Volume 3 Issue 1, January 2021
ISSN: 2687-4245

Turkish Journal of Internal Medicine

Turkish Journal of Internal Medicine

http://www.tjim.org

e-ISSN: 2687-4245

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Publisher

Turkish journal of Internal Medicine

Nizameddin KOCA

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Turkish Journal of Internal Medicine

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Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Editorial

Oral Glucose-Lowering Agent Treatments in Type 2 Diabetes Mellitus

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Turk J Int Med 2021;3(1):1-5
DOI: 10.46310/tjim.815794

Keywords: *oral treatment, anti-diabetics, type 2 diabetes mellitus,*

Type 2 diabetes is manifested by impaired insulin secretion in pancreatic beta cells, increased glucagon secretion in alpha cells, and generally has a history of insulin resistance.[1,2] The treatment of glucose metabolism disorder and the resulting hyperglycemia constitute an important part of the treatment of type 2 diabetes.[3-5] Glycemic targets can be targeted with A1C <7% to reduce the risk of micro and macrovascular complications in eligible patients, and A1C <6.5% to reduce the risk of diabetic chronic renal failure and retinopathy in those with low risk of hypoglycemia.[5-8] We can consider the treatment of hyperglycemia in two components; lifestyle changes and glucose lowering agent therapy.[5]

Lifestyle Changes

All type 2 diabetics should be given adequate training on lifestyle changes (nutrition therapy, physical activity and weight maintenance, no smoking, improvement of lifestyle) and self-monitoring of their diabetes, and these trainings should be reinforced as the patient comes to control.[5-11]

Glucose-Lowering Agent Treatments

We can consider the glucose-lowering agent therapies necessary for the regulation of glycemia in type 2 diabetes as glucose-lowering oral agent and injection therapies and insulin therapy. Glucose-lowering oral agents are indicated for patients with noninsulin-dependent stage of type 2 diabetes.[5]

In this article, I will review the glucose lowering oral agent therapy used in the treatment of type 2 diabetes *(Table 1)*.

Glucose-Lowering Oral Agent Treatments

The glucose lowering oral agent treatment to be applied should be personalized according to the medical conditions (age, duration of diabetes, risk of hypoglycemia, co-morbidities and life expectancy) and other risk factors of the patients.[4-7]

Monotherapy

- **Biguanide (Metformin)**

Metformin enhances insulin sensitivity in liver and peripheral tissues by activation of AMP-activated protein kinase.[12,13] With the diagnosis of type 2 diabetes, lifestyle changes and

Received: October 24, 2020; Accepted: November 4, 2020; Published Online: January 29, 2021

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Table 1. The characteristics of the glucose lowering oral agents

	Metformin	SGLT-2 Inhibitors	DDP-4 Inhibitors	Oral GLP-1 Receptor Agonist (*Semaglutide*)	Thiazolidinedione (*Pioglitazone*)	Sulphonylurea / Glinide
Efficacy on glycemia	High	Intermediate	Intermediate	High	High	High
Risk of hypoglycemia	No	No	No	No	No	Yes
Atherosclerotic Cardiovascular Disease	Potential benefits	Benefit *(Empagliflozine, Canagliflozine)*	Neutral	Benefit	Potential benefits *(Pioglitazone)*	Neutral
Heart Failure	Neutral	Benefit *(Empagliflozine, Canagliflozine, Dapagliflozine)*	Potential risk *(Saxagliptin)*	Neutral	Increased risk	Neutral
Effects on Progression of Diabetic Kidney Disease	Neutral	Benefit *(Empagliflozine, Canagliflozine, Dapagliflozine)*	Neutral	Benefit	Neutral	Neutral
Weight change	Neutral/Potential for modest loss	Loss	Neutral	Loss	Gain	Gain
Dosing for Renal function/Contraindications	• Contraindicated with eGFR<30 ml/min/1.73 m2	• Dose adjustment required *(Empagliflozine Canagliflozine Dapagliflozine)*	• Renal dose adjustment required *(sitagliptin, saxagliptin, allogliptine):* can be used in renal impairment • No dose adjustment required for *(linagliptine)*	• Caution: *When initiating or increasing dose due to potential risk of acute kidney injury*	• No dose adjustment required • Generally, not recommended in renal impairment due to for fluid retention	• Risk of hypoglycemia *Glipizide and Glimepiride initiate conservatively to avoid hypoglycemia*
Additional consideration	• Gastrointestinal side effects *(diarrhea, nausea)* • B12 deficiency	• FDA blacklist Risk of amputation *(canagliflozine)*	• Potential risk acute pancreatitis • Joint pain	• Gastrointestinal side effects *(nausea, vomiting, abdominal pain)* • Amylase, lipase increase • Acute pancreatitis risk • Thyroid C-cell cancer risk	• Fluid retention • Congestive heart failure • Risk for bone fracture • Bladder cancer • Benefit for NASH	• FDA specially warning on risk of cardiovascular mortality based on studies of an older sulphonylurea *(tolbutamide)*

initiation of metformin treatment in the absence of any contraindications [allergy to metformin, renal failure (eGFR <30%)] is the first step.[4,9,14]

Metformin is a safe drug that is considered to reduce the cardiovascular events and related deaths that can be caused by diabetes.[4,5] Besides the vitamin B12 deficiency, metformin has rare side effects such as nausea, vomiting and diarrhea.[15,16] If the glycemic goal is not achieved within 3-6 months with metformin treatment and life changes, metformin treatment and life changes should be questioned, if there is no deficiency in their application, the addition of a second drug should be considered.[5,17]

Combination Treatments

When a second oral agent is added to the treatment, a patient-centered assessment should be made. In this evaluation; clinical characteristics such as the presence of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), diabetic kidney disease (DKD), diabetic retinopathy, diabetic neuropathy and other co-morbidities, as well as the effect of the second drug on glycemia, the risk of hypoglycemia, the effect of weight change and diabetes complications, and the side effects of the drug should be considered.[5,18,20]

- **Sodium Glucose Co-Transporter-2 (SGLT-2) Inhibitors**

Glucose excretion from the kidneys is decreased in patients with type 2 diabetes. SGLT-2's is effective in the reabsorption of glucose in the proximal renal tubule in the kidneys. SGLT2 inhibitors inhibit glucose reabsorption in the kidney and promote urinary glucose excretion, thus improve glycemic control independently of insulin-mediated mechanisms.[9,20]

SGLT-2 inhibitors are quite safe, well tolerated and do not cause hypoglycemia.[20] SGLT-2 inhibitors significantly reduce cardiovascular death or hospitalization and heart failure in patients with cardiovascular problems or pre-existing heart failure problems.[21-23] This effect is not statistically significant in patients without cardiovascular problems.[21-23]

SGLT-2 inhibitors in use today significantly reduce the deterioration of kidney function due to diabetes, end-stage renal failure and kidney-related deaths.[24-26] This effect appears to be present in both groups with and without atherosclerotic cardiovascular disease.[24-26]

Side effects of SGLT-2 inhibitors such as vaginal fungal infections, urinary infections, volume depletion, low blood pressure, increased risk of

diabetic ketoacidosis, increased LDL-cholesterol can be seen.[24-26]

Canagliflozin studies have reported an increase in bone fractures and leg amputations, although not in other SGLT-2 inhibitors.[25]

- **Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**

DPP-4 inhibitors maintain the effects of incretin hormones (GLP-1, GIP) for a long time by inhibiting the DPP-4 enzyme that enzymatically degrades incretin hormones.[27] Incretin hormones increase insulin secretion in pancreatic beta cells according to serum glucose concentration, inhibit glucagon secretion in alpha cells and delay gastric emptying.[27] In this group of drugs with neutral cardiovascular effects and some weight reduction, the risk of heart failure was found to only be high in saxagliptin studies.[27-30] Pancreatitis and joint pain may rarely be seen in patients using DPP-4 inhibitors.[27]

- **Oral Glucagon Like Peptid-1 (GLP-1) Receptor Agonist (Semaglutide)**

Semaglutide is an oral GLP-1 receptor agonist. Semaglutide stimulates GLP-1 receptors and promote insulin secretion in a glucose dependent manner while at the same time inhibiting glucagon secretion and delay gastric emptying.[31] Studies with Semaglutide reported that it reduced cardiovascular death and all-cause death compared to placebo.[32,33] In a study comparing the efficacy and tolerability oral semaglutide with empagliflozin and sitagliptin, it was reported that the capacity of oral semaglutide to lower A1C was superior to empagliflozin and sitagliptin, and this superiority in weight reduction was not observed with empagliflozin.[34] Semaglutide may show side effects such as gastrointestinal (nausea, vomiting, diarrhea, abdominal pain), increased amylase and lipase, risk of acute pancreatitis, risk of thyroid c cell cancer (not seen in human studies), risk of acute renal failure.[32] Semaglutide is to be initiated at a low dose, with its dose titrated upwards as appropriate.[32,33]

- **Thiazolidinedione (TZD)'s (Pioglitazone)**

TZDs activate one of the nuclear receptors, peroxisome proliferator-activated receptors gamma (PPAR-gamma), increase specific genes and also increase the synthesis of certain proteins involved in fat and glucose metabolism, which reduces levels of certain types of lipids, and circulating free fatty acids.[35,36] TZDs are shown to improve glycemic control by promoting peripheral insulin sensitivity and inhibiting hepatic glucose release. TZDs generally decrease triglycerides and increase high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).[37,38]

TZDs are also often associated with weight gain due to their ability to promote fluid retention and they also carry risks such as the development of edema, congestive heart failure, anemia, bladder cancer, and bone fracture.[39-43] Patients should also be monitored in these aspects.

- **Sulphonylurea (SU)s / Glinides**

SUs and glinides binding a channel protein in the ATP-sensitive potassium channels on the membrane of pancreatic beta cells, they promote the secretion of insulin from pancreatic beta-cell.[44] SUs are not recommended for people who are overweight or obese, as their mode of action (increase in insulin secretion) means that weight gain can be a relatively common side effect.[45-47] Their effect on insulin levels also means users are at increased risk of hypoglycemia, although this risk is reduced with newer sulphonylureas.[47]

- ***α*-Glucosidase inhibitors (AGIs)**

AGIs inhibit intestinal glycolysis and delay intestinal glucose absorption and suppress postprandial hyperglycemia and hyperinsulinemia.[48,49] AGIs are also often associated with flatulans and diarrhea.[48,49]

Conflict of interest

The author declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Original Article

Assessment of The Performances of Hepatitis C Virus Viral Markers, Age-Platelet Index and Aspartate aminotransferase to Alanine Aminotransferase Ratio Scores in Predicting Liver Histopathology

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Abstract

Background This study aimed to reveal the utility of age-platelet (AP) index and aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AAR), which are non-invasive markers, in patients with chronic Hepatitis C virus (HCV) infection in prediction of fibrosis and evaluate whether viral markers could be used for that purpose or not.

Material and Methods A total of treatment-naïve 49 patients with chronic HCV who underwent liver biopsy were included in this retrospective study. Anti-HCV S/CO and HCV-RNA viral load (copy/mL) values measured simultaneously with biopsy were determined. AP index and AAR score were calculated and compared.

Results Staging of liver biopsy samples of 49 HCV patients was assessed. Comparable diagnostic accuracies of AP index and AAR in prediction of significant fibrosis (F≥2) were showed with ROC curve analysis. The areas under the ROC (AUROCs) were 0.713 and 0.506, respectively. Diagnostic accuracy of API in prediction of significant fibrosis was superior to that of AAR (p=0.03). AUROC of HCV-RNA viral load in prediction of F≥2 was 0.531. Anti-HCV S/CO value (AUROC=0.464) was not found as a suitable marker in prediction of fibrosis.

Conclusions AP index, AAR score and HCV viral load among non-invasive markers assessed in this study were useful in predicting significant fibrosis. Especially API was the most useful test in predicting significant fibrosis. AP index can be preferred in patients with near normal ALT values.

Turk J Int Med 2021;3(1): 6-12
DOI: 10.46310/tjim.825814

Keywords: *liver fibrosis, non-invasive test, AST to ALT ratio (AAR), age-platelet (AP) index, HCV viral load, anti-HCV*

Received: November 16, 2020; Accepted: December 24, 2020; Published Online: January 29, 2021

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Introduction

The stage of liver fibrosis is important for clinical management of chronic hepatitis C. Patients without fibrosis or with mild fibrosis have the chance to receive more positive results compared to the patients with severe fibrosis.[1–3] Development of cirrhosis is closely related with the stage of fibrosis. Therefore, liver biopsy is recommended before antiviral treatment.[4] The available gold standard for assessment of liver disease is degree and stage determined with liver biopsy. However, liver biopsy has limitations, risks and costs.[5] Therefore, invasive methods are needed to determine the severity of liver disease, especially the degree of fibrosis. An ideal noninvasive method to assess liver biopsy should be both reliable and based on readily available blood tests.[6]

This study aimed to reveal the utility of age-platelet (AP) index and aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AAR), which are non-invasive markers, in patients with chronic Hepatitis C virus (HCV) infection in prediction of fibrosis and evaluate whether viral markers could be used for that purpose or not.

Material and Methods

Study Group

The population of this retrospective, single-center and cross-sectional study consisted of 49 patients diagnosed with chronic HCV. Patients above the age of 18 who underwent liver biopsy and who were diagnosed with chronic HCV were included in the study. Patients under the age of 18, patients diagnosed with hepatocellular carcinoma, patients diagnosed with hepatitis B, hepatitis D and other hepatotropic viruses or human immunodeficiency virus infections, patients with active alcoholism history and patients diagnosed with other defined liver diseases were excluded from the study. A total of 49 patients who met the inclusion and exclusion criteria were included in the study. This study was approved by the Ethics Committee of Gulhane Training and Research Hospital at the University of Health Sciences (Reference number: 2020/03/62).

Serological and Molecular Analysis

Patients whose serum samples were sent to Microbiology Virology Laboratory between 1st of October 2016 and 31st of December 2019 for HCV-RNA test and whose results were anti-HCV reactive were evaluated in this study. Anti-HCV test was performed with chemiluminescent microparticular immunoassay (CMIA) technique in serum samples by using anti-HCV Reactive Kit (Abbott, Germany) on Architect i2000SR system (Abbott, USA). Anti-HCV test results were assessed on Sample/Cut-off (S/CO) ratio and S/CO value <1.0 was accepted as nonreactive and S/CO value ≥1 as reactive. All the samples found as an intermediate value between 0.80-0.99 were reanalyzed according to instructions of the manufacturer.

Isolation device (Magnesia 2448 Anatolia Geneworks, Turkey) and HCV-RNA isolation kit (Viral RNA Isolation kit, Anatolia Geneworks, Turkey) were used in detection of HCV-RNA. The PCR mixture prepared with Real-time PCR kit (Bosphore HCV Quantification Kit v2, Turkey) was amplified on Real-Time PCR device (Montania 4896 Anatolia Geneworks, Turkey). Patient results were retrospectively obtained from the laboratory operating system.

Non-invasive tests and formulation

Age, platelet count, and AST and ALT levels were used in calculations of AST to ALT ratio (AAR) and AP index scores of patients included in the study. Tests were conducted in the Biochemistry Laboratory of Gulhane Training and Research Hospital.

AAR: AST to ALT ratio.[7] AP Index: Age Score + Platelet Score.

Age (years) <30 = 0; 30–39 = 1; 40–49 = 2; 50–59 = 3; 60–69 = 4; ≥70 = 5.

Platelet count (10^9/L): ≥225 = 0; 200–224 = 1; 175–199 = 2; 150–174 = 3; 125–149 = 4; <125 = 5.[8]

Diagnostic accuracies of these markers in prediction of significant fibrosis were assessed with Receiver Operating Characteristic (ROC) curve analysis.

Histopathological diagnosis

Patients liver needle biopsy histopathology reports obtained from the Department of Pathology archive were reassessed. All the liver biopsy samples were stained with hematoxylin-eosin and Masson's trichrome for histological assessment. Liver biopsy samples were assessed by pathologists and scored according to Ishak

scoring system. Ishak modified-hepatitis activity index (mHAI) grading and staging system was used in detecting chronic hepatitis activity level and fibrosis level in microscopic examination performed with histochemical preparations. In this scoring system, activity level ranged from 0 to 18 and fibrosis stage from 0 to 6. Significant fibrosis was defined as stage 2 fibrosis.

Statistical Analysis

Statistical analysis was performed with SPSS 25 software program (SPSS, Inc., Chicago, IL). Continuous variables were expressed as median (interquartile range). Mann-Whitney U test was used in comparison of continuous variables between two groups. Pearson's Chi-square or Fisher's Exact tests were used in comparison of categorical variables. Spearman's correlation analysis was used to evaluate the relationship between variables. Performances of anti-HCV, HCV viral load, and API index and AAR scores, which are among viral markers, in prediction of significant F≥2 and HAI≥5 were assessed with ROC curve analysis. Statistical significance level was accepted as $p<0.05$.

Results

Data of 49 patients whose ages ranged from 20 to 82, who met the inclusion and exclusion criteria, and who were diagnosed with chronic HCV infection were analyzed. Of the patients included in the study, 34 (69%) were male. Median ages of male and female patients were 21 (interquartile range [IQR]: 20-39) and 62 (IQR: 40-72) respectively ($p<0.001$). Median age of the patients with fibrosis score of 2 and above was 61.5 and significantly high ($p=0.005$).

According to the results of liver biopsy, 21(43%) out of 49 patients had significant fibrosis (F≥2). Fibrosis score in 32% (11/34) of male patients and 67% (10/15) of female patients was 2 and above ($p=0.02$).

AAR score and AP index of all the patients were calculated. Patients with chronic HCV infection (n=49) were divided into two groups according to their liver biopsy histopathology stages of F<2 and F≥2. They were compared in terms of age, gender, serum platelet, AST, ALT, total bilirubin, albumin, anti-HCV (S/CO), HCV viral load, HAI score, AP index and AAR score *(Table 1)*. Ages of female patients with significant fibrosis were

Table 1. Basic characteristics of patients (n=49) who underwent liver biopsy due to chronic HCV

Characteristic	Fibrosis stage <2	Fibrosis stage ≥ 2	P- value
Gender n (%)			
- Female	5 (33)	10(67)	0.02
- Male	23 (68)	11(32)	
Age: years	21 (20-39)	61.5 (21-72)	0.005
- Female	39 (35-46)	68(61-76)	0.004
- Male	20(20-24)	23(20-62)	0.33
Anti-HCV (S/CO)	14.2(13.7-14.2)	14.4(13.5-15.3)	0.82
HCV viral load (copy/mL)	$91x10^4$ ($69x10^2$-$16x10^6$)	$26x10^5$ ($203x10^3$-$63x10^5$)	0.84
HAI	5 (4-6)	7 (6-9)	<0.001
AST (U/L)	35.5 (23.8-57.8)	36.0 (23.8-50.8)	0.68
ALT (U/L)	41 (32-98)	41(24-63)	0.38
Total bilirubin (mg/dL)	0.6(0.5-0.8)	0.7(0.6-0.9)	0.27
Albumin (g/dL)	4.5 (4.0-5.0)	4.0 (4.0-4.8)	0.49
Platelet count (10^9/L)	244 (203-279)	263 (193-296)	0.80
AAR	0.66 (0.56-1.10)	0.86 (0.55-1.02)	0.88
API	1 (0-2)	4 (0-6)	0.006

HAI, histological activity index; AST, aspartate aminotransferase; ALT, alanine transaminase; AAR, aspartate aminotransferase to alanine transaminase ratio; API, age-platelet index; viral, biochemical and pathological parameters were presented as median values.

more advanced (p=0.004). HAI score was higher in patients with significant fibrosis (p<0.001). AAR score and AP index were higher in patients with significant fibrosis and this difference was statistically significant for API (p=0.006) *(Table 2)*.

The relationship between AAR, AP index, anti-HCV S/CO, and HCV-RNA viral load values and fibrosis and HAI scores was assessed with Spearman's correlation analysis. A moderately significant correlation was found between AP index and fibrosis and HAI scores (Spearman's rho=0.471, p=0.001 and Spearman's rho=0.470, p=0.001 respectively) *(Table 2)*.

The areas under the ROC curve were specified in order to determine the accuracy of serum anti-HCV S/CO, HCV-RNA viral load, AAR score and AP index of patients in detecting significant fibrosis (F≥2) and HAI≥5. The presence of significant fibrosis as a result of liver biopsy was accepted as a reference and sensitivity and specificity rates of HCV-RNA viral load, AAR score, and AP index were calculated.

While the areas under the ROC curve in prediction of F≥2 for anti-HCV S/CO and HCV-RNA viral load were 0.464 and 0.531 respectively AUROCs in prediction of HAI≥5 were 0.335 and 0.382 respectively. Sensitivity and specificity rates were 60% and 59.1% at HCV-RNA viral load cut-off value of 1.65X106 in prediction of F≥2 (p=0.57) *(Figure 1)*.

While the areas under the ROC curve in prediction of F≥2 for API and ARR were 0.713 and 0.506 respectively AUROCs in diagnosis of HAI≥5 were 0.579 and 0.512 respectively. Optimal cut-off values providing total maximum sensitivity and specificity rates and predicting F≥2 and HAI≥5 were given in Table 3 and ROC curves were given in Figure 2.

Discussion

For centuries, scientists have attempted to define thIn this study, we investigated the diagnostic performances of biochemical biomarkers such as AAR and API and viral markers such as anti-HCV and viral load in order to predict the presence and absence of significant fibrosis in patients with chronic HCV. The limitation of all indices developed up to now is that they cannot differentiate the fibrosis stages alone.[9] As a result of our study, AP index was more successful in predicting significant fibrosis (F≥2) compared to the AAR score. AP index had higher sensitivity and specificity. Sensitivity and specificity rates for optimal cut-off value of 2.5 for API in diagnosing significant fibrosis were 68.4% and 78.9% respectively. While the area under the ROC curve was 0.713 for API it was 0.506 for AAR. API can also predict the degree of significant histological activity level, but we found a more important correlation with significant fibrosis stage (p=0.03 and p=0.77 respectively). AP index was the sum of age and platelet count scores.[10] It has been asserted in various studies that AP index is a good one in predicting the stage of liver fibrosis. In a study on patients with HCV by Lackner et al., the area under the ROC curve was 0.740 in prediction of significant fibrosis and predicted fibrosis.[11]

Male gender, duration of the disease and acquiring the disease above the age of 40 are factors that can affect the rate of fibrotic progression in the liver.[10,12] Sensitivity to environmental factors (especially oxidative stress) increases with aging and a decrease occurs in blood flow, mitochondrial capacity or immune capacity. Annual rate of fibrosis regression in men especially between the ages of 61 and 70 was 300 times higher

Table 2. Assessment of the correlation between fibrosis and HAI scores and AAR, API and viral markers with Spearman's rho correlation analysis

	Fibrosis score Correlation		HAI Correlation	
	Coefficient	P value	Coefficient	P value
AAR	0.174	0.303	0.160	0.343
API	0.471	0.001	0.470	0.001
Anti-HCV S/CO	0.005	0.975	-1.00	0.545
HCV-RNA viral load	0.077	0.626	0.066	0.674

HAI, histological activity index; AAR, aspartate aminotransferase to alanine transaminase ratio; API, age-platelet index

Table 3. Performances of API and AAR in diagnosis of significant fibrosis and HAI

Category	Cut-off value	Sn,%	Sp,%	AUROC	95%Cl	P value
F stage ≥2						
API	2.5	68.4	78.9	0.713	0.538-0.888	0.03
AAR	0.78	57.9	63.2	0.506	0.317-0.694	0.95
HAI ≥5						
API	1.5	56.7	71.4	0.579	0.384-0.773	0.77
AAR	0.79	50	57.1	0.512	0.281-0.743	0.74

F, fibrosis; HAI, histological activity index; Sn, sensitivity; Sp, specificity; AUROC, area under the ROC curve; AAR, aspartate aminotransferase to alanine transaminase ratio; API, age-platelet index

than in men between the ages of 21 and 40.[13] Thrombopoietin (TPO) is mainly produced in liver hepatocytes and promotes the production of platelets from megakaryocytes. Serum TPO levels in patients with chronic hepatitis and liver cirrhosis are negatively correlated with progression of fibrosis in the liver.[14] Decline in hepatic TPO production, increased splenic sequestration of platelets secondary to portal hypertension, and myelosuppressive effect of HCV are among the causes of thrombocytopenia.[15,16]

No significant correlation was found between AAR and liver fibrosis stage and inflammatory activity scores in our study. Moreover, AAR had a weak diagnostic (AUROC=0.506) accuracy for significant fibrosis. Guéchot et al. revealed that ROC curve analysis and AST to ALT ratio did not differentiate significant fibrosis (F≥2) (AUROC=0.531) in 590 treatment-naïve patients with chronic HCV and that they had only a very weak diagnostic accuracy for fibrosis (F≥3) (AUROC=0.584) or cirrhosis (F4) (AUROC=0.626), which is similar to the results of our study. They also found that AST to ALT ratio significantly increased with histological stage of liver fibrosis and that there was a significant correlation (r=0.129, p<0.0035) between METAVIR fibrosis stage and AST to ALT ratio.[17] No significant correlation was found between AAR and fibrosis stage in this study. It was reported that although liver fibrosis developed very slowly in most of HCVs which continuously had normal or near normal ALT levels within years a progress in liver fibrosis occurred in about 40% of asymptomatic patients with HCV infection and cirrhosis developed in a few patients with near normal ALT level.[18] Elevation of AST to ALT ratio in cirrhotic patients can be explained by the increase in serum AST levels due to reduction in AST clearance. Moreover, AST release from mitochondria and cytoplasm can increase as a result of mitochondrial damage in advanced liver disease.[19]

In this study, no significant difference was found between HCV viral load and anti-HCV S/CO levels and groups of F<2 and F≥2. In addition, no correlation was found between increasing fibrosis stage and histological activity

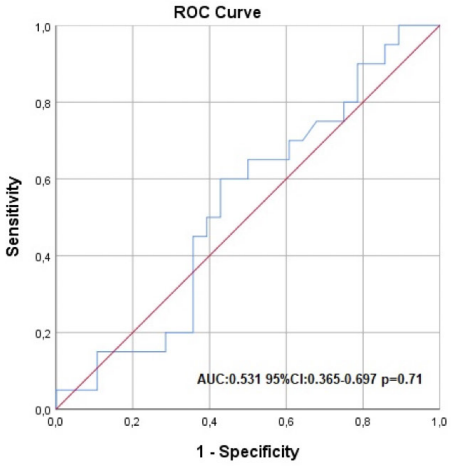

Figure 1. Receiver-operating characteristic (ROC) curve of HCV-RNA viral load for predicting the results of F ≥ 2 in 49 patients diagnosed with chronic hepatitis C.

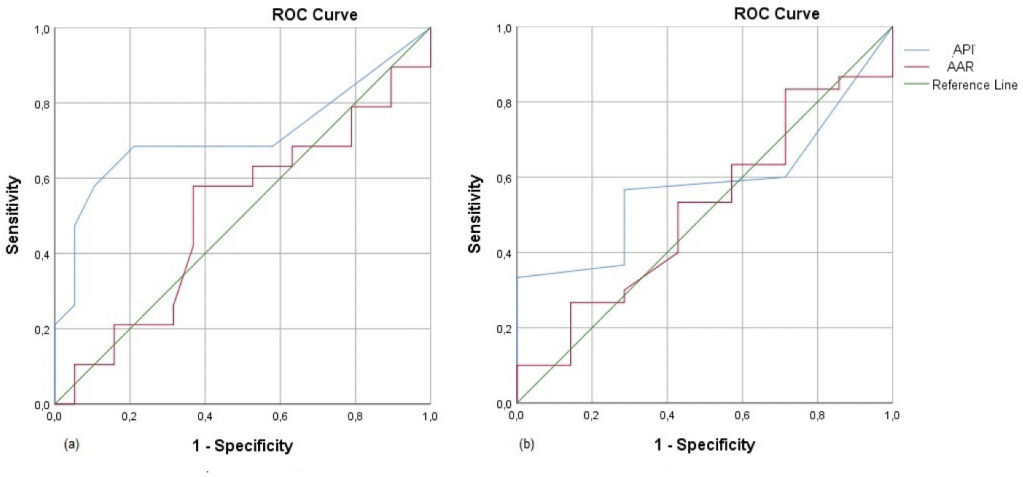

Figure 2. Receiver-operating characteristic (ROC) curve of API and AAR for predicting the results of (a) F≥2 and (b) HAI≥5 in 49 patients diagnosed with chronic hepatitis C.

scores. Similarly, there are studies revealing no correlation between histological result and HCV-RNA levels.[20–22] However, it was asserted in some study reports that viral titer may affect the severity of liver damage and that high viremia titer was associated with severe liver damage.[20–23] These different results can be associated with the truth that serum HCV-RNA viral load shows a fluctuation and is an unstable parameter.[24] Moreover, HCV is known to increase in both liver and areas outside of liver. Therefore, high HCV in circulation does not always mean an active viral replication in the liver or indicate a more severe liver disease.[25,26] The most important limitation of this study is that the number of patients included in the study is limited.

In conclusion, AP index, AAR score and HCV viral load, which are non-invasive markers, assessed in this study were useful in predicting significant fibrosis in chronic HCV. Especially API was the most useful test in predicting significant fibrosis. AP index can be preferred in patients with near normal ALT values.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Original Article

Investigation of the Relationship Between Individuals' Knowledge Levels Regarding Coronavirus Disease and E-Health Literacy Levels

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Abstract

Background This research investigated the relationship between individuals' knowledge levels regarding coronavirus disease and e-health literacy levels.

Material and Methods This study was designed as a descriptive type, was carried out between June and July 2020 by individuals living in the eastern provinces of Turkey.

Results According to the findings obtained from the study, it was found that the total mean score of individuals for Knowledge Test for Coronavirus Disease was 13.59±2.30. E-Health Literacy Level total score mean was found to be 26.12±9.35. It was found that there was a positive statistically significant relationship between the level of knowledge regarding coronavirus disease and the total score means of e-health literacy ($p<0.05$).

Conclusions It was determined that the mean level of the knowledge level of the individuals for coronavirus disease was high, and the e-health literacy level was mean. It is recommended that the study be carried out in larger groups.

Turk J Int Med 2021;3(1): 13-20
DOI: 10.46310/tjim.800533

Keywords: *e-health literacy, coronavirus disease, individuals*

Received: September 26, 2020; Accepted: December 21, 2020; Published Online: January 29, 2021

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Introduction

COVID-19, which was detected in Wuhan city of Hubei province of China at the end of 2019 and spread to the whole world in a short time, has become a very important and urgent public health problem. The existing treatment of patients for the disease and efforts to prevent the spread of the virus while new information is obtained, on the other hand, scientific studies are conducted, approaches are frequently updated. There is no vaccine yet developed against the virus. The most important way to prevent disease is not to be exposed to the virus.[1] According to the available evidence, the SARS-CoV-2 virus is transmitted through human droplets and contact. Effective methods of contamination are the washing of hands frequently with soap and water for at least 20 seconds.[2] Hand washing is very effective in killing viruses likely to be present.[3] Washing hands is very important, especially when found in public places or when contacting other people. In cases where water and soap cannot be reached, it is recommended to use hand disinfectants containing at least 60% alcohol.[1,4] In addition to hand hygiene, it should be paid attention that the hands do not come into contact with the face, eyes and mouth during the day.[3] One of the most important protection methods is to maintain social distance.[5] The virus can spread to a distance of 1-2 meters by droplet. It is important to make this distance a habit in daily life and to avoid close contacts in the society.[1] Avoid crowded areas as much as possible and should not travel unless necessary.[6] Another effective measure is the regular cleaning and disinfection of frequently contacted surfaces. Environmental cleanliness should be given importance, transportation means should be frequently ventilated and common surfaces should be disinfected.[7] It is effective and evidence-based measures to suspend mass meetings and activities, which are recommended for social isolation and implemented in our country, by taking into account the possibility of infecting children in adults even though the effects of the disease in children are poor.[8] 41.5% of individuals think that the internet is a good source of information about health.[9] In the present day, the internet is used frequently, and it is stated that their perceptions and attitudes about e-health literacy are little known, and that they need to browse the internet securely, especially for important health issues.[10,11] The effectiveness of measures for coronavirus disease depends on the level of knowledge of the community. This research investigated the relationship between individuals' knowledge levels regarding coronavirus disease and e-health literacy levels.

Material and Methods

Descriptive research type planned this study was conducted between June and July 2020 by individuals living in the eastern provinces of Turkey.

The universe of the research; It has created an individual living in the eastern provinces of Turkey. The inclusion of a sample of the research work of individuals living in the eastern provinces of Turkey has created accepting individuals.

Collection of Data

In the collection of research data, Introductory Information Form, Knowledge Test for Coronavirus Disease and E-Health Literacy Scale. After explaining the purpose of the research, after obtaining verbal consent from those who voluntarily agreed to participate in the research, the data were collected online with the Google form prepared by the researchers.

Data Collection Tools

Introductory Information Form: It consists of questions that are created by researchers and contain the introductory features of individuals.

Knowledge Test for Coronavirus Disease: This test is created with questions that will measure the level of knowledge and cover the whole subject. A minimum of 0 and a maximum of 20 points can be obtained from the scale consisting of 20 questions. True, false and I don't know options are found in the scale and 1 point is taken from the true option and 0 points are taken from the wrong and I don't know option. Questions 2, 4, 6, 14, 15 and 17 are inverted. The increase in the score indicates that the level of knowledge has increased. In our study, Cronbach Alpha value was found to be 0.72.

E-Health Literacy Scale: "E-Health Literacy Scale" developed by Cameron D. Norman and Harvey A. Skinner in 2006 and accepted by performing validity and reliability tests was adapted to Turkish by Gencer.[12] Since the method used in the e-Health literacy scale is a

5-point Likert type measurement, reliability was calculated with the Cronbach Alpha method. The calculated value of 0.91 alpha has a high degree of reliability since it is between 0.80 and 1.00.[12] In our study, Cronbach Alpha value was found to be 0.96.

Statistical Analysis

The analysis of the data was done on the computer using the SPSS statistical software. Frequency, descriptives, percentage, mean, standard deviation, median, explore and normality plots with tests were used as descriptive statistical methods. Kolmogorov – Smirnov test was used to test normality distribution with analytical tests. Mann-Whitney U test was used for binary groups. Kruskal-Wallis test was used for groups more than two. Spearman correlation test was used to determine whether there is a linear relationship between the two numerical measurements, the direction and severity of this relationship, if any. In our study ($p<0.05$), it was accepted as statistically significant difference.

Ethical Principles

This study was approved by the Agri Ibrahim Cecen University Scientific Research Ethics Committee with the protocol number of 95 was in accordance with the ethical standards established in the Declaration of Helsinki.

Table 1. Introductory characteristics of individuals (N=611)

Variables		n	%
Nationality	Turkey	476	77.9
	Azerbaijan	135	22.1
Gender	Female	362	59.2
	Male	249	40.8
Marital status	Single	454	74.3
	Married	157	25.7
Education Level	Primary education	33	5.4
	Secondary education	288	47.1
	High education	290	47.5
Income rate	Less than income	267	43.7
	Income equal to expense	255	41.7
	More than income	89	14.6
Health Insurance	Yes	413	67.6
	No	198	32.4
Job	Officer	61	10.0
	Health personnel	59	9.7
	Worker	39	6.4
	Not working	121	19.8
	Housewife	28	4.6
	Other	303	49.6
Information channel for coronavirus disease	Television	206	33.7
	Internet	345	56.5
	Scientific works	60	9.8
The idea of taking adequate precautions for coronavirus disease	Yes	385	63.0
	No	226	37.0
Thought of losing his/her job due to coronavirus disease	Yes	235	38.5
	No	376	61.5
Have you applied coronavirus disease to it?	Yes	83	13.6
	No	528	86.4
How stressful do you feel due to coronavirus disease	Low	95	15.5
	Middle	319	52.2
	High	197	32.2
		$\bar{X}$ ±SD	
Age		25.13±7.41 (min.18, max.67)	

Results

Turkey citizens of 77.9% of the individuals participating in the study, of 59.2% were female, were single of 74.3%, higher education graduates, 47.5%, is less than costs of revenues of 43.7%, that of the 67.6% health insurance, 49.6%. The other group has profession, 56.5% of them get information from the internet, 63.0% of them think that they take enough precautions, 61.5% of them think they will not lose their job due to the corona, 86.4% of them do not apply online corona, 52.2% of them have coronavirus disease. It was determined that she experienced moderate stress due to her and the mean age of the group was 25.13±7.41 *(Table 1).*

The Knowledge Test for Coronavirus Disease was found to be statistically significantly higher in higher education graduates, those with health insurance, those working as health personnel, those who read scientific studies as a corona information channel, and those who did not have the idea of losing their job due to corona ($p<0.05$) *(Table 2).*

E-Health literacy Level score was found to be statistically significantly higher in women, higher education graduates, those with health insurance, those working as health personnel, those who read scientific studies as a corona information channel, and those who did not have the idea of losing their job due to corona ($p<0.05$) *(Table 3).*

Table 2. Comparison of individuals' demographic characteristics and knowledge test for coronavirus disease

Variables		n	$\overline{X}$ ±SD	Statistic
Nationality	Turkey	476	13.66±2.24	U=30651.50
	Azerbaijan	135	13.37±2.52	p=0.410
Gender	Female	362	13.63±2.29	U=43801.50
	Male	249	13.54±2.32	p=0.551
Marital status	Single	454	13.59±2.22	U=35237.00
	Married	157	13.59±2.54	P=0.832
Education Level	Primary	33	12.33±2.80	**KW=12.061**
	Secondary	288	13.44±2.19	**p=0.002**
	High education	290	13.89±2.30	
Income rate	Less than income	267	13.47±2.18	KW=3.448
	Income equal to expense	255	13.54±2.28	p=0.178
	More than income	89	14.12±2.67	
Health Insurance	Yes	413	13.88±2.26	**U=35386.00**
	No	198	12.99±2.29	**p=0.000**
Job	Officer	61	14.08±2.49	**KW=28.200**
	Health personnel	59	14.38±2.55	**p=0.000**
	Worker	39	12.02±2.18	
	Not working	121	13.47±2.10	
	Housewife	28	13.10±2.04	
	Other	303	13.64±2.23	
Information channel for coronavirus disease	Television	206	13.38±2.19	**KW=9.902**
	Internet	345	13.56±2.22	**p=0.007**
	Scientific works	60	14.53±2.87	
The idea of taking adequate precautions for coronavirus disease	Yes	385	13.64±2.24	U=42152.00
	No	226	13.51±2.41	p=0.517
Thought of losing his/her job due to coronavirus disease	Yes	235	12.94±2.25	**U=32977.00**
	No	376	14.01±2.24	**p=0.000**
Have you applied coronavirus disease to it?	Yes	83	13.72±2.39	U=21032.50
	No	528	13.57±2.29	p=0.553
How stressful do you feel due to coronavirus disease	Low	95	13.49±2.31	KW=0.954
	Middle	319	13.66±2.35	p=0.621
	High	197	13.53±2.23	

According to the findings obtained from the study, it was found that the lowest mean score was 6 and the highest score was 20 and the mean score was 13.59±2.30. It was determined that the mean score level of the individuals for coronavirus disease was high. E-Health literacy Level total score mean was 26.12±9.35 and the lowest score was 8 and the highest score was 40. E-Health literacy Level mean score was determined to be high *(Table 4)*.

It was found that there was a statistically significant correlation between the level of knowledge and e-health literacy level for coronavirus disease ($p<0.05$) *(Table 5)*.

Discussion

It is very important to stay away from false information in preventing disease and combating the epidemic. Speculative suggestions made because of incomplete information and evidence-based approaches or to benefit from panic environment are far from scientific and such explanations cause more harm than benefit in society.

According to the findings obtained from the study, it was found that the lowest mean score was 6 and the highest score was 20 and the mean score was 13.59±2.30. It was determined that the mean score level of the individuals for coronavirus disease was high. Case of Turkey

Table 3. Comparison of individuals' demographic characteristics and e-Health literacy level scores

Variables		n	$\bar{X}$±SD	Statistic
Nationality	Turkey	476	25.91±9.30	U=29889.50
	Azerbaijan	135	26.87±9.54	p= 0.215
Gender	Female	362	26.80±9.02	**U=40873.00**
	Male	249	25.14±9.75	**p=0.050**
Marital status	Single	454	26.25±9.36	U=34718.00
	Married	157	25.75±9.34	p=0.628
Education Level	Primary	33	24.30±6.51	**KW=9.016**
	Secondary	288	25.42±9.43	**p= 0.011**
	High education	290	27.02±9.49	
Income rate	Less than income	267	24.81±9.55	KW=3.448
	Income equal to expense	255	26.80±8.96	p= 0.178
	More than income	89	28.10±9.41	
Health Insurance	Yes	413	27.04±9.19	**U=33162.50**
	No	198	24.21±9.43	**p= 0.000**
Job	Officer	61	28.03±8.89	
	Health personnel	59	28.94±8.62	
	Worker	39	20.17±9.94	
	Not working	121	25.67±9.61	**KW=28.200**
	Housewife	28	21.71±9.45	**p= 0.000**
	Other	303	26.54±8.98	
Information channel for coronavirus disease	Television	206	24.57±9.14	**KW=9.902**
	Internet	345	26.23±9.40	**p= 0.007**
	Scientific works	60	30.78±8.27	
The idea of taking adequate precautions for coronavirus disease	Yes	385	26.74±8.95	**U=39078.50**
	No	226	25.06±9.93	**p=0.035**
Thought of losing his/her job due to coronavirus disease	Yes	235	23.89±9.38	**U=33700.50**
	No	376	27.51±9.07	**p=0.000**
Have you applied coronavirus disease to it?	Yes	83	27.15±9.52	U=20304.00
	No	528	25.96±9.32	p=0.281
How stressful do you feel due to coronavirus disease	Low	95	27.43±9.99	KW=0.954
	Middle	319	26.73±8.75	p= 0.621
	High	197	24.49±9.80	

Table 4. Knowledge test for coronavirus disease and e-Health literacy level total score means

	$\bar{X}$ ±SD	Min- Max
Knowledge Test for Coronavirus Disease	13.59±2.30	6.00-20.00
E-Health Literacy Level	26.12±9.35	8.00-40.00

and should be seen in many countries before the relevant ministries and local governments, as well as greater use of the media in the very origin is thought to have become more conscious society.

In our study, the mean knowledge level for coronavirus disease was found statistically significantly higher in higher education graduates ($p<0.05$). In the study conducted by Demirbilek on the knowledge, attitude and behavior of nurses about flu vaccine, it was found that those with higher education level had higher knowledge level.[13] In the study carried out by Tekbas towards infectious diseases, it was found that individuals with low education level had a low mean score.[14]

In our study, the mean knowledge level for coronavirus disease was found statistically significantly higher in those with health insurance ($p<0.05$). It is thought that there is no similar study in the literature and this is due to the insufficiency of access to resources depending on the income level of those who do not have health insurance.

In our study, the mean knowledge level for coronavirus disease was found to be statistically significantly higher in those working as health personnel ($p<0.05$). The fact that healthcare personnel receive information face-to-face and on the web in continuous preventive and therapeutic areas also suggests that the level of knowledge is high when they learn by experience rather than just knowledge.

In our study, the mean knowledge level for coronavirus disease was found to be statistically significantly higher in those who read scientific studies as a channel of receiving information for coronavirus disease ($p<0.05$). In addition to the information that needs to be produced based on evidence in the light of the information that is renewed every day, some wrong or useless applications can cause disinformation either in media tools such as television, newspapers or via social media. In this context, in order to reach correct information, it is considered that scientific evidence should be avoided, the source of the transferred information should be checked and filtered.

In our study, the mean knowledge level for coronavirus disease was found to be statistically significantly higher in those who did not have the idea of losing their job due to coronavirus disease ($p<0.05$). It is thought that the individuals who have a specific job and who are deemed authorized by their institutions are isolated from home and that the period of benefiting from social media, television and scientific studies for the purpose of occupation is high. E-Health Literacy Level was found to be 26.12±9.35 on mean. Similar results were found in the literature.[15-17]

E-Health literacy Level mean score was found statistically significantly higher in women ($p<0.05$). Ertas et al. similar results were found in the study conducted by.[18]

E-Health Literacy Level mean score was found statistically significantly higher in higher education graduates ($p<0.05$). Similar results were found in the literature.[18-20]

E-Health Literacy Level score mean was found to be statistically significantly higher in those with health insurance ($p<0.05$). This situation suggests that it is due to the limited access to the internet and social media due to the financial situation. In the studies in the literature, it was found that as the level of income increases, literacy scores also increase.[21,22]

Table 5. Relationship Between Knowledge Test for Coronavirus Disease and E-Health Literacy Level Total Score Means

	E-Health Literacy Level	
	r	p
Knowledge Test for Coronavirus Disease	**0.301**	**0.000**

E-Health Literacy Level mean score was found to be statistically significantly higher in those working as health personnel ($p<0.05$). In addition to a health education focused education, it is thought that the unit they work in is high due to the fact that the internet and health related concepts are widely included.

E-Health Literacy Level score mean was found to be statistically significantly higher in those who read scientific studies as a channel to receive information from coronavirus disease ($p<0.05$). This situation makes us think that it is caused by the fact that there is a lot of wrong information besides useful information on the internet. Scientific studies based on evidence are thought to increase e-health literacy.

E-Health Literacy Level mean score was found statistically significantly higher in those who did not have the idea of losing their job due to coronavirus disease ($p<0.05$). The idea of losing his job suggests that health literacy is lower due to the inadequate opportunities, since it is made up of individuals who are in the working class and who do not have a high income.

It was found that there was a positive statistically significant relationship between the level of knowledge regarding coronavirus disease and the total score means of e-health literacy ($p<0.05$). This situation suggests that in parallel with the increase in interest in e-health literacy, the intake of information about coronavirus disease has also increased.

Conclusions

It was determined that the knowledge level of the individuals for coronavirus disease was high, and the e-health literacy level was mean. It is recommended that the study be carried out in larger groups.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Original Article

From Activated Charcoal to Selective Plasma Exchange: A Retrospective Analysis of Mushroom Poisoning Cases Treated in The Intensive Care Unit

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Abstract

Background This study aims to evaluate the treatment modalities of adult patients presenting with mushroom poisoning treated in the intensive care unit (ICU) with special consideration of extracorporeal liver support systems.

Material and Methods Records of patients with mushroom poisoning treated in the ICU between January 2007 and December 2014 were analyzed retrospectively.

Results Sixteen adult patients were treated in the ICU for mushroom poisoning during the designated study period. Average time from ingestion of mushrooms to first symptoms was 17.81 hours, and to ICU admission was 2.38 days. In cases with elevated liver transaminases, penicillin G, silibinin and N-acetyl cysteine were used. Extracorporeal support systems were used for detoxification and as a bridge to liver transplantation in 9 cases. Of these, 4 were plasmapheresis, 3 were selective plasma exchange, 1 was hemoperfusion and 1 was direct adsorption from plasma. Two cases underwent emergency liver transplantation.

Conclusions Liver transplantation is the most definitive and effective treatment in indicated cases of mushroom poisoning. Extracorporeal support systems should be considered in the early period both as a treatment modality on their own or to save time until the definitive treatment is possible. The question of which extracorporeal detoxification technique to use is difficult to answer and controlled clinical trials which compare their efficacy are needed.

Turk J Int Med 2021;3(1):21-27
DOI: 10.46310/tjim.832864

Keywords: *mushroom poisoning, activated charcoal, selective plasma exchange, intensive care unit*

Received: November 28, 2020; Accepted: January 08, 2021; Published Online: January 29, 2021

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Introduction

Mushroom poisoning poses an important public health problem worldwide. There are around 5,000 species of mushroom, of which around 3% are responsible for poisoning.[1,2] Turkey is rich in terms of the mushroom flora. They are consumed widely in the spring and autumn seasons which accounts for the increased number of poisonings seen at this time.[3,4] The clinical presentation depends on the type of mushroom ingested. Generally, mushroom poisoning presents a wide range of symptoms from nausea, vomiting, abdominal pain and diarrhea to symptoms of full-blown acute liver failure.[1,4]

The treatment of mushroom poisoning begins in the emergency department where the patients first present, and usually continues into the intensive care unit (ICU). The first step in treatment is provision of supportive measures (fluid resuscitation, correction of electrolyte imbalances, etc.), after which gastric lavage and repetitive doses of activated charcoal can be used.[5] Poisoning with the *Amanita phalloides* species especially leads to kidney and liver dysfunction. Although treatments such as silibinin, high dose penicillin-G, N-acetyl cysteine (NAC) and extracorporeal support systems are effective when commenced promptly; in cases of fulminant liver failure, liver transplantation (LT) is the only acceptable treatment modality.[5,6]

Many extracorporeal methods of toxin removal (hemoperfusion, plasma exchange) are used, but they seem to be effective only at the initial stage of poisoning (up to 48 hours after ingestion).[7] Therefore, early diagnosis and aggressive treatment of mushroom poisoning, as well as prompt transfer to a transplantation center can be regarded as life-saving for this condition. The expanding use of liver support systems and experience with LT makes these cases increasingly worthy of close follow-up.[6,7]

This study aims to evaluate the medical and extracorporeal treatment modalities, the need for LT and outcomes of treatment in the ICU for adult patients presenting with mushroom poisoning.

Material and Methods

The institutional Medical Ethics committee granted ethical permission for the conduction of this study. Records of adult (18 years-old) patients who required treatment for mushroom poisoning in ICU between January 2007 and December 2014 were retrospectively analyzed.

The following parameters were recorded for each patient: age, sex, presenting signs and symptoms and time of commencement, various scores for predicting morbidity and mortality (Acute Physiology and Chronic Health Evaluation [APACHE] II and Sequential Organ Failure Assessment [SOFA]), treated organ failures, Model for End-Stage Liver Disease (MELD) scores of those who developed liver failure, treatments applied (medical, extracorporeal or liver transplantation), laboratory findings, length of stay in the ICU, and results of treatments.

Statistical analysis was conducted using the "Statistical Package for the Social Sciences- SPSS 22.0" program. Categorical variables are expressed as percentage (%) and continuous variables are expressed as mean±standard deviation (mean±SD).

Results

Seventeen adult patients were treated in the ICU for mushroom poisoning during the designated study period. Demographic properties, ICU scores and properties specific to their mushroom poisoning are presented in Table 1.

The most common pathological laboratory finding during ICU admission was elevation of liver transaminases (n:12). Specific laboratory findings and values are presented in Table 2.

Eight cases (50%) required mechanical ventilation therapy and 6 cases (37.5%) required inotropic and vasopressor agents in the ICU. Nine cases (56.25%) developed acute liver failure (ALF). The average MELD score for these patients was 29.96±9.12. The lactate levels for one of these patients could not be found. The average lactate level for the remaining 8 patients was 101.92±92.07 mg/dL (min-max: 20.1-290.09 mg/dL). MELD scores and laboratory findings of patients who developed ALF in the ICU are summarized in Table 3.

A review of treatment modalities revealed that the most commonly used modality was repetitive doses of activated charcoal which was used in 10 cases (62.5%). In cases with elevated liver transaminases, silibinin, N-acetyl cysteine (NAC) and penicillin G was used for hepatoprotective

Table 1. Baseline characteristics of the patients.

Age (years) (mean±SD)	55.38±17.42
Sex [n (%)]	
Female	10 (62.5)
Male	6 (37.5)
Month of presentation [n (%)]	
May	1 (6.3)
June	3 (18.8)
October	10 (62.5)
November	1 (6.3)
December	1 (6.3)
Time from ingestion to first symptom [n (%)]	
<6 hours	2 (12.5)
>6 hours	14 (87.5)
Time from ingestion to ICU admission (days) (mean±SD)	2.38±1.41
ICU scores (mean±SD)	
APACHE II	13.44±7.22
SOFA	4.13±4.52
Presenting symptoms [n (%)]	
Nausea	16 (100)
Vomiting	15 (93.8)
Diarrhea	10 (62.5)
Alteration of consciousness	5 (31.3)
Abdominal pain	4 (25)
Hallucination	1 (6.3)
Hematuria	1 (6.3)

ICU: Intensive Care Unit; APACHE: Acute Physiology and Chronic Health Evaluation; SO Sequential Organ Failure Assessment.

purposes. Extracorporeal support systems were used for detoxification and as a bridge to liver transplantation in 9 cases. Of these, 1 was hemoperfusion (HP) (6.3%), 1 was direct adsorption from plasma (6.3%) (Fractioned Plasma Separation and Adsorption [FPSA], Prometheus®, Fresenius Medical Care, Germany), 4 were plasmapheresis (25%), and 3 were selective plasma exchange (SPE) (18.8%) (Evaclio™, Plasauto, Germany). Treatments applied in all patients are summarized in Table 4.

Two cases (12.5%) underwent successful emergency LT due to development of ALF. These patients had received SPE before transplantation. One patient developed brain death during ICU stay. The average length of ICU stay was 5.13±6.14 days and 6 cases (37.5%) died despite treatment.

Table 2. Laboratory parameters of the patients.

Laboratory parameters	Admission to ICU (n:16)	24 hours after admission to ICU (n:15)*	Last recorded (n:16)	Normal Ranges
AST (U/L)	2126.2±3352.1	2050.0±3335.5	1049.94±296.6	11-25
ALT (U/L)	674.1±1739.0	1674.1±1739	349.00±51.72	7-28
Ammonia (µg/dL)	213.1±274.1	198.3±146.1	133.83±104.60	31-123
INR	2.6±2.2	2.6±2.5	1.51±0.61	0.85-1.15
Total bilirubin (mg/dL)	2.4±1.6	2.4±1.6	3.21±4.67	0.2-1.2
Direct bilirubin (mg/dL)	1.3±1.1	1.4±0.99	1.81±2.75	0.0-0.5
Urea (mg/dL)	57.0±41.5	38.0±34.7	40.31±38.4	15-45
Creatinine (mg/dL)	1.2±0.94	0.99±0.56	1.34±1.04	0.56-0.85
Blood glucose (mg/dL)	120.4±39.5	124.4±54.2	121.38±65.88	70-100

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; INR: International normalized ratio for prothrombin time. Results are expressed as mean ± SD.
*One patient died within first 24 hours.

Discussion

Mushroom poisoning is a health problem in many countries resulting in both morbidity and mortality.[5] The difficulties related to the management of patients depend mostly on the type of ingested mushroom and the patient's symptoms. Although mostly results in mild to moderate cases of gastroenteritis which are usually self-limiting, poisoning with *Amanita phalloides* results in 90% mortality and even minimal amounts of ingestion can result in death.[8,9] The possibility of A. phalloides should be considered, especially in cases where type analysis cannot be made in the laboratory.[5,9]

The most basic steps in the treatment of mushroom poisoning are early hospitalization, IV fluid resuscitation, and supportive and symptomatic treatment. Since there is no antidote for mushroom poisoning, some medications such as silibinin, NAC, penicillin G and cimetidine can be used for hepatoprotective purposes, especially for amatoxin poisoning.[10,11] Silibinin prevents amanitin from binding to the hepatocyte membrane and entering the cell.[6,12] NAC removes free oxygen radicals from the environment and thereby reduces hepatocyte damage, and in addition to its minimal side effects, accounts for its reason for use in mushroom poisoning.[13] Penicillin G reduced uptake of amanitin by hepatocytes and thereby protects hepatocytes.[14] Conducted studies support the use of multitherapy rather than monotherapy with these drugs.[5,12,14] Nine cases in our study were treated with a combination of these drugs.

One of the most serious consequences of mushroom poisoning is acute liver failure. Extracorporeal liver support systems can be used to remove toxins as well as to act as a bridge to LT in those cases that are suitable.[7] Hemoperfusion, FPSA, plasmapheresis and SPE are major extracorporeal detoxification methods used in mushroom poisoning. Sometimes, they allow time for regeneration of liver tissue, thereby removing the need for transplantation.[7,15]

Hemoperfusion has been used in amatoxin poisonings since 1978 and is more effective when commenced in the first 24 hours after ingestion.[16] Amatoxins do not bind to proteins circulate and freely in serum. They also possess a relatively small molecular weight (around 900 Da) and have a high affinity for charcoal and polymers used in conduction of HP.[16] In FPSA the patient's plasma is separated with the use of membrane with a molecular permeability of 250 kDa and then passed through 2 columns with different adsorbents. Water soluble substances, on the other hand, can be removed through high flow dialysis of blood directly in circulation.[17] Bergis et al.[17] reported the successful use of FPSA until the urinary amatoxin level reached nil in 9 of 20 patients. Plasmapheresis involves the clearance of large molecular weighted substances and protein bound molecules with a small volume

Table 3. MELD scores and laboratory results of patients treated for acute live failure*

	MELD	Encephalopathy**	Lactate (mg/dL)	INR	AST (U/L)	ALT (U/L)
Case 1	40.7	2	20.1	8.9	>4202	>4113
Case 2	28.09	3	46.3	6.6	259	483
Case 3	14.6	4	53.5	3.07	613	1562
Case 4	33.02	3	158	3.0	12804	2621
Case 5	26.8	None	25	3.4	5670	4130
Case 6	18.08	None	76	3.02	4318	4575
Case 7	15.41	2	147	2.1	1008	667
Case 8	33.7	3	290.09	2.6	1940	1654
Case 9	32.27	4	Missing data	2.6	254	159

MELD: Model for End-Stage Liver Disease; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; INR: International Normalized Ratio for prothrombin time.
*Highest values during follow-up. **West Haven Criteria for Encephalopathy
Reference values: Lactate: 0-20 mg/dL, AST: 11-25 U/L, ALT: 7-28 U/L, INR: 0.85-1.15.

of distribution from plasma and consequent replacement with appropriate IV fluids.[18,19] It is important to note the low mortality rates achieved through the use of conservative treatment in combination with plasmapheresis especially when commenced in the first 36 hours.[18-20] The mechanism for SPE involves the use of a filter for the removal of substances in plasma according to their molecular size. Hemofiltration and plasma exchange can occur concurrently according to the filter used. There are studies reporting that SPE increases survival in patients with ALF. Unlike conventional plasma exchange, in SPE, coagulation proteins are not removed.[21,22]

In our study, extracorporeal support systems were used in 9 cases. In one patient HP was used 5 times and a positive result to treatment was observed. Fractioned plasma separation and adsorption was used in one patient on the 7th day after ingestion but the patient died due to multiorgan failure. The fact that the patient was admitted to the ICU on the 5th day after ingestion and that the FPSA was initiated in the late period was probably the reason for failure. Plasmapheresis was used unsuccessfully in 4 patients and these patients died at the end of treatment, most probably because these patients were admitted to the ICU after the first 36 hours (48-120 hr.) after ingestion and only then could plasmapheresis be administered. Three patients underwent SPE. Two cases of them proceeded to undergo LT, whereas 1 patient was able to be treated without LT.

Table 4. Treatments applied for patients with mushroom poisoning.

Patient	Year of Presentation	Acute Liver Failure	Drugs	Extracorporeal Treatment	Outcome
Case 1	2007	Yes	IV hydration*	-	Died
Case 2	2008	Yes	Silibinin	FPSA	Died
Case 3	2009	No	Activated charcoal	-	Survived
Case 4	2009	Yes	Activated charcoal	Plasmapheresis	Died
Case 5	2009	No	Activated charcoal	-	Survived
Case 6	2010	No	Silibinin, penicillin	-	Survived
Case 7	2010	Yes	Activated charcoal, silibinin, penicillin	Plasmapheresis	Died
Case 8	2010	No	Activated charcoal	-	Survived
Case 9	2010	Yes	Silibinin, penicillin, NAC	Hemoperfusion	Survived
Case 10	2010	No	Activated charcoal, penicillin	-	Survived
Case 11	2012	Yes	Silibinin, penicillin, NAC	Plasmapheresis	Died
Case 12	2014	Yes	Silibinin, penicillin	Plasmapheresis	Died
Case 13	2014	No	Activated charcoal	-	Survived
Case 14	2014	Yes	Activated charcoal, silibinin, penicillin, NAC	SPE	Liver transplantation-Survived
Case 15	2014	Yes	Activated charcoal, silibinin, penicillin, NAC	SPE	Liver transplantation-Survived
Case 16	2014	No	Activated charcoal, silibinin, penicillin, NAC	SPE	Survived

FPSA: Fractioned Plasma Separation and Adsorption, **NAC:** N-acetyl cysteine; **SPE:** Selective plasma exchange;
*Patient was in multiorgan failure when admitted to ICU and died before any specific treatment was begun; Brain death.

There are studies present which report the successful use of molecular adsorbent recirculating system (MARS) in patients with ALF due to amatoxin ingestion, either as a bridge to LT or as a treatment modality on its own.[23] This method is an extracorporeal system which uses a closed circuit to allow for the dialysis of protein bound and water-soluble substances in the plasma using albumin.[23,24] We were unable to use MARS due to technical reasons.

The use of extracorporeal systems to remove toxins from circulation has increased in the last 30 years.[20] The mortality rates reported in studies which used extracorporeal systems are significantly lower than those studies in which conservative approaches were preferred.[20,22-24] The question of which detoxification technique to use is one that is difficult to answer as there are no controlled clinical trials which compare their efficacy. The early (with 36 hours of ingestion) use of the method chosen for detoxification, as well as the clinical and laboratory follow-up and measurement of toxin levels in bodily fluids is essential in determining the duration and repetition of application, as well as in ensuring its success.[7,18,22]

The limitations of our study include the fact that it is retrospective with a limited amount of cases from a single center. Although mushroom poisonings are actually encountered more commonly than those reported here, we aimed to give place only to those cases which required ICU admission. Also, due to technical reasons mushroom typing was not possible.

Consequently, early recognition and treatment are essential in decreasing morbidity and mortality from mushroom poisonings. Acute or fulminant liver failure is characterized . by clinical findings accompanying a sudden total or near total deterioration of liver function. Its definitive treatment is LT. The use of extracorporeal methods as organ support systems can extend the time until transplantation is possible, as well as ameliorating the clinical condition of the patient. Further randomized controlled trials are needed to put forth the net effects of extracorporeal liver support systems. Nevertheless, we believe that these modalities should be considered and used more often for the treatment of such patients in the ICU.

Conflict of interest

All authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; any other relationships or activities that could appear to have influenced the submitted work.

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Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Case Report

A Young Female With Low Back Pain Caused by Stage IV Lung Cancer

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Abstract

Low back pain is one of the most common symptoms, having a broad range of etiologies in differential diagnosis, such as inflammatory and degenerative disorders, malignancy and infections. Herein, we present an interesting patient who initially presented with sacroiliitis and was ultimately diagnosed with stage IV lung cancer. She was initially misdiagnosed as having axial spondyloarthritis. We aim to emphasize red flags in the differential diagnosis of sacroiliitis.

Turk J Int Med 2021;3(1):28-31
DOI: 10.46310/tjim.794913

Keywords: *lung cancer, sacroiliitis, hypercalcemia*

Introduction

Back pain is one of the most common symptoms of patients seeking medical care in both primary healthcare centers and emergency settings. There is a broad range of etiologies in differential diagnosis, such as inflammatory and degenerative disorders, malignancy and infections. Presence of inflammatory back pain and subchondral bone marrow edema of sacroiliac joints (SIJs) on magnetic resonance imaging (MRI) is highly associated with a diagnosis of spondyloarthritis, and both findings reflect inflammation in rheumatology practice.[1] Besides bone marrow edema, all of the following- subchondral sclerosis, uniform joint space alterations and bone erosions, progression to ankylosis and obliteration of the SIJ are consistent with the main radiographic signs of sacroiliitis.[2]

Received: September 14, 2020; Accepted: October 27, 2020; Published Online: January 29, 2021

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Case Report

A 38-year-old woman presented with inflammatory lower back pain that had been apparent for three months with marked morning stiffness. She rated it as an 8/10 on a numeric pain scale. Response to non-steroidal anti-inflammatory drugs (NSAIDs) was initially present but after time was not sufficient and the pain persisted day and night. The pain was constant but worse after long periods of rest. She had bilateral paravertebral spasm and tenderness, and her low back motions were painful on physical examination. Flexion adduction internal rotation (FADIR) and flexion abduction external rotation (FABER) tests were positive on compression of right SIJs.

After radiographs were obtained, MRI of the SIJs confirmed sacroiliitis and bone marrow edema *(Figure 1)*. Laboratory analysis revealed neutrophilic leukocytosis, moderate normocytic normochromic anemia, negative brucella agglutination tests and normal liver and kidney function tests. The following laboratory parameters were determined: ESR (erythrocyte sedimentation rate): 86 mm/hour, CRP (C-reactive protein): 81 mg/L, calcium: 11.5 mg/dL, alkaline phosphatase: 185 IU/L, LDH (lactate dehydrogenase): 609 U/L and D-dimer: 3333 ng/mL.

Initially she was treated with NSAIDs and high dose pulse steroids for axial spondyloarthritis (axSpA). But in the following two weeks her pain was progressive and became gradually unbearable. She underwent chest X-ray and computed tomography (CT) scan that showed a left lung lesion in the lower lobe *(Figure 2)*. A bronchoscopy was performed and the evaluation of pathology specimens led to the diagnosis of non-small cell lung cancer (NSCLC) *(Figure 3)*. A positron emission tomography/computerized tomography (PET/CT) scan excluded late stage disease and additional disease localization in bones and liver *(Figure 4)*.

After the administration of subcutaneous denosumab and chemotherapy, the patient's symptoms were dramatically improved without requiring any NSAIDs, which further suggested that sacroiliitis and inflammatory back pain were onset presentations of metastatic lung cancer.

Discussion

Sacroiliitis is one of the cancer-associated rheumatic syndromes. In our literature search, Humphrey et al.[3] reported the first and only patient having metastatic lung cancer with sacroiliitis. Our patient also presented with sacroiliitis as the first manifestation of metastatic lung carcinoma. Neoplastic involvement of the sacroiliac joint itself via cytology was not seen, as in the case mentioned above. The bone scan and hypercalcemia confirmed widespread metastatic bone lesions in our patient.

Today, use of SIJs MRI has important value in the assessment of axSpA patients. But there is currently an "overdiagnosis" of sacroiliitis on MRI. Although bone marrow edema has a central role in the definition of positive MRI findings, it is not specific for spondyloarthritis (SpA).[4] A substantial proportion of healthy individuals without inflammatory back pain also have

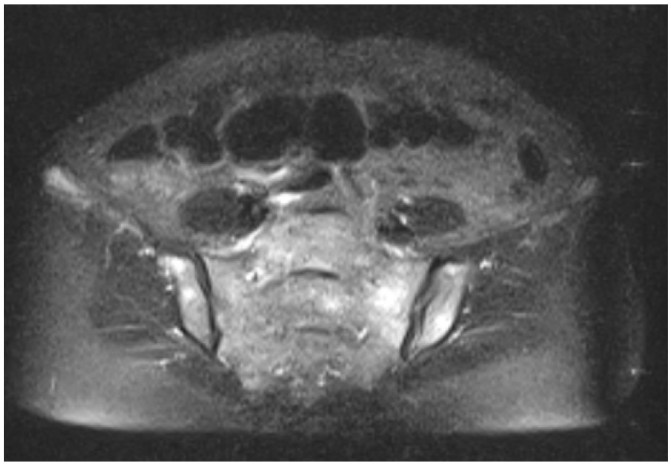

Figure 1. Sacroiliitis on T2 weighted magnetic resonance imaging of the sacroiliac joint.

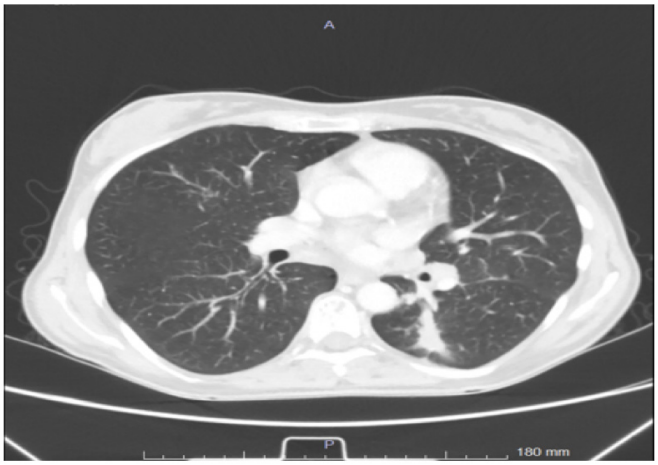

Figure 2. Torax CT: a left lung lesion in the lower lobe.

positive MRI findings for sacroiliitis as well as malignant patients.[5] Zhao et al.[6] investigated the final diagnoses and MRI findings of 34 patients with the chief complaint of back pain who were misdiagnosed as having SpA. In four patients neoplastic disease was found, and bone marrow edema in MRI was found in all of the neoplasm patients.[6] As a result, sacroiliitis of SIJs may be a presenting paraneoplastic radiographic finding in patients.

Acute onset of unilateral or bilateral sacroiliitis with elevated ESR/CRP, fever, positive bone scintigraphy, diagnostic changes in the peripheral blood count, concurrent lymphadenopathy and obvious weight loss may primarily suggest hematological and/or solid malignancies.[7] In a comprehensive review, three red flags were noted for malignancy ('history of cancer', 'unintentional weight loss', 'pain at rest') in patients with low back pain.[8] In addition, progressive pain that was unresponsive to NSAIDs in the follow-up suggested to us further investigation and imaging modalities, since one of the positive SpA features in the Assessment of Spondyloarthritis International Society (ASAS) classification criteria is a marked clinical improvement with NSAIDs.[9] Especially in the presence of alarm symptoms as mentioned above, presence of sacroiliitis alone should not be accepted as SpA.

Malignant osseous lesions or metastases in the pelvis should be included in the differential diagnosis of sacroiliitis on MRI of SIJs. Extraosseous spread to the anatomic borders of bones of SIJs and to the extracapsular area of the joint cavity generally indicate a neoplastic process rather than an inflammatory process. Aggressive-appearing multifocal lesions of bone marrow edema and other skeletal metastases are commonly seen in malignant diseases.[10] Acute destruction of intervening cartilage and/or opposing bones of the joint may also suggest an underlying malignancy when it is incompatibly present with the duration of the illness.[11]

Recently it was also noticed that patients with stage IV lung-cancer-associated hypercalcemia have a poor prognosis, and abnormal elevation of alkaline phosphatase level is accepted as one of the significant factors shortening patient survival time.[12] In addition, plasma D-dimer levels may also be useful for early diagnosis and staging of patients with NSCLC.[13] Hypercalcemia and elevated levels of ALP and D-dimer were also poor prognostic laboratory results in our patient. Denosumab is initially preferred for reducing the risk of developing skeletal-related events.

Conclusion

Our case illustrates that malignancy such as metastatic lung carcinoma should be considered in the differential diagnosis of sacroiliitis. Progressive pain unresponsive to NSAIDs and hypercalcemia require a reconsideration of diagnosis with appropriate further imaging studies, as in our case. Clinicians should keep in mind red flags in the disease course, response to treatment modalities and abnormal laboratory findings for patients presenting with sacroiliitis.

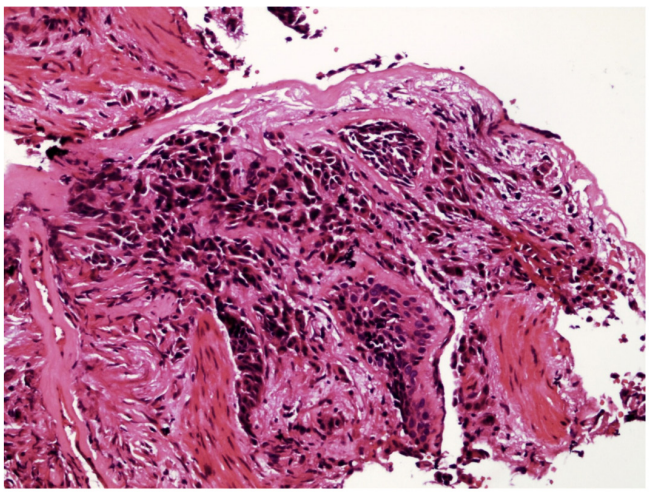

Figure 3. Non-small cell carcinoma, showing islands-style development consisting of pleomorphic cells with large cytoplasm 'NOS'.

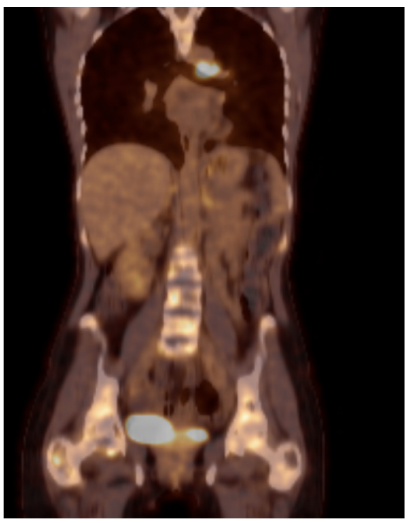

Figure 4. Widespread stage 4 disease, additional disease localization in bones and liver.

Conflict of Interests

Authors declare that there are none.

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Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Case Report

An Unusual Cause of Hypoglycemia: Insulin Autoimmune Syndrome

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Abstract

Insulin autoimmune syndrome (IAS) is a rare cause of hyperinsulinemic hypoglycemia characterized by antibodies to endogenous insulin without exposure to exogenous insulin. In this report, we presented a case of insulin autoimmune syndrome with a history of fasting hypoglycemia. After work up and exclusion of other causes such as insulinoma, hyperinsulinemic hypoglycemic state of the patient was considered to have been induced by etofenamate. Although IAS is generally self-limiting and dietary management and withdrawal of trigger drug are enough to maintain euglycemia, in some cases corticosteroids, plasmapheresis, rituximab can be used for treatment. In our case, despite dietary management, hypoglycemia was severe and the patient's life quality was adversely affected. After treatment with prednisolone, hypoglycemic episodes became less and less frequent. IAS should be considered as a differential diagnosis of hyperinsulinemic hypoglycemic states to avoid unnecessary interventions.

Turk J Int Med 2021;3(1):32-36
DOI: 10.46310/tjim.786828

Keywords: *insulin autoimmune syndrome, hyperinsulinemic hypoglycemic state, corticosteroids*

Introduction

Insulin autoimmune syndrome (IAS) is characterized by hypoglycemia and presence of antibodies to endogenous insulin in insulin naive patients. This syndrome is also known as Hirata's disease who first described the syndrome in 1970.[1]

Viruses and mostly drugs trigger formation of anti-insulin antibodies. Autoantibodies bind to insulin molecules secreted from pancreas following meal and rendering them unable to exert their effects. As glucose concentration falls, insulin molecules dissociate from the autoantibodies and causes hypoglycemia.[2]

Received: October 5, 2020; Accepted: December 18, 2020; Published Online: January 29, 2021

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In IAS, insulin and C-peptide levels are high and antibodies to insulin are positive. The patients are not having a history of exposure to exogenous insulin. Several autoimmune diseases can be associated with this syndrome. The first line treatment is withdrawal of trigger drug and diet with low glycemic index but in some severe cases other treatment strategies can be considered like prednisolone.

Case Report

A 55-year-old male patient with a history of hypertension and chronic obstructive pulmonary disease was presented to endocrinology clinic with a month history of symptoms of hypoglycemia such as weakness and sweating. Hypoglycemia attacks were occurred in the fasting period and alleviated with food intake. Detailed history review did not identify any suspicion for insulin and/or insulin secretagogues, herbal substances. He did not smoke or drink alcohol. There was no known diagnosis of diabetes mellitus in the patient and his family history. His symptoms of hypoglycemia had started after using etofenamate, nonsteroidal anti-inflammatory medication, administered intramuscularly due to lower back pain for a month. Vital signs were normal and physical examination was not significant.

In laboratory evaluation, complete blood count, renal, liver and thyroid function tests were normal. ACTH - cortisol axis was evaluated as normal. A random blood glucose level was 146 mg/dL. During the follow up, fingerstick blood glucose levels were observed as in Table 1.

When the patient's fingerstick blood glucose level was 44 mg/dL, he was symptomatic and experienced sweating and weakness. Blood samples were collected during hypoglycemic attack and then he was given continuous intravenous infusion of dextrose to sustain euglycemia. Laboratory investigations taken during hypoglycemia indicated that hypoglycemia was associated with markedly increased insulin and C-peptide levels compatible with hyperinsulinemic hypoglycemic state *(Table 2)*.

There was no pathological finding in the abdominal computed tomography evaluated for insulinoma. Selective arterial calcium stimulation test was performed to differentiate pancreatic pathologies.

Regardless of the sampling site, all specimens taken from different site had raised insulin and C-peptide levels *(Table 3)*. As insulin to C-peptide molar ratio >1 and autoantibodies to insulin were found to be markedly increased at more than 100 IU/mL (reference range: 0-10 IU/mL), autoimmune hypoglycemia was considered as the cause of hypoglycemia.

Etiology of autoimmune hypoglycemia was considered due to usage of etofenamate; so that it was discontinued. The patient was advised to start a low glycemic index diet with frequent small meals. The diet was insufficient to improve the hypoglycemic attacks so that prednisolone treatment was started as 30 mg daily. Work up for other autoimmune diseases revealed increased anti-double stranded DNA (anti-dsDNA) level of 38 IU/mL (12-18) and positive anti-nuclear antibody (ANA) level, elevated anti thyroid

Table 1. Fingerstick blood glucose levels

	Morning blood glucose (mg/dL)		Noon blood glucose (mg/dL)		Evening blood glucose (mg/dL)		Overnight blood glucose (mg/dL)
	Fasting	Postprandial	Fasting	Postprandial	Fasting	Postprandial	
First day					156	172	52 - 96
Second day	56	87	108	214	166	103	69 - 157
Third day	41	59	78	205	55	116	70

Table 2. Laboratory investigations performed during hypoglycemic period

Parameters	Results	Reference ranges
Serum glucose (mg/dL)	44	70 - 100
Serum insulin (mIU/L)	>600	2.6 – 24.9
Serum C-peptide (µg/L)	7	0.78 – 5.19
Insulin/C-peptide molar ratio	>85.7	<1

peroxidase antibody (anti-TPO) level of 34.8 KU/L (0-5.61), elevated anti thyroglobulin antibody level of 20 KU/L (0-4.11). Imaging studies for thyroid gland was compatible with autoimmune thyroid disease. After consultation to rheumatology clinic, no pathology was considered. Also, blood work for monoclonal gammopathy was not significant.

During hospital stay, the occurrence of hypoglycemic episodes decreased, and he was stopped intravenous dextrose infusion. Since he remained euglycemic with treatment of prednisolone, dosage of treatment was gradually decreased to 20 mg/day.

At his follow up visit, two months after discharge from hospital, hypoglycemia did not occur and his dosage of prednisolone treatment was decreased to 15 mg/day. His most recent laboratory investigations demonstrated persistently raised anti insulin antibody levels >100 IU/mL (reference range: 0-10 IU/ mL). In the follow up of the patient, it was planned that the prednisolone treatment should be gradually decreased and discontinued.

Discussion

IAS is a rare cause of hyperinsulinemic hypoglycemia. This syndrome is characterized by autoantibodies to endogenous insulin without pathology of pancreatic islet cells in patients without history of previous exposure to exogenous insulin.[3] It is usually seen in adults older than 40 years of age. At least 400 cases have been seen in Japan[4] and it is more common in Asian people.

The etiology of antibody formation is multifactorial. Exposure to drugs, viral infections like mumps, rubella, influenza, measles, autoimmune diseases like Graves' disease, hematologic diseases like multiple myeloma can trigger autoimmune hypoglycemia syndrome.[5-7] Also, strong association was observed with the presence of human leukocyte antigen (HLA-DR4) in cases.[8] IAS is associated with exposure to medications containing a sulfhydryl group like methimazole, captopril, hydralazine, procainamide etc.[9] In the literature, patients developed IAS response to nonsteroidal antiinflammatory drugs such as loxoprofen

Table 3. Selective arterial calcium stimulation test results

Time (seconds)	Insulin levels (mIU/L)		
	Superior mesenteric artery	Gastroduodenal artery	Splenic artery
0. sec	2082.6	2028.9	2088.6
20. sec	2026.3	2162.8	2121.5
40. sec	2021.4	2116.8	2064.6
60. sec	2098.6	2117.5	2109.4

sodium and diclofenac sodium. In our case unlike the literature, onset of hypoglycemia after intake of etofenamate treatment of lower back pain suggested IAS.[3]

After food intake, autoantibodies bind to secreted insulin and proinsulin making the insulin to be ineffective. This causes postprandial hyperglycemia and increasing insulin release from pancreas. After dissociation insulin from antibodies, high levels of insulin cause hypoglycemia.[5]

Hypoglycemia can be observed on fasting state or postprandially in IAS. In our case fasting hypoglycemia was observed. The patient experienced hypoglycemia symptoms especially in the overnight period and before breakfast in the morning. Due to insulinoma is the first preliminary diagnosis that comes to mind, with the combination of fasting hypoglycemia and endogenous hyperinsulinemia, the investigations planned in this direction. Because of no mass in pancreas in the abdominal computed tomography, very high levels of insulin and C-peptide, excessively high values at insulin levels in all samples in the calcium stimulation test and positivity of anti-insulin antibody, autoimmune hypoglycemia was considered as diagnosis in our case. Positivity of ANA and elevated thyroid autoantibodies supported the association of IAS and autoimmunity.

In IAS, antibody bounds to insulin, half-life of insulin increases from 5 minutes to hours, while the half-life of C-peptide usually remains unaffected (30–35 minutes).[10] Patient with IAS thus have more than one insulin to C-peptide molar ratio.

IAS is generally self-limiting, and most patients can achieve remission of the disease after stopping use of the medication.[11] Food with low glycemic index remains the first line of the treatment to avoid postprandial hyperglycemia and then secretion of insulin. In more severe cases like in our case, euglycemia can be achieved by using corticosteroid therapy.

As we did not consider interference from heterophile antibodies, we did not do heterophile antibody test. Treatment with prednisolone and then clinical improvement of the patient may suggest that interference was low.

Consequently, for diagnosis, patient's detailed history including age, sex, personel and family history of diseases such as autoimmune and hematological diseases, intake of any drugs or health supplements, infections, time and mode of hypoglycemia is very important. In all hyperinsulinemic hypoglycemic cases, especially in patients taking medications known to be associated with this syndrome and having very high insulin levels, the diagnosis of IAS should be kept in mind.

Conclusion

IAS should be considered as a differential diagnosis in hyperinsulinemic hypoglycemic patient to avoid any unnecessary and invasive procedures.

Conflict of Interests

Authors declare that there are none.

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