ISSN 1948-9358 (online)

# World Journal of *Diabetes*

*World J Diabetes* 2019 January 15; 10(1): 1-62

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

Contents

Monthly Volume 10 Number 1 January 15, 2019

## REVIEW



## MINIREVIEWS



## ORIGINAL ARTICLE

### Case Control Study



### Retrospective Cohort Study

*World Journal of Diabetes*
Volume 10 Number 1 January 15, 2019

# Contents



**NAME OF JOURNAL**
*World Journal of Diabetes*

**ISSN**
ISSN 1948-9358 (online)

**LAUNCH DATE**
June 15, 2010

**FREQUENCY**
Monthly

**EDITORS-IN-CHIEF**
Timothy R Koch

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/1948-9358/editorialboard.htm

**EDITORIAL OFFICE**
Jin-Lei Wang, Director

**PUBLICATION DATE**
January 15, 2019



**INSTRUCTIONS TO AUTHORS**
https://www.wjgnet.com/bpg/gerinfo/204

**GUIDELINES FOR ETHICS DOCUMENTS**
https://www.wjgnet.com/bpg/GerInfo/287

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**
https://www.wjgnet.com/bpg/gerinfo/240

**PUBLICATION MISCONDUCT**
https://www.wjgnet.com/bpg/gerinfo/208

**ARTICLE PROCESSING CHARGE**
https://www.wjgnet.com/bpg/gerinfo/242

**STEPS FOR SUBMITTING MANUSCRIPTS**
https://www.wjgnet.com/bpg/GerInfo/239

**ONLINE SUBMISSION**
https://www.f6publishing.com

World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

*World J Diabetes* 2019 January 15; 10(1): 57-62

DOI: 10.4239/wjd.v10.i1.57

ISSN 1948-9358 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Early *vs* late oral nutrition in patients with diabetic ketoacidosis admitted to a medical intensive care unit

Kirill Lipatov, Kevin K Kurian, Courtney Shaver, Heath D White, Shekhar Ghamande, Alejandro C Arroliga, Salim Surani

**ORCID number:** Kirill Lipatov (0000-0002-3481-7700); Kevin K Kurian (0000-0002-7867-1459); Courtney Shaver (0000-0002-9936-4597); Heath D White (0000-0003-1065-3681); Shekhar Ghamande (0000-0001-6924-9494); Alejandro C Arroliga (0000-0002-7245-2159); Salim Surani (0000-0001-7105-4266).

**Author contributions:** Lipatov K designed research; Lipatov K and Kurian KK performed research; Ghamande S, White HD and Arroliga AC revised methodology, Shaver C analyzed data; Lipatov K and Kurian KK wrote the paper; Ghamande S, White HD, Arroliga AC and Surani S revised and edited the paper.

**Institutional review board statement:** This study was reviewed and approved by the Institutional Review Board of Baylor Scott and White Health.

**Informed consent statement:** This was waived by the Institutional Review Board of Baylor Scott and White Health due to retrospective nature of the study.

**Conflict-of-interest statement:** All authors declare no conflicts of interest related to this article.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE statement and checked the manuscript accordingly.

**Kirill Lipatov, Kevin K Kurian, Heath D White, Shekhar Ghamande, Alejandro C Arroliga,** Department of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Baylor Scott and White Health, Temple, TX 76508, United States

**Courtney Shaver,** Department of Biostatistics, Baylor Scott and White Health, Temple, TX 76508, United States

**Salim Surani,** Department of Medicine, Texas A and M University, Corpus Christi, TX 78404, United States

**Corresponding author:** Shekhar Ghamande, MD, FAASM, FCCP, Clinical Associate Professor, Senior staff physician. Department of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Baylor Scott and White Health, 2401 S. 31st Street, Temple, TX 76508, United States. shekhar.ghamande@bswhealth.org
**Telephone:** +1-254-7249887
**Fax:** +1-254-7244539

## Abstract

### *BACKGROUND*

Diabetic ketoacidosis (DKA) has an associated mortality of 1% to 5%. Upon admission, patients require insulin infusion and close monitoring of electrolyte and blood sugar levels with subsequent transitioning to subcutaneous insulin and oral nutrition. No recommendations exist regarding the appropriate timing for initiation of oral nutrition.

### *AIM*

To assess short-term outcomes of oral nutrition initiated within 24 h of patients being admitted to a medical intensive care unit (MICU) for DKA.

### *METHODS*

A retrospective observational cohort study was conducted at a single academic medical center. The patient population consisted of adults admitted to the MICU with the diagnosis of DKA. Baseline characteristics and outcomes were compared between patients receiving oral nutrition within (early nutrition group) and after (late nutrition group) the first 24 h of admission. The primary outcome was 28-d mortality. Secondary outcomes included 90-d mortality, MICU and hospital lengths of stay (LOS), and time to resolution of DKA.

### *RESULTS*

There were 128 unique admissions to the MICU for DKA with 67 patients

**Manuscript source**: Invited manuscript

**Received:** August 29, 2018
**Peer-review started:** August 29, 2018
**First decision:** October 26, 2018
**Revised:** December 10, 2018
**Accepted:** December 29, 2018
**Article in press:** December 30, 2018
**Published online:** January 15, 2019

receiving early nutrition and 61 receiving late nutrition. The APACHE (Acute Physiology and Chronic Health Evaluation) IV mortality and LOS scores and DKA severity were similar between the groups. No difference in 28- or 90-d mortality was found. Early nutrition was associated with decreased hospital and MICU LOS but not with prolonged DKA resolution, anion gap closure, or greater rate of DKA complications.

*CONCLUSION*
In patients with DKA, early nutrition was associated with a shorter MICU and hospital LOS without increasing the rate of DKA complications.

**Key words:** Diabetes mellitus; Diabetic ketoacidosis; Diabetic complications; Acidosis; Ketosis; Critical care



**Core tip:** Considering variability of timing in reinstitution of oral diet in patients with diabetic ketoacidosis and lack of guideline recommendations, we investigated whether early oral nutrition is safe. We found that oral feeding instituted in the first 24 h appeared safe and resulted in shorter intensive care unit and hospital lengths of stay.

**Citation:** Lipatov K, Kurian KK, Shaver C, White HD, Ghamande S, Arroliga AC, Surani S. Early *vs* late oral nutrition in patients with diabetic ketoacidosis admitted to a medical intensive care unit. *World J Diabetes* 2019; 10(1): 57-62
**URL**: https://www.wjgnet.com/1948-9358/full/v10/i1/57.htm
**DOI**: https://dx.doi.org/10.4239/wjd.v10.i1.57

## INTRODUCTION

Diabetic ketoacidosis (DKA), a potentially dangerous complication of diabetes, has an associated mortality of 1% to 5%[1]. It causes severe insulin deficiency, electrolyte abnormalities, and dehydration, and often requires admission to an intensive care unit (ICU). Upon admission, patients require insulin infusion and close monitoring of electrolyte and blood sugar levels with subsequent transitioning to subcutaneous insulin and oral nutrition. No recommendations exist regarding the appropriate timing for initiation of oral nutrition. Potential disadvantages of oral nutrition administered within the first 24 h of admission to an ICU (early nutrition) include difficulty in blood sugar monitoring and insulin dosing, altered mental status predisposing to aspiration, and worsening of nausea, vomiting, and abdominal pain.

Due to these concerns and the lack of definitive recommendations, many institutions have varying protocols regarding the initiation of oral nutrition. Our study investigates the safety of early nutrition in adult DKA patients admitted to a medical ICU (MICU).

## MATERIALS AND METHODS

A retrospective observational cohort study was conducted at a single academic institution (Baylor Scott and White Heath, Temple, TX, United States) from December 2015 to January 2017. The study was approved by the local institutional review board and granted a waiver of informed consent. The study participants included all patients admitted to the MICU with the diagnosis of DKA. Only the first admission during the specified time frame for each patient was included. Exclusion criteria were age less than 18 years old, pregnancy, admission with DKA to a general ward or other type of ICU and leaving the hospital against medical advice. Data was collected by review of the electronic medical records. The time of first oral intake was labeled as the initiation of oral nutrition. The resolution of DKA was defined as achieving a serum glucose < 200 mg/dL and satisfying two of the following three criteria: pH ≥ 7.3, serum bicarbonate ≥ 15 meq/L, and anion gap ≤ 12. The anion gap was corrected using the value of the closest serum albumin measurement[1]. The severity of DKA was defined by arterial pH, serum bicarbonate, anion gap, and presence of altered

mentation according to the American Diabetes Association consensus statement[1]. Early nutrition was defined as the initiation of nutrition within the first 24 h of admission. Late nutrition was defined as the initiation of nutrition after the first 24 h of admission.

### Statistical analysis

Characteristics of the study sample were assessed using descriptive statistics. Frequencies and percentages were reported for categorical variables and means and standard deviations (or medians and ranges, if appropriate) were reported for continuous variables. Wilcoxon-Mann-Whitney tests were used to compare non-normally distributed continuous variables between groups. Chi-square and Fisher exact tests were used to compare categorical variables between groups. SAS version 9.4 and StatXact version 11 software was used to perform the statistical analysis. Statistical significance is expressed as $^{a}P < 0.05$, $^{b}P < 0.01$.

## RESULTS

There were 330 admissions to the MICU for a diagnosis of DKA. After excluding repeated hospitalizations and those satisfying exclusion criteria, the final cohort consisted of 128 unique patient admissions. Of those patients, 67 received early nutrition and 61 received late nutrition.

Baseline characteristics are described in Table 1. The patient population had a mean age of 47.3 (SD = 17.7) years, 50.8% were female and race was predominately white (65%). The severity of illness scores, Acute Physiology and Chronic Health Evaluation (APACHE) IV mortality and APACHE IV length of stay (LOS) scores, were 9.9 (SD = 18.5) and 4.6 (SD = 1.75), respectively. Comparing the early and late nutrition groups found no statistically significant difference between the groups in age, race, severity of illness based on APACHE IV mortality and LOS indices and DKA severity. A statistically significant difference between the early and late nutrition groups existed in terms of sex (37% *vs* 62% female, $P$=0.0047).

Outcomes are described in Table 2. The overall 28-d mortality was 3.1 % (4 patients) and 90-d mortality was 3.9% (5 patients). Mean hospital and MICU LOS were 6.16 (SD = 6.54) and 2.21(SD = 3.37) days respectively. There were no differences in the early and late nutrition groups in terms of mortality at 28 d (2.34% vs 0.78%, $P$=0.62) and at 90 d (2.36% *vs* 1.57%, $P$=1.00). Early nutrition group was not associated with longer mean time to anion gap closure ($P$=0.1642) or DKA resolution ($P$=0.1410). There was a significant decrease in the ICU LOS (1.38 *vs* 3.12, $P$=0.0002) and overall hospital LOS (4.16 *vs* 8.35 $P$=0.0001) in the early versus the late nutrition group.

Additionally, no significant difference in mean number of episodes of hyperkalemia (0.56 *vs* 0.43, $P$=0.37), hypoglycemia (0.97 *vs* 1.54, $P$=0.18), or severe acidosis (0.04 *vs* 0.20, $P$=0.18) existed between the early and late nutrition groups. However, fewer episodes of hypokalemia (1.18 *vs* 2.21, $P$=0.0022) and hypophosphatemia (0.73 *vs* 1.67, $P$=0.0052) occurred in the early nutrition group.

## DISCUSSION

We found that initiating oral nutrition in patients with DKA within the first 24 h of admission to the MICU was safe and decreases hospital and MICU LOS in our cohort of patients. Our 90-d mortality rate is consistent with prior studies[2]. The overall low mortality rate made the comparison between the early and late nutrition groups unlikely to reach statistical significance. Our analysis also demonstrated no difference in secondary outcomes, including time to normalization of the anion gap and resolution of DKA, and mean instances of hypoglycemia, hyperkalemia, and severe acidosis. However, a significant decrease in instances of hypokalemia and hypophosphatemia occurred. Finally, ICU and overall hospital LOS was significantly shorter for the early nutrition group.

DKA results in over 100000 admissions per year in the United States and has significant medical costs[1]. Mortality rates remain low between 1%-2.4%, with the cause of death in DKA patients often stemming from concurrent acute medical conditions and comorbidities[2,3]. The most appropriate location of care delivery for these patients is dictated by local practices, and recent studies report favorable outcomes with management on general hospital wards[4].

The role of nutrition in critical care cannot be overemphasized. The stress of critical illness places an enormous metabolic demand on the body[5]. Adequate nutrition has multiple advantages that include replenishing energy stores and protecting against

**Table 1 Baseline characteristics**

| | Entire cohort | Early nutrition | Late nutrition | *P* value |
|---|---|---|---|---|
| *n* | 128 | 67 | 61 | |
| Age, mean (yr) | 47.3 (SD = 17.7) | 45.7 (SD = 18.4) | 49.1 (SD = 16.9) | 0.1970 |
| Race (*n*) | | | | |
| African American | 25% (32) | 23.9% (16) | 26.2% (16) | 0.1950 |
| Caucasian | 65% (83) | 67.2% (45) | 62.3% (38) | |
| Other | 10% (13) | 8.9% (7) | 11.5% (7) | |
| Female sex (*n*) | 50.8% (65) | 37.3% (25) | 62% (38) | 0.0047 |
| DKA severity | | | | |
| Mild | 51 | 33 | 28 | 0.8997 |
| Moderate | 36 | 19 | 17 | |
| Severe | 31 | 15 | 16 | |
| Mean APACHE IV Mortality | 9.9 (SD = 18.5) | 6.0 (SD = 12.7) | 14.1 (SD = 22.5) | 0.1170 |
| Mean APACHE IV LOS | 4.6 (SD = 1.8) | 4.2 (SD = 1.5) | 4.8 (SD = 2.0) | 0.8400 |

APACHE: Acute Physiology and Chronic Health Evaluation; LOS: Length of stay; SD: Standard deviation.

ICU- and hospital-acquired complications[5]. However, the optimal nutritional components in the ICU remain controversial, and new evidence challenges the intuitive tendency to supplement critically ill patients with high-calorie nutrition[6].

Increasing evidence suggests that ketone bodies play a role in hunger control through a yet an unknown process[7]. This facilitated introduction of the ketogenic diet as an effective modality of weight loss. Additionally, elevated free fatty acid (FFA) levels, which are often observed in starvation states, have been shown to reduce food intake by acting on specific hypothalamic neurons[7]. As it pertains specifically to DKA, a higher degree of ketonemia and elevated circulating FFA could suppress hunger and potentially explains the delay in oral intake when initiated upon the patient's demand. In our study, beta hydroxybutyrate (BHB) and FFA levels were not measured. Varying degrees of of ketonemia in the study groups may have contributed to the difference in LOS and time to resolution of DKA. However, we found no statistical difference between the groups in either the level of severity of DKA in both groups.

The potential for certain types of food to exacerbate ketosis may lead many physicians to withhold oral nutrition during DKA. Although reducing patients' initial oral intake of a low- carbohydrate diet might promote ketogenesis, the magnitude of its effect is low compared with the ketosis caused by uncontrolled diabetes. The maximum level of ketonemia achieved by a physiologic ketosis due to diet is 7-8 mmol/L as compared with >25 mmol/L found in DKA[7]. The dietary augmentation of ketosis likely becomes even less significant with the initiation of insulin treatment and carbohydrate delivery to the cells.

In our institution, every patient diagnosed with DKA is admitted to the MICU as a result of level of clinical care related to a continuous insulin infusion. This practice provided the opportunity to assess the safety of early nutrition in all DKA patients. Despite the widespread use of DKA severity for the purposes of deciding the appropriate level of care, the direct link between estimated severity and outcomes has not been established. Nevertheless, individual components of severity assessment, such as mental status and pH, have been associated with worsened outcomes. Altered mental status in particular could be a manifestation of a more severe underlying condition preventing patients from early nutrition and disproportionately worsening outcomes in the late nutrition group. The DKA severity based on available measurements of initial bicarbonate concentration, pH, and GCS did not differ between the groups in our study. Additionally, there was no statistically significant differences between the groups in the severity of illness represented by APACHE IV mortality and LOS scores.

Patients with DKA often have abdominal pain, nausea, and vomiting, ultimately leading to oral-intake intolerance. Consensus guidelines associate patients' readiness to eat with resolution of ketoacidosis[1]. However, it is possible that when oral nutrition was administered on demand in our study, patients having more severe DKA and worse symptoms on presentation would end up in the late oral nutrition group. This may have implications in further studies investigating any benefit of mandatory early oral nutrition in DKA where randomization would be a key to

**Table 2 Outcomes**

| | Early nutrition | Late nutrition | *P* value |
|---|---|---|---|
| Mean time to AG normalization (h) | 11.7 (SD = 15.6) | 20.0 (SD = 40.7) | 0.1642 |
| Mean time to DKA resolution (h) | 15.4 (SD = 18.8) | 19.6 (SD = 32.6) | 0.1410 |
| Mortality at 28 d (*n*) | 2.34% (3) | 0.78 (1) | 0.6300 |
| Mortality at 90 d (*n*) | 2.34% (3) | 1.57% (2) | 1.0000 |
| Hospital LOS (d) | 4.16 (SD = 2.63) | 8.35 (SD = 8.85) | 0.0001 |
| ICU LOS (d) | 1.38 (SD = 1.17) | 3.12 (SD = 4.58) | 0.0002 |
| Mean number of complication occurrences: | | | |
| Hypoglycemia | 0.97 (SD = 1.49) | 1.54 (SD = 2.47) | 0.1804 |
| Hypokalemia | 1.18 (SD = 1.4) | 2.21 (SD = 2.1) | 0.0022 |
| Hyperkalemia | 0.43 (SD = 0.72) | 0.56 (SD = 0.89) | 0.3706 |
| Hypophosphatemia | 0.73 (SD = 0.9) | 1.67 (SD = 2.4) | 0.0052 |
| Severe acidosis | 0.04 (SD = 0.21) | 0.20 (SD = 0.73) | 0.1356 |

DKA: Diabetic ketoacidosis; ICU: Intensive care unit; LOS: Length of stay; SD: Standard deviation.

ensure similar severity of ketoacidosis in the investigation groups.

To control for possible delay in meeting the strict DKA resolution criteria, we separately analyzed the time to normalization of anion gap as this likely represents cessation of ketosis with no change in outcomes. Both of these results were consistent with prior studies[8]. While patients starting oral nutrition after the first 24 h of admission had longer time to DKA resolution and anion gap normalization, neither was statistically significant. Notably, both the time to AG closure and to resolution of acidosis in the late nutrition group were less than 24 h. It is possible that the delay in oral diet resumption may have contributed to delayed transfer of these patients out of the MICU.

Our study confirmed the existing variability among physicians regarding the optimal timing of initiating oral nutrition in patients DKA. Although the study population size was likely too small to demonstrate a significant difference in the mortality, oral nutrition provided to DKA patients on demand appears to be safe. Early reinstitution of oral nutrition did not result in worsening of DKA complications and was associated with improvement in hypokalemia and hypophosphatemia. Finally, on-demand oral nutrition reinitiated within the first 24 h of admission has the potential to shorten ICU and overall hospital LOS.

## ARTICLE HIGHLIGHTS

### *Research background*

Diabetic ketoacidosis (DKA) is a common reason for hospitalization in patients with diabetes. It results in significant morbidity, mortality, and financial burden. Research and quality improvement efforts have been put forth to investigate the triggers and risk factors associated with ketoacidosis to prevent initial episode of DKA and minimize recurrence. In the meantime, the standard of care in management of DKA has been more clearly defined attention to serum glucose levels, electrolytes, acidosis and diligent evaluation for and treatment of the underlying etiology. Together, these advances resulted in significant reduction of mortality associated with DKA over the years. Nevertheless, many aspects of care for DKA patients remains unanswered, including severity stratification and appropriate level of care. Many institutions continue to accept patients with DKA to the intensive care unit (ICU) due to frequent electrolyte and glucose monitoring and meticulous insulin titration. Minimizing financial burden and hospital acquired complications associated with frequent and prolonged ICU stay is the subject of current and future investigations.

### *Research motivation*

Tolerance of oral diet is regarded as a marker for resolution of ketoacidosis in DKA patients. Its administration is often postponed until biochemical confirmation of the resolution of ketoacidosis due to fear of unpredictable glucose and electrolyte changes. We hypothesized that allowance of on demand oral nutrition in DKA patients is safe and has a potential to decrease the length of hospitalization.

### *Research objectives*

We aim to compare the mortality, rate of complications, and length of stay between DKA patients receiving oral nutrition before and after the first 24 h of ICU admission.

### Research methods
Retrospective data collection was conducted establishing the demographics, initial biochemical characteristics, and outcomes of patients admitted to our single academic medical center. Outcomes included common complications of DKA, 28- and 90-d mortality, and length of ICU and hospital stay. Bivariate analysis was then performed comparing these variables between the two subgroups defined by the timing of their first oral intake.

### Research results
The timing of oral nutrition in DKA patients was heterogenous between different care teams with 52.3% of patients restarting oral intake in the first day of admission. This did not result in increased mortality (2.34% *vs* 0.78%, $P$=0.62) or rate of complications such as hyperkalemia (0.56 *vs* 0.43, $P$=0.37), hypoglycemia (0.97 *vs* 1.54, $P$=0.18), or severe acidosis (0.04 *vs* 0.20, $P$=0.18). Despite having similar overall illness severity and severity of DKA itself, the DKA patients who received oral nutrition in the first 24 h of their admission had a shorter ICU (1.38 *vs* 3.12, $P$= 0.0002) and (4.16 *vs* 8.35 $P$=0.0001) hospital stay.

### Research conclusions
Early oral nutrition (defined as oral intake in the first 24 h) administered on demand in patents admitted to ICU with DKA has a potential to safely reduce the length of stay.

### Research perspectives
The study introduces the possibility of early oral nutrition in DKA to improve the length of stay. Further prospective randomized investigation is necessary to validate this finding.

## REFERENCES


1 **Kitabchi AE**, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; **32**: 1335-1343 [PMID: 19564476 DOI: 10.2337/dc09-9032]
2 **Venkatesh B**, Pilcher D, Prins J, Bellomo R, Morgan TJ, Bailey M. Incidence and outcome of adults with diabetic ketoacidosis admitted to ICUs in Australia and New Zealand. *Crit Care* 2015; **19**: 451 [PMID: 26715333 DOI: 10.1186/s13054-015-1171-7]
3 **Barski L**, Nevzorov R, Rabaev E, Jotkowitz A, Harman-Boehm I, Zektser M, Zeller L, Shleyfer E, Almog Y. Diabetic ketoacidosis: clinical characteristics, precipitating factors and outcomes of care. *Isr Med Assoc J* 2012; **14**: 299-303 [PMID: 22799061]
4 **Malone ML**, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. *J Am Geriatr Soc* 1992; **40**: 1100-1104 [PMID: 1401693 DOI: 10.1111/j.1532-5415.1992.tb01797.x]
5 **Desai SV**, McClave SA, Rice TW. Nutrition in the ICU: an evidence-based approach. *Chest* 2014; **145**: 1148-1157 [PMID: 24798840 DOI: 10.1378/chest.13-1158]
6 **Rugeles S**, Villarraga-Angulo LG, Ariza-Gutiérrez A, Chaverra-Kornerup S, Lasalvia P, Rosselli D. High-protein hypocaloric vs normocaloric enteral nutrition in critically ill patients: A randomized clinical trial. *J Crit Care* 2016; **35**: 110-114 [PMID: 27481744 DOI: 10.1016/j.jcrc.2016.05.004]
7 **Paoli A**. Ketogenic diet for obesity: friend or foe? *Int J Environ Res Public Health* 2014; **11**: 2092-2107 [PMID: 24557522 DOI: 10.3390/ijerph110202092]
8 **Andrade-Castellanos CA**, Colunga-Lozano LE, Delgado-Figueroa N, Gonzalez-Padilla DA. Subcutaneous rapid-acting insulin analogues for diabetic ketoacidosis. *Cochrane Database Syst Rev* 2016; CD011281 [PMID: 26798030 DOI: 10.1002/14651858.CD011281.pub2]


**P- Reviewer:** Tzamaloukas AH
**S- Editor:** Ma RY **L- Editor:** A **E- Editor:** Wu YXJ

Published By Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk:https://www.f6publishing.com/helpdesk
https://www.wjgnet.com