World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i25.4066

World J Gastroenterol 2013 July 7; 19(25): 4066-4071
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Clinical significance of melatonin concentrations in predicting the severity of acute pancreatitis

Yin Jin, Chun-Jing Lin, Le-Mei Dong, Meng-Jun Chen, Qiong Zhou, Jian-Sheng Wu

Yin Jin, Chun-Jing Lin, Le-Mei Dong, Meng-Jun Chen, Qiong Zhou, Jian-Sheng Wu, Department of Gastroenterology, First Affiliated Hospital of Wenzhou Medical College, Wenzhou 325000, Zhejiang Province, China
Author contributions: Wu JS designed the research; Jin Y, Dong LM and Zhou Q performed the research; Lin CJ and Chen MJ provided analytic tools; Jin Y wrote the paper.
Supported by The Wenzhou Municipal Science and Technology Commission Major Projects Funds, No. 20090006
Correspondence to: Jian-Sheng Wu, Professor of Medicine, Department of Gastroenterology, First Affiliated Hospital of Wenzhou Medical College, No. 2 Xuefu Road, Lucheng District, Wenzhou 325000, Zhejiang Province, China. wzwujs@163.com
Telephone: +86-577-55559191 Fax: +86-577-55559192
Received: December 19, 2012 Revised: April 15, 2013
Accepted: June 5, 2013
Published online: July 7, 2013

Abstract

AIM: To assess the value of plasma melatonin in predicting acute pancreatitis when combined with the acute physiology and chronic health evaluation Ⅱ (APACHE Ⅱ) and bedside index for severity in acute pancreatitis (BISAP) scoring systems.

METHODS: APACHE Ⅱ and BISAP scores were calculated for 55 patients with acute physiology (AP) in the first 24 h of admission to the hospital. Additionally, morning (6:00 AM) serum melatonin concentrations were measured on the first day after admission. According to the diagnosis and treatment guidelines for acute pancreatitis in China, 42 patients suffered mild AP (MAP). The other 13 patients developed severe AP (SAP). A total of 45 healthy volunteers were used in this study as controls. The ability of melatonin and the APACHE Ⅱ and BISAP scoring systems to predict SAP was evaluated using a receiver operating characteristic (ROC) curve. The optimal melatonin cutoff concentration for SAP patients, based on the ROC curve, was used to classify the patients into either a high concentration group (34 cases) or a low concentration group (21 cases). Differences in the incidence of high scores, according to the APACHE Ⅱ and BISAP scoring systems, were compared between the two groups.

RESULTS: The MAP patients had increased melatonin levels compared to the SAP (38.34 ng/L *vs* 26.77 ng/L) (P = 0.021) and control patients (38.34 ng/L *vs* 30.73 ng/L) (P = 0.003). There was no significant difference inmelatoninconcentrations between the SAP group and the control group. The accuracy of determining SAP based on the melatonin level, the APACHE Ⅱ score and the BISAP score was 0.758, 0.872, and 0.906, respectively, according to the ROC curve. A melatonin concentration ⩽ 28.74 ng/L was associated with an increased risk of developing SAP. The incidence of high scores (⩾ 3) using the BISAP system was significantly higher in patients with low melatonin concentration (⩽ 28.74 ng/L) compared to patients with high melatonin concentration (> 28.74 ng/L) (42.9% *vs* 14.7%, P = 0.02). The incidence of high APACHE Ⅱ scores (⩾ 10) between the two groups was not significantly different.

CONCLUSION: The melatonin concentration is closely related to the severity of AP and the BISAP score. Therefore, we can evaluate the severity of disease by measuring the levels of serum melatonin.

Key words: Pancreatitis; Melatonin concentrations; Predict; Cutoff; Bedside index for severity in acute pancreatitis; Acute physiology and chronic health evaluation Ⅱ

Core tip: It is important to assess the severity and changes in a patient's condition in a timely and accurate manner. Thus, a comprehensive treatment plan for acute pancreatitis patients is critical. Melatonin plays a protective role in the early course of human acute pancreatitis, and melatonin concentration variations

are closely related to the severity of acute pancreatitis and the bedside index for severity in acute pancreatitis score. We can determine the severity of disease in the clinic more objectively, accurately and rapidly by measuring the levels of serum melatonin than by using the standard scoring systems. When the serum concentration of melatonin is below 28.74 ng/L, it is possible that acute pancreatitis patients will develop severe acute pancreatitis.

Jin Y, Lin CJ, Dong LM, Chen MJ, Zhou Q, Wu JS. Clinical significance of melatonin concentrations in predicting the severity of acute pancreatitis. *World J Gastroenterol* 2013; 19(25): 4066-4071 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i25/4066.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i25.4066

INTRODUCTION

Most patients with acute pancreatitis have a favorable prognosis. However, the mortality rate of acute pancreatitis (AP) has been reported as 6%-23%[1]. Effectively treating the disease becomes more difficult as it develops into severe AP (SAP). Therefore, it is important to assess the disease severity in a timely and accurate manner to provide comprehensive treatment to AP patients. Accurate treatment can improve the prognosis and reduce mortality[2]. As a result, there is an urgent need for an objective, accurate, fast and simple method of monitoring changes in AP patients.

Melatonin is best known as the activator of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxydase, or glutathione reductase[3-6]. Melatonin is also well-known as a scavenger of radical oxygen and nitrogen species[7-9]. Melatonin, together with reduced glutathione, vitamins C and E, uric acid, selenium, and creatinine, belongs to the category of nonenzymatic scavengers[6,10,11]. A number of studies have shown that melatonin (MT) plays a protective role in AP. In acute pancreatitis, melatonin was demonstrated to inhibit nuclear binding of nuclear factor kappa B (NF-κB). NF-κB is a transcription factor that controls the expression of genes involved in immunity and inflammation and the production of prostaglandins, cytokines, cell adhesion molecules, nitricoxide (NO), and inhibitors of apoptosis[12,13]. Melatonin has been demonstrated to reduce gene expression and synthesis of proinflammatory cytokines such as tumor necrosis factor α (TNFα) and proinflammatory interleukins such as interleukin (IL)-1β, IL-6, IL-8, and prostaglandins[1,14,15]. In addition, melatonin was also reported to modulate the processes of apoptosis and necrosis by stimulating the production of vascular endothelial growth factor to activate angiogenesis[16-18]. Furthermore, MT plays a protective role in AP-associated organ injuries in animal models[19-21]. For example, Huai *et al*[22] found that melatonin protects rats against acute pancreatitis-associated lung injury through the upregulation of IL-22 and Th22. The upregulation of IL-22 increases innate immunity in tissues and enhances regeneration.

Data on the relationship between the levels of MT in patients with AP and the severity and prognosis of this disease have not been reported. The aims of this study were to assess the value of plasma MT in determining the severity of AP and in predicting SAP. Additionally, we analyzed changes in plasma MT levels and the use of two scoring systems in AP patients.

MATERIALS AND METHODS

Patients

This study enrolled 55 consecutive patients with AP (35 men and 20 women) admitted to department of gastroenterology of our hospital between July 2010 and March 2011 (median age 51 years, range 17-82 years). The diagnosis and classification of AP were based on the diagnosis and treatment guidelines for acute pancreatitis in China (2009)[23]. SAP was diagnosed by the presence of organ failure and (or) local complications. Organ failure included shock (systolic blood pressure < 90 mmHg), pulmonary insufficiency (arterial PO_2 < 60 mmHg at room air or the need for mechanical ventilation), or renal failure (serum creatinine level > 2 mg/dL after rehydration or hemodialysis). Examples of localcomplications included pancreatic necrosis, a pseudocyst, or a pancreatic abscess. According to the diagnosis and treatment guidelines for acute pancreatitis in China, 42 cases were defined as mild AP (MAP), and 13 cases were classified as SAP. Within the population of SAP patients, there were 11 patients (84.6%) with pseudocysts and 2 patients (15.4%) with pancreatic necrosis. There were also 2 patients (15.4%) with acute renal failure. The disease etiology was biliary in 19 cases (34.5%), hyperlipidemic in 14 cases (25.5%), and idiopathic in 14 cases (25.5%). The causes of the remaining 8 cases (14.5%) were hyperlipidemic and biliary, alcoholic and biliary, or alcoholic and pancreatic (duct obstruction). There were no patient deaths during the study period (Table 1). We also analyzed 45 healthy individuals as controls for the study. There were 27 men and 18 women in the control group. The median age of the controls was 44 years (range of 24-64 years).

Monitoring

The study protocol was reviewed and approved by the local ethics committee. The study patients and healthy volunteers were enrolled after providing written informed consent. The patient-acute physiology and chronic health evaluation Ⅱ (APACHE Ⅱ) and bedside index for severity in acute pancreatitis (BISAP) scores were calculated within the first 24 h after admission in all patients with AP. The APACHE Ⅱ score is the most commonly used scoring system for determining the severity and prognosis of AP. This scoring system contains 12 monitoring indicators, and the final score is composed of an acute

Table 1 Characteristics of 55 patients with acute pancreatitis *n* (%)

Variables	Total (*n* = 55)	Mild (*n* = 42)	Severe (*n* = 13)
Age, yr (range)	51 (17-82)	51 (17-77)	50 (30-82)
Male	35 (63.6)	27 (64.3)	8 (61.5)
Female	20 (36.4)	15 (35.7)	5 (38.5)
Etiology			
Biliary	19 (34.5)	17 (40.5)	2 (15.4)
Hyperlipidemia	14 (25.5)	8 (19)	6 (46.2)
Idiopathic	14 (25.5)	11 (26.2)	3 (23.1)
Other	8 (14.5)	6 (14.3)	2 (15.4)
APACHE Ⅱ (range)	7 (2-22)	6 (2-12)	12 (6-22)
BISAP (range)	2 (0-5)	1 (0-4)	3 (2-5)
Operations	10 (18.2)	9 (21.4)	1 (7.7)
Organ failure	2 (3.6)	0 (0.0)	2 (15.4)
Pancreatic necrosis	2 (3.6)	0 (0.0)	2 (15.4)
Pseudocyst	11 (20.0)	0 (0.0)	11 (84.6)
Mortality	0 (0.0)	0 (0.0)	0 (0.0)

APACHE Ⅱ: Acute physiology and chronic health evaluation Ⅱ; BISAP: Bedside index for severity in acute pancreatitis.

physiology score, an age index and a chronic health index[24]. The BISAP scoring standard consists of five elements: blood urea nitrogen, disturbance of consciousness, systemic inflammatory response syndrome, age and pleural effusion[25]. A 3 mL sample of fasting peripheral venous blood was obtained from all patients on the first morning (6:00 AM) after admission. A blood sample was also collected from the control participants.

Laboratory methods

The blood samples from patients with AP and healthy controls were immediately centrifuged at 2500 *g* for 5 min. The sample supernatants were then stored at -80 ℃ until further investigation. The melatonin levels in serum were measured using an enzyme-linked immunosorbent assay (Changfeng Chemical Company, Shanghai, China).

Statistical analysis

The statistical analysis was performed using the SPSS 13.0 statistical program. The measurement data are expressed as the mean ± SE. Differences in MT between the mean values of various groups of experiments were compared using one-way analysis of variance and SNK post hoc analysis. The incidences of high scores for the APACHE Ⅱ and BISAP scoring systems in the high MT concentration group and the low MT concentration group were compared with a χ^2 test. A difference with a P value of < 0.05 was considered statistically significant. An receiver operating characteristic (ROC) curve was generated to analyze the ability of melatonin and the APACHE Ⅱ and BISAP scoring systems to predict SAP.

RESULTS

There was no significant difference in the age ($P = 0.751$) or sex ratio ($P = 1.000$) between patients with mild pancreatitis and severe pancreatitis. Biliary problems were the main factor in the MAP group. Conversely, most cases of SAP were caused by hyperlipidemia (46.2%). Both the APACHE Ⅱ scores and the BISAP scores in severe pancreatitis were significantly higher than in the mild cases at admission. The APACHE Ⅱ scores in the severe and mild AP cases were 12 points *vs* 6 points ($P < 0.001$), while the BISAP scores were 3 points *vs* 1 point ($P < 0.001$).

Table 2 Comparison of the capability to predict severe acute pancreatitis

Variables	Sensitivity	Specificity	Youden index	Accuracy
MT ≤ 28.74 ng/L	73.80%	76.90%	0.507	0.758
APACHE Ⅱ score ≥ 9.5	76.90%	83.30%	0.602	0.872
BISAP score ≥ 2.5	76.90%	90.50%	0.674	0.906

MT: Melatonin; APACHE Ⅱ: Acute physiology and chronic health evaluation Ⅱ; BISAP: Bedside index for severity in acute pancreatitis.

The median value of melatonin levels in the MAP group, the SAP group and the control group was 38.34, 26.77 and 30.73 ng/L, respectively. The melatonin level was significantly higher in patients with mild AP compared to patients with severe pancreatitis (38.34 ± 13.76 ng/L *vs* 26.77 ± 11.88 ng/L, $P = 0.021$). A similar trend was also observed in patients with mild disease compared to controls ($P = 0.003$). There was no significant difference in melatonin levels between MAP patients and healthy individuals (38.34 ± 13.76 ng/L *vs* 30.73 ± 2.96 ng/L, $P > 0.05$)

The Youden index of MT, the APACHE Ⅱ score and the BISAP score for predicting severe acute pancreatitis was 0.507, 0.602 and 0.674, respectively. The optimal cut-off value, sensitivity, specificity, Youden index and accuracy of the respective parameters in predicting SAP are shown in Table 2. The ROC curves of MT and the APACHE Ⅱ and BISAP scoring systems are presented in Figure 1.

The optimal cutoff concentration of 28.74 ng/L for SAP, as determined from the ROC curve, was used to classify the patients into a high concentration group (34 cases) and a low concentration group (21 cases). The incidence of a high BISAP score (≥ 3) was significantly greater in patients with alow melatonin concentration (≤ 28.74 ng/L) compared to patients with a high melatonin concentration (> 28.74 ng/L). The incidence of a high BISAP score was 42.9% in patients with low melatonin compared to 14.7% in patients with high melatonin ($P = 0.02$). There was no significant difference in the incidence of high scores (≥ 10) according to the APACHE Ⅱ scoring system between patients with high and low melatonin levels ($P > 0.05$) (Table 3).

DISCUSSION

In the clinic, 10%-20% of AP patients will develop severe acute pancreatitis, characterized by longer duration of disease, organ failure, systemic inflammatory response syndrome, and pancreatic necrosis. As a result, the disease pathogenesis is serious and complex. It has been reported

Table 3 Relationship between melatonin concentration and patient scores

Group[1]		APACHE Ⅱ score[2]				BISAP score[3]			
	Total cases	High score cases	Incidence	χ^2 value	*P* value	High score cases	Incidence	χ^2 value	*P* value
Low concentrations	21	8	8/21	0.821	> 0.05	9	9/21	5.422	0.02
High concentrations	34	9	9/34			5	5/34		

[1]≤ 28.74 ng/L is defined as a low concentration, > 28.74 ng/L is defined as a high concentration; [2]APACHE Ⅱ score ≥ 10 is defined as a high score, the two groups, $P > 0.05$; [3]BISAP ≥ 3 is defined as a high score. BISAP ≥ 3, low melatonin concentration compared to high concentration, $P = 0.02$. APACHE Ⅱ: Acute physiology and chronic health evaluation Ⅱ; BISAP: Bedside index for severity in acute pancreatitis.

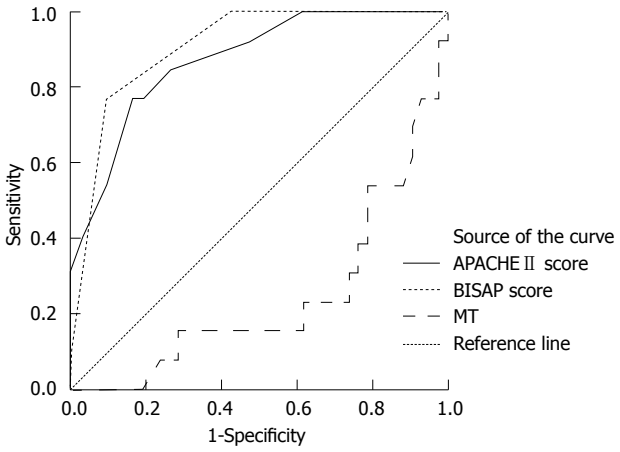

Figure 1 Receiver operating characteristic curves of melatonin, acute physiology and chronic health evaluation Ⅱ score and bedside index for severity in acute pancreatitis score to predict severe acute pancreatitis. MT: Melatonin; APACHE Ⅱ: Acute physiology and chronic health evaluation Ⅱ; BISAP: Bedside index for severity in acute pancreatitis.

that oxidative stress and lipid peroxidation caused by oxygen free radicals cause the destruction of acinar cells and abnormal expression of cytokines during AP pathogenesis[26]. Studies published in the literature concerning MT have demonstrated that it can stabilize cell membranes and protect the cells from oxidative damage. Moreover, MT can also penetrate all of the morphophysiological barriers in the human body and restore acinar cells with their lipophilic and hydrophilic characteristics[27]. Not only is melatonin itself an antioxidant; its metabolites can also reduce oxygen radicals. Additionally, melatonin can strengthen the activity of many antioxidants, such as SOD, Glutathione and CAT, and scavenges both oxygen free radicals and nitrogen free radicals[28,29]. MT has also been reported to have powerful anti-inflammatory and immunomodulatory effects by regulating the production of cytokines[30]. Furthermore, MT was found to promote the spontaneous regeneration process of pancreatic tissue through the activation of stellate cells[31]. MT is potentially capable of limiting pancreatic and associated organ damage produced during AP.

In our study, MT levels in the MAP group were significantly higher than the controls on the first day after admission. This result highlights the importance of the human endocrine system in AP development. The inflammatory response occurs in the early stage of AP prior to the activation of trypsinogen. The organism defense against inflammation occurs primarily through the action of the hypothalamus-pituitary-adrenal axis to increase the secretion of endogenous cortisol. However, the adrenal glands of patients with AP are in a state of relative insufficiency at the onset of disease[32]. Therefore, they may be protected by other mechanisms such as the recruitment of MT to reduce pancreatic damage; thus, an increase in MT will promote a mild disease course. It is well known that inflammation in acute pancreatitis is caused by the imbalance of pro-inflammatory factors and anti-inflammatory factors. This imbalance is more severe in patients with SAP. Perras *et al*[33] showed a clear negative correlation between disease severity and MT levels in patients suffering from severe inflammation. The pineal secretions from patients with profound systemic inflammatory responses were inhibited. This finding could explain why MT concentrations in the SAP group were significantly lower than those in the MAP group in this study. Our results indicate that the MT level is closely related to AP severity. Thus, a lower MT concentration is associated with more severe disease. Conversely, higher MT concentrations are associated with less severe disease. Our data are consistent with the view supported by Belyaev *et al*[32], who indicated that endogenous high levels of serum MT play a protective role in the early course of AP. Our findings have raised the hope that we may be able to control disease severity by using early detection of serum MT concentrations.

The ROC curve is used to compare the accuracy of two or more diagnostic tests. The ROC is considered the most reliable method of evaluating patient prognosis. In this study, we used the ROC curve to assess the relationship between MT and SAP by combining MT values with the APACHE Ⅱ and BISAP scoring systems. As shown in the results, the accuracy of the two scores for SAP were 0.872 and 0.906, respectively. This result indicates that both scoring systems can predict SAP accurately. However, these scoring systems are clinically cumbersome and difficult to remember for clinicians. In addition, it is time-consuming to monitor changes in condition accurately and rapidly using these systems[34,35]. The accuracy of SAP detection using MT was 0.758, and the optimal cut-off concentration was 28.74 ng/L in this study. Our data show that MT levels can predict SAP. Our results further demonstrate that the severity of disease can be determined objectively and accurately by early measurement of serum MT levels. Patients with AP may develop SAP when their MT concentration is below 28.74 ng/L.

Singh *et al*[36] reported that a BISAP score ≥ 3 was associated with an increased risk of developing organ failure. Thus, a BISAP score of 3 was used to divide the patients into the high score and low score groups. A key result of this study was the observation that MT levels were closely related to the BISAP score. The incidence of high score (≥ 3) was significantly increased in patients with low melatonin concentration (≤ 28.74 ng/L) compared to patients with high melatonin concentration (> 28.74 ng/L). Our results clearly demonstrate that a high BISAP score reflects a more severe AP condition and is associated with reduced MT concentration. Conversely, patients with higher MT concentrations had fewer incidences of a high BISAP score. Thus, our results agree with previously published data[36].

Chatzicostas *et al*[37] reported that SAP and its complications could be predicted accurately when the patient had an APACHE Ⅱ score ≥ 10. Therefore, patients were classified into high score and low score groups, with a dividing score of 10 between the groups. However, in our study there was no significant difference in the high score incidence between the low MT concentration group and the high MT concentration group. The reasons for this result include the following: (1) the APACHE Ⅱ score requires knowledge of the patient history, which may not be available if the patient is unconscious, intubated, or transferred from an outside hospital lacking detailed records, thus resulting in an incorrect number of points; and (2) the APACHE Ⅱ score includes a chronic health index, which is not directly correlated with AP. Thus, the relationship between MT levels and the APACHE Ⅱ score will require further studies.

In conclusion, the results of the present study reveal that exogenous melatonin may prevent the damage caused during acute pancreatitis due to its antioxidant, anti-inflammatory, and immunomodulatory properties. The variations of MT concentration might reflect the degree of AP severity to some extent. As a result, we can determine the severity of disease more objectively, accurately and rapidly by measuring the levels of serum melatonin. In addition, a melatonin concentration ≤ 28.74 ng/L was associated with an increased risk of developing SAP. The current clinical study was performed in a single center, and this research had some limitations. Therefore, large sample investigations will be needed to explore the value of serum melatonin in determining the severity of AP.

COMMENTS

Background

Acute pancreatitis (AP) includes both severe AP (SAP) and mild AP (MAP). SAP has a high reported mortality rate. It is important to assess the severity and changes in a patient's condition in a timely and accurate manner to provide comprehensive treatment. This approach could improve the prognosis and reduce mortality. Therefore, authors assessed the predictive value of plasma melatonin in identifying acute pancreatitis in combination with the acute physiology and chronic health evaluation Ⅱ (APACHE Ⅱ) and bedside index for severity in acute pancreatitis (BISAP) scoring systems.

Research frontiers

A number of studies have showed that melatonin (MT) plays a protective role in AP and its associated organ injuries using animal models. The research objective herein was to assess the value of plasma MT in determining the severity of AP. Additionally, authors predicted SAP and analyzed the changes of plasma MT levels and the use of two scoring systems.

Innovations and breakthroughs

The authors have evaluated the ability of melatonin and the APACHE Ⅱ and BISAP scoring systems to predict SAP by using a receiver operating characteristic (ROC) curve. The optimal cutoff concentration for SAP from the ROC curve was used to classify the patients into a high concentration group and a low concentration group. The differences in the incidence of high scores for the APACHE and BISAP scores scoring systems were compared between the two groups. In the present study, melatonin was shown to play a protective role in the early course of human acute pancreatitis, and concentration variations were closely related to the severity of AP and the BISAP score. The authors can determine the severity of AP more objectively, accurately and rapidly by measuring the levels of serum melatonin. When the melatonin concentration is at or below 28.74 ng/L, AP patients may develop SAP.

Applications

The study results suggest that exogenous melatonin may prevent the damage caused by AP due to its antioxidant, anti-inflammatory, and immunomodulatory properties. Variations of MT concentration might reflect the degree of severity of AP to some extent.

Terminology

The APACHE Ⅱ score contains 12 monitoring indicators, and the final score is composed of an acute physiology score, an age index and a chronic health index. The APACHE Ⅱ scoring system is the most commonly used scoring system for determining the severity and prognosis of AP. The BISAP scoring standard consists of five elements: blood urea nitrogen, disturbance of consciousness, systemic inflammatory response syndrome, age and pleural effusion.

Peer review

The authors focus on the clinical significance of melatonin concentrations in predicting the severity of AP. The results suggest that melatonin concentration variations are closely related to the severity of AP and the BISAP score. The serum melatonin level can be used to evaluate the severity of disease objectively, accurately and rapidly.

REFERENCES

1 **Gülben K**, Ozdemir H, Berberoğlu U, Mersin H, Yrkin F, Cakýr E, Aksaray S. Melatonin modulates the severity of taurocholate-induced acute pancreatitis in the rat. *Dig Dis Sci* 2010; **55**: 941-946 [PMID: 19399617 DOI: 10.1007/s10620-009-0808-2]

2 **Whitcomb DC**. Clinical practice. Acute pancreatitis. *N Engl J Med* 2006; **354**: 2142-2150 [PMID: 16707751]

3 **Ochoa JJ**, Díaz-Castro J, Kajarabille N, García C, Guisado IM, De Teresa C, Guisado R. Melatonin supplementation ameliorates oxidative stress and inflammatory signaling induced by strenuous exercise in adult human males. *J Pineal Res* 2011; **51**: 373-380 [PMID: 21615492 DOI: 10.1111/j.1600-079X.2011.00899.x]

4 **Tan DX**, Manchester LC, Terron MP, Flores LJ, Reiter RJ. One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species? *J Pineal Res* 2007; **42**: 28-42 [PMID: 17198536]

5 **Miller E**, Mrowicka M, Malinowska K, Kedziora J, Majsterek I. The effects of whole-body cryotherapy and melatonin supplementation on total antioxidative status and some antioxidative enzymes in multiple sclerosis patients. *Pol Merkur Lekarski* 2011; **31**: 150-153 [PMID: 21991843]

6 **Shagirtha K**, Muthumani M, Prabu SM. Melatonin abrogates cadmium induced oxidative stress related neurotoxicity in rats. *Eur Rev Med Pharmacol Sci* 2011; **15**: 1039-1050 [PMID: 22013727]

7 **Lahiri S**, Singh P, Singh S, Rasheed N, Palit G, Pant KK. Melatonin protects against experimental reflux esophagitis. *J Pineal Res* 2009; **46**: 207-213 [PMID: 19067786 DOI: 10.1111/j.1600-079X.2008.00650.x]

8 **Peyrot F**, Ducrocq C. Potential role of tryptophan derivatives

in stress responses characterized by the generation of reactive oxygen and nitrogen species. *J Pineal Res* 2008; **45**: 235-246 [PMID: 18341517 DOI: 10.1111/j.1600-079X.2008.00580.x]
9 **Reiter RJ**, Paredes SD, Korkmaz A, Jou MJ, Tan DX. Melatonin combats molecular terrorism at the mitochondrial level. *Interdiscip Toxicol* 2008; **1**: 137-149 [PMID: 21218104 DOI: 10.2478/v10102-010-0030-2]
10 **Martínez-Cruz F**, Osuna C, Guerrero JM. Mitochondrial damage induced by fetal hyperphenylalaninemia in the rat brain and liver: its prevention by melatonin, Vitamin E, and Vitamin C. *Neurosci Lett* 2006; **392**: 1-4 [PMID: 16309833]
11 **Durante P**, Romero F, Pérez M, Chávez M, Parra G. Effect of uric acid on nephrotoxicity induced by mercuric chloride in rats. *Toxicol Ind Health* 2010; **26**: 163-174 [PMID: 20176775 DOI: 10.1177/0748233710362377]
12 **Sun XF**, Zhang H. NFKB and NFKBI polymorphisms in relation to susceptibility of tumour and other diseases. *Histol Histopathol* 2007; **22**: 1387-1398 [PMID: 17701919]
13 **Czyz M**. Specificity and selectivity of the NFkappaB response. *Postepy Biochem* 2005; **51**: 60-68 [PMID: 16209343]
14 **Jung KH**, Hong SW, Zheng HM, Lee HS, Lee H, Lee DH, Lee SY, Hong SS. Melatonin ameliorates cerulein-induced pancreatitis by the modulation of nuclear erythroid 2-related factor 2 and nuclear factor-kappaB in rats. *J Pineal Res* 2010; **48**: 239-250 [PMID: 20210857 DOI: 10.1111/j.1600-079X.2010.00748.x]
15 **Chen HM**, Chen JC, Ng CJ, Chiu DF, Chen MF. Melatonin reduces pancreatic prostaglandins production and protects against caerulein-induced pancreatitis in rats. *J Pineal Res* 2006; **40**: 34-39 [PMID: 16313496]
16 **Muñoz-Casares FC**, Padillo FJ, Briceño J, Collado JA, Muñoz-Castañeda JR, Ortega R, Cruz A, Túnez I, Montilla P, Pera C, Muntané J. Melatonin reduces apoptosis and necrosis induced by ischemia/reperfusion injury of the pancreas. *J Pineal Res* 2006; **40**: 195-203 [PMID: 16499554]
17 **Soybir G**, Topuzlu C, Odabaş O, Dolay K, Bilir A, Köksoy F. The effects of melatonin on angiogenesis and wound healing. *Surg Today* 2003; **33**: 896-901 [PMID: 14669079]
18 **Ganguly K**, Sharma AV, Reiter RJ, Swarnakar S. Melatonin promotes angiogenesis during protection and healing of indomethacin-induced gastric ulcer: role of matrix metaloproteinase-2. *J Pineal Res* 2010; **49**: 130-140 [PMID: 20492444 DOI: 10.1111/j.1600-079X.2010.00776.x]
19 **Ni Y**, Wu JS, Fang PP, Wu XL, Sun XC, Jia GB, Zhang RZ. Mechanism of liver injury in severe acute pancreatitis rats and role of melatonin. *Zhonghua Yixue Zazhi* 2008; **88**: 2867-2871 [PMID: 19080501]
20 **Alhan E**, Kalyoncu NI, Kural BV, Erçin C. Effects of melatonin on acute necrotizing pancreatitis in rats. *Z Gastroenterol* 2004; **42**: 967-972 [PMID: 15455265]
21 **Cöl C**, Dinler K, Hasdemir O, Büyükaşik O, Buğdayci G, Terzi H. Exogenous melatonin treatment reduces hepatocyte damage in rats with experimental acute pancreatitis. *J Hepatobiliary Pancreat Sci* 2010; **17**: 682-687 [PMID: 20464559 DOI: 10.1007/s00534-010-0265-5]
22 **Huai JP**, Sun XC, Chen MJ, Jin Y, Ye XH, Wu JS, Huang ZM. Melatonin attenuates acute pancreatitis-associated lung injury in rats by modulating interleukin 22. *World J Gastroenterol* 2012; **18**: 5122-5128 [PMID: 23049224 DOI: 10.3748/wjg.v18.i36.5122]
23 **Wang YT**, Chen YX. Diagnosis and treatment guidelines for acute pancreatitis of China. *Zhongguo Shiyong Neike Zaizhi* 2009; **29**: 317-319
24 **Knaus WA**, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818-829 [PMID: 3928249]
25 **Wu BU**, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. *Gut* 2008; **57**: 1698-1703 [PMID: 18519429 DOI: 10.1136/gut.2008.152702]
26 **Park BK**, Chung JB, Lee JH, Suh JH, Park SW, Song SY, Kim H, Kim KH, Kang JK. Role of oxygen free radicals in patients with acute pancreatitis. *World J Gastroenterol* 2003; **9**: 2266-2269 [PMID: 14562390]
27 **Eşrefoğlu M**, Gül M, Ateş B, Selimoğlu MA. Ultrastructural clues for the protective effect of melatonin against oxidative damage in cerulein-induced pancreatitis. *J Pineal Res* 2006; **40**: 92-97 [PMID: 16313504]
28 **Maharaj DS**, Maharaj H, Daya S, Glass BD. Melatonin and 6-hydroxymelatonin protect against iron-induced neurotoxicity. *J Neurochem* 2006; **96**: 78-81 [PMID: 16300638]
29 **Leja-Szpak A**, Jaworek J, Tomaszewska R, Nawrot K, Bonior J, Kot M, Palonek M, Stachura J, Czupryna A, Konturek SJ, Pawlik WW. Melatonin precursor; L-tryptophan protects the pancreas from development of acute pancreatitis through the central site of action. *J Physiol Pharmacol* 2004; **55**: 239-254 [PMID: 15082881]
30 **Jaworek J**, Konturek SJ, Leja-Szpak A, Nawrot K, Bonior J, Tomaszewska R, Stachura J, Pawlik WW. Role of endogenous melatonin and its MT2 receptor in the modulation of caerulein-induced pancreatitis in the rat. *J Physiol Pharmacol* 2002; **53**: 791-804 [PMID: 12510864]
31 **Sidhu S**, Pandhi P, Malhotra S, Vaiphei K, Khanduja KL. Melatonin treatment is beneficial in pancreatic repair process after experimental acute pancreatitis. *Eur J Pharmacol* 2010; **628**: 282-289 [PMID: 19958759 DOI: 10.1016/j.ejphar.2009.11.058]
32 **Belyaev O**, Herzog T, Munding J, Bolik B, Vosschulte A, Uhl W, Müller CA. Protective role of endogenous melatonin in the early course of human acute pancreatitis. *J Pineal Res* 2011; **50**: 71-77 [PMID: 20964708 DOI: 10.1111/j.1600-079X.2010.00811.x]
33 **Perras B**, Kurowski V, Dodt C. Nocturnal melatonin concentration is correlated with illness severity in patients with septic disease. *Intensive Care Med* 2006; **32**: 624-625 [PMID: 16477409]
34 **De Waele JJ**, Delrue L, Hoste EA, De Vos M, Duyck P, Colardyn FA. Extrapancreatic inflammation on abdominal computed tomography as an early predictor of disease severity in acute pancreatitis: evaluation of a new scoring system. *Pancreas* 2007; **34**: 185-190 [PMID: 17312456]
35 **Papachristou GI**, Muddana V, Yadav D, O'Connell M, Sanders MK, Slivka A, Whitcomb DC. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol* 2010; **105**: 435-441; quiz 442 [PMID: 19861954 DOI: 10.1038/ajg.2009.622]
36 **Singh VK**, Wu BU, Bollen TL, Repas K, Maurer R, Johannes RS, Mortele KJ, Conwell DL, Banks PA. A prospective evaluation of the bedside index for severity in acute pancreatitis score in assessing mortality and intermediate markers of severity in acute pancreatitis. *Am J Gastroenterol* 2009; **104**: 966-971 [PMID: 19293787 DOI: 10.1038/ajg.2009.28]
37 **Chatzicostas C**, Roussomoustakaki M, Vlachonikolis IG, Notas G, Mouzas I, Samonakis D, Kouroumalis EA. Comparison of Ranson, APACHE II and APACHE III scoring systems in acute pancreatitis. *Pancreas* 2002; **25**: 331-335 [PMID: 12409825]

P- Reviewer Mofleh IAA **S- Editor** Zhai HH **L- Editor** A
E- Editor Li JY