracture healed properly without any complications 6 months after corrective surgery.

INTRODUCTION

Intramedullary (IM) interlocking nailing for the treatment of femoral shaft fractures is traditionally considered as the gold standard procedure [1, 2]. A secondary high-energy trauma to a previously stabilized long bone fracture with an intramedullary nail is exceedingly rare [3-7].

A broken nail can be removed easily through the fracture site. However, no standard protocol exists precisely in the literatures regarding the removal of bent nails, as very few cases have been documented [8]. Straightening of bent nails intraoperatively is difficult and considered by many authors practically impossible, especially when bending involves a high-strength nail or titanium nail [9-11].

We present a surgical technique for the treatment of a patient with a bent nail after femoral shaft re-fracture following a car accident.

CASE PRESENTATION

A 21-year-old male patient was admitted to hospital following a car accident. He had a history of right femoral shaft fracture treated by interlocking IMN three years before.

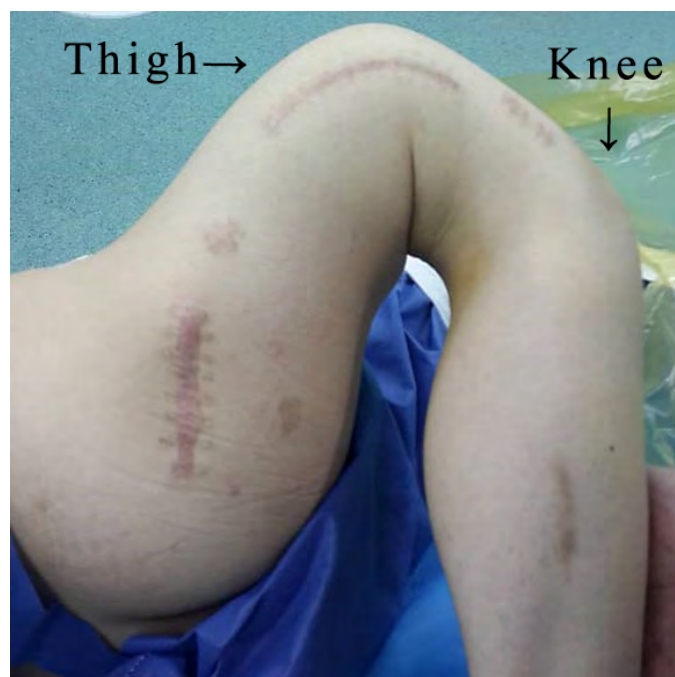


Figure 1. Obvious anterior angulation deformity in right leg



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Figure 2. 20° varus angulation and 105° anterior angulation

The patient suffered from severe pain and deformity of the right thigh without any other associated injuries. The neurovascular status was intact (Figure 1).

Plain radiography of right thigh revealed significant bending of the nail and femoral shaft fracture. The IM nail had a 105° anterior angulation in anterior-posterior (AP) view with a 20° varus angulation in lateral view while continuity of the nail was intact (Figure 2). After obtaining the informed consent of the emergency operation, in the preoperative analysis, straightening out the nail was considered to be impossible.

With a 7.5cm lateral approach to the apex of deformity, the fracture area was exposed; the bent nail was cut by an 8-mm cobalt drill.

Another incision in the previous surgical site was performed; the proximal part of the nail from the proximal site and the distal part from the fracture site extracted.

The femoral canal was then reamed to 2.5 mm greater than the diameter of the original nail. A new nail, with a similar length but 2 mm larger in circumference than the original nail was inserted. After the passage of the new nail, four interlocking bolts were inserted through the new nail as a static model. The reduction was checked under fluoroscopy and was considered to be satisfactory. Iliac crest bone grafting was done. Postoperatively, there were no compli-

cations and radiographs showed both good reduction and the alignment of fracture fragments in the AP and lateral views. The patient's deformity was corrected clinically and radiologically (Figure 3).

The patient started toe-touch mobilization and knee hip mobilization exercises 3 days after surgery. After 6 months the fracture healed without any complications (Figure 4). In the one-year follow-up, the patient had no problems related to this surgery.

DISCUSSION

Bent nail is a rare yet distressing complication and there are some challenges in management of this complication. The use of intramedullary nails for the treatment of femoral fractures is the gold standard [3].

Results in the literature have shown up to 98% union rates, with few complications. Known complications of antegrade femoral nailing include neuropraxia associated with traction, angular or rotational malalignment, heterotopic ossification, hip pain, re-fracture, malunion, non-unions, and implant complications[5-7].

Due to the relative rarity of bent intramedullary nails secondary to trauma, only case reports are found in the literature addressing the treatment options. The first step in approaching fractures recurrences is the well-planned attempt to remove the deformed intramedullary nail. Few methods have been described in literature, such as manipulation of the bent nail via external force on the femur, percutaneous technique with locking compression plate and collinear reduction clamp, weakening the bent nail using high-speed burr, the sectioning of the nail using diamond edge blades and removal of each piece separately, and the re-bending of the nail with the help of a specialized device and locking plate [4].

Canton et al declared that in management of this complication some factors should be considered, including deformity degree, direction and location, and also patient's condition and the surgeon's experience. Proper amount of preop-

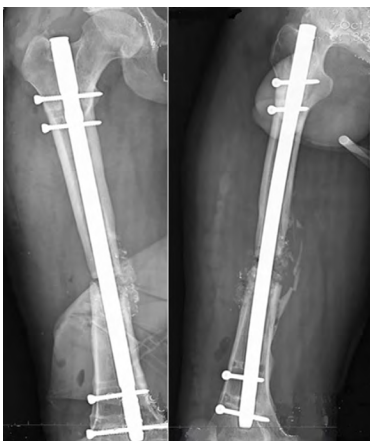


Figure 3. Post-operative X-ray. Anteroposterior and lateral view



Figure 4. Six months-post operative evaluation

Furthermore, this condition happens more in new high-energy trauma cases, however, sometimes it occurs in nonunion and often without trauma which has a different management plan. More soft tissue damage and co-morbid injuries with acuter general conditions may be expected in high energy trauma cases that benefit from a damage control approach for stabilizing a more accurate plan for definite surgery [8].

Nicolaides et al. suggested a lateral longitudinal femoral osteotomy for resection of the bent nail and reconstructing femur with a new nail. Fixation of the osteotomy was achieved with plate and cerclage wires. Five months after surgery, callus formation was evident and standard ranges of motion and gait were regained for the patient, walking with a single cane. Formerly he presented two cases of bent femoral nail removal. The treatment option was a metal cutting blade for nail sectioning, partially or completely. In one patient, lateral approach was combined with a small anteromedial incision for a better blade movement across the thigh. One nail was removed in one piece and the other in two pieces separately. Despite the severity of injuries and co-morbidities, the ultimate result for both patients was satisfying and they maintained complete union after applying interlocking nail in revision surgery [4].

Shen et al. introduced a novel technique with one dynamic compression plate and two bone-holding forceps to straighten a bent nail. This method is simple and efficient [5].

In the method of Otsuka et al., under minimal soft tissue dissection, the nail was straightened by sectioning through half of its diameter with a drill for metal, then removed and replaced with another nail. Femur union occurred without any complications [11].

Heffernan et al. described a novel technique combining the utilization of a Midas Rex MR7 high-speed burr (Medtronic, Minneapolis, Minnesota) and the F-Tool (Synthes, West Chester, Pennsylvania) to facilitate nail removal. In the lateral decubitus position, after limited exposure at the fracture site, the intramedullary nail was diminished at the apex of the deformity with a Midas Rex MR7 high-speed burr. Next the F-Tool was used to straighten the nail extraction through the original proximal insertion site. The F-Tool concentrate forces at the apex of the deformity and reduces soft tissue damage. The additional benefit is one-piece nail exertion [10].

Shishir et al. reported a 33-year-old male patient with 5 weeks postoperative bent intramedullary femoral nail due to a minor fall. With a varus deformity, the IM nail was bent to 30° and the former fracture was still healing. After general anesthesia the nail was unbent, and exchange nailing was carried out. He suggested closed manipulation before surgery for preventing soft tissue and bone damage and major surgeries complications [2].

Banerjee and Posner, in a case report study of post-traumatic sagittal plane deformity, described a simple surgical approach to straighten the sagittal plane bend in situ, then performed nailing while maintaining the symmetric femoral length and rotation. In this technique, disturbance of the

fracture is minimal, and also with a small incision, soft tissue and blood supply of the femur are more preserved. The nail was extracted in a sole piece by straightening the nail in situ, however there is a described technique with transection of the nail which is an option but it poses challenges in extracting the distal part. Also, symmetric length and rotation are achievable. Ipsilateral hip arthrofibrosis and ipsilateral knee ligament injury are the contraindications of this method. Before the operation, the surgeon should become ensured of the knee stability with a physical exam, or else it is possible that this injury may get worse, as the nail is straightened against the fulcrum by engaging force to the distal femur. Ipsilateral hip arthrofibrosis restricts femur excursion and therefore it may be impossible to straighten the femur against the fulcrum [9].

CONCLUSION

We exposed the fracture site at the apex of deformity and transected the nail with an 8mm cobalt drill bit and removed each part of the nail and exchange the nail with another nail 2mm larger than the original one, and the iliac crest autograft was done. The fracture had union in 6 months without any complications. This technique is effective, cost effective and can be considered in such cases. Our technique is simple and cost-effective.

CONFLICT of INTEREST

The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organizations or entity with any financial interests or non-financial interests in the subject matter or materials discussed in this manuscript.

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Persian literature course in the undergraduate medical curriculum

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A serious criticism of contemporary medicine is that it is dehumanized, meaning that it ignores the patient and his/her experiences, values, and priorities as an individual human and only seeks treatment based on the latest findings in the biomedical sciences. To modify and improve this situation, the field of “medical humanities” was formed, which seeks to include human considerations in clinical practice. One of the important domains of the field of “medical humanities” is “Literature and Medicine” [1, 2].

Literature and medicine are now taught in medical schools at all undergraduate (both in basic sciences and clinical periods) and residency levels. Broadly speaking, the reasons for this implementation are threefold. The first concerns the patient: such courses teach physicians how to listen more wisely to their patients' narratives and how to emphasize with the patient's and family members' points of view on the experience of illness and treatment. The second reason concerns the physician: Reading literature enhances personal awareness and fosters the habit of self-scrutiny. The third concerns ethics: literature and literary skills empower physicians to think both empathetically and critically about moral issues and dilemmas in daily clinical practice [3].

By reviewing the texts in the field of literature and medicine, we come across various educational programs in medical schools around the world. One of the courses in the Doctor of Medicine (MD) curriculum of Iran is Persian literature (code: 16) which three theoretical units (51 hours). This course, for which a lesson plan has not been designed in the curriculum, is usually offered to students in one of the first year. Since the Persian literature course is in the general courses section, like other courses in this section such as philosophy of ethics, Islamic ethics, and familiarity with the Constitution of the Islamic Republic of Iran, it is taught similarly with a single source in both medical sciences and engineering majors [4]. The book of selected Persian literary texts (third edition) has been compiled by five professors of Persian literature and published in 264 pages, and officially introduced as the textbook of this course. In this book, prose and poetry pieces by classical and sometimes contemporary writers and poets have been collected. Selected texts do not specifically address health and disease issues. In general, it seems this general course of Persian literature cannot fulfill what the medical humanities expect from literature [5].

A survey conducted by the authors using an online questionnaire in 2020 showed that most students who had taken this course believe that passing this course would not affect their future career as a doctor. However, most of them agreed that if the content changed, this course could help build necessary skills related to medicine.

Therefore, it seems that three changes, namely changing the name of the Persian literature course to literature and medicine, changing the position of the course from general courses to specific courses, and changing the lesson plan, can help make better use of this opportunity to train physicians with higher quality.

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Right to Left Shunt in Agitated Saline Test

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Video 1

Video 2

An 11-year-old girl was presented to the cardiology clinic with a history of atypical chest pain and nonspecific shortness of breath. The patient underwent echocardiography that revealed interatrial septum redundancy with signs of shunt flow in the color-doppler study (Video 1). The differential diagnosis included atrial septal aneurysm (ASA) associated with patent foramen oval (PFO) and atrial septal defect (ASD). Agitated saline test was performed via left cubital vein (Video 3) and significant leakage of contrast through interatrial septum was confirmed (Video 2). For further evaluation, the patient underwent the transesophageal echocardiography (TEE) to rule out the ASD. No left to right shunt was seen in TEE and the color-doppler study showed right to left shunt, hence the diagnosis of ASD was ruled out (video 4). The final diagnosis was PFO. PFO is a congenital cardiac abnormality as a fetal blood communication tunnel between two atria (right to left) is remained open after one year of age. It has a high prevalence of about 25% in the general population. No intervention and follow up is needed; except for those who have large-sized PFO with significant right to left shunt and a history of neurological event especially in younger ages without other risk

factors for atherosclerosis [1].

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Cardiology, Echocardiography, Interatrial Septum, Patent Foramen Ovale, Atrial Septal Defect, Transesophageal Echocardiography, Agitated Saline Echo Test, Bubble Study

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