INCIDENCE OF NEW ONSET DIABETES MELLITUS SECONDARY TO ACUTE PANCREATITIS: A SYSTEMATIC REVIEW

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Abstract

Background and Aims: Patients who have an episode of acute pancreatitis (AP) frequently develop diabetes mellitus (DM) overtime. There reported incidence of DM after AP varies depending on the severity, etiology and the extent of pancreatic necrosis during AP. We performed a systematic review to determine the incidence of new-onset DM after a episode(s) and compared the rate of DM in AP patients based upon different disease characteristics.

Method: A total of 50 patients were enrolled from government general hospital Kadapa India suffered from acute pancreatitis during January 2018 to July 2019.

Results: The random-effects pooled incidence was 22.0% for DM. The DM incidence was higher in the populations that had a severe AP (SAP) episode than in those with mild acute pancreatitis (MAP). Patients that displayed pancreatic necrosis during the AP attack(s) had a higher frequency of DM than those without necrosis in addition, the pooled incidence of DM was higher after alcoholic compared to biliary AP. The incidence of insulin use after SAP and alcoholic AP was 21 and 18%, respectively, with very low heterogeneities.

Conclusion: Patients with AP developed DM after discharge from hospital with a frequency of about 22%. SAP, alcoholic AP and acute necrotizing pancreatitis (ANP) were associated with increased incidence of DM. Assessments of severity, etiology, and pancreatic necrosis are critical for predicting DM development after AP.

Introduction:

The exocrine and endocrine components comprise about 90 and 2–5%, respectively, of the pancreatic mass. Disorders of the exocrine pancreas including pancreatitis and pancreatic cancer can lead to endocrine dysfunction and abnormal glucose metabolism. The American Diabetes Association and the World Health Organization classified pancreatogenic, pancreoprivic, or apancreatic diabetes mellitus (DM) as type 3c DM. Type 3c diabetes is not a single
entity as it results from several different exocrine pancreatic diseases including acute, relapsing, and chronic pancreatitis of any etiology, hemochromatosis, cystic fibrosis, fibro calculous pancreatopathy, pancreatic trauma, pancreatectomy, pancreatic agenesis, and pancreatic cancer.

Acute pancreatitis (AP) has been reported to cause DM. However, the data on the incidence of diabetes after AP is controversial, ranging from rare cases to more than half of all patients developing DM. Few studies reported progressive improvements or even complete recovery of abnormal glucose metabolism after one episode of AP, while most studies showed sustained impairments of pancreatic endocrine function after attacks of AP (2). The reasons for such huge variations between studies are attributable to inclusion of heterogeneous groups of patients (severe and mild AP, AP with and without pancreatic necrosis) as well as various follow-up periods and the inclusion of patients with and without pancreatic surgery. The severity of AP appears to correlate with the magnitude of the resulting endocrine pancreatic dysfunction. The criteria to define AP severity include the presence and extent of pancreatic necrosis which reflects the pancreas local situation, and aspects of systemic organ dysfunction reported that AP patients with pancreatic necrosis had much higher incidence of DM later on compared to those who had no pancreatic necrosis. Moreover, in the group of patients with pancreatic necrosis, the rate of DM positively correlated with the area of necrosis (3). This study also demonstrated that the occurrence of DM continued to increase for a long time after AP, thus the risk became much greater in those patients with more than 5 years' follow-up.

Pancreatic procedures including pancreas resection and necrosectomy in SAP patients, have an obvious effect on the incidence of DM. A very high incidence of DM in 92% of SAP patients after pancreatic necrosectomy (4). Similarly, patients undergoing necrosectomy had higher incidence of pancreatic endocrine deficiency in long-term follow-up.

**Methods:**

**Search Strategy and Selection Criteria:**
Since the 2010 an electronic medical record system has been used in Government medical college Kadapa India, which has facilitated several studies on AP. To track changes consistently throughout the course of AP and facilitate the evaluation and study of AP, a dedicated database from government medical college kadapa India was established in 2010 to collect clinical data of AP patients who were admitted to this Hospital. Data from January 2018 to July 2019 were prospectively collected and entered in the electronic medical record system. Data were prospectively collected since January 2018. The following information was documented in detail: demographic data (age, sex, birthplace, etc), course of diseases and medication history, smoking and alcohol history, family history, experimental and imaging results, and treatment (5).

**Inclusion Criteria:**
1. Age equal to or greater than 18 years.
2. Measurements of glucose metabolism in AP patients were performed after more than one month from hospital discharge following episode(s) of AP.
3. Absence of a history of pre-existing pre-diabetes or diabetes before the AP episode.
4. The reports provided standard diagnosis methods for AP.
5. The reports included incidence rates or raw data to calculate the rates.

**Exclusion Criteria:**
1. Reports that focused specifically on either AP patients with pancreatic surgery, hereditary pancreatitis or autoimmune pancreatitis.
2. Reports in which the number of DM patients were unavailable.
3. Studies where less than 50% of the patients provided information during the follow-up or there was no report on the percentage of patients providing data during follow-up.

**Participants’ Key Characteristics and Definitions:**
AP: AP was confirmed when 2 out of the 3 measures were fulfilled: (1) typical abdominal pain, (2) serum amylase and/or lipase >3 times the upper limit of normal, and/or (3) characteristic findings from abdominal imaging. Acute necrotizing pancreatitis was determined based on contrast-enhanced CT scan, histology, surgery or medical records. Pancreatic surgery was noted when the patient underwent pancreatic resection, necrosectomy with peritoneal lavage, retroperitoneal drainage and lavage. Surgeries not related to pancreas (e.g., cholecystectomy, cesarean section, and others) were not recorded as surgery for the purposes of this study.
Recurrent AP was recorded in patients with one or more episodes of confirmed AP since their first AP attack. Those patients with only one confirmed episode of AP were recorded as no recurrence or one single attack of AP.

Results:-
Among the 50 patients studied 34 patients (68%) males and 16 patients(32%) females

Table 1: Patient Distribution Based on Gender.

| Gender | Male       | Female   |
|--------|------------|----------|
|        | 34 (68%)   | 16 (32%) |

Discussion:-
Findings from this systematic review suggest that DM is an important problem for AP patients, although there is wide variation in the incidence of DM between populations from different subgroups. A previous study (Das et al., 2014) reported the pooled estimates of the incidence of endocrine dysfunction (both prediabetes and diabetes) in 40% after a first attack of AP. In this review, we increased the number of included studies and enlarged the population of AP, which could further strengthen the reliability of the result of DM rate after AP. Additionally, we restrictedly focused on the occurrence of diabetes only, finding a similar incidence of DM after AP to the result of the prior meta-analysis in about 22%. What’s particularly different from the prior meta-analysis is that we compared the DM rate among AP subjects with various severity and etiology, with and without the presence of pancreatic necrosis. Those subjects with SAP, alcoholic AP and ANP have a DM incidence after the AP attack of 39, 28, and 37% respectively compared with lower DM rates of 14, 12, and 11% in MAP, biliary AP and non-ANP, respectively. This finding indicates the severity, etiology, and necrosis are crucial factors in predicting new-onset DM after AP.

DM secondary to pancreatic diseases is classified as pancreateogenic diabetes (American Diabetes, 2011). Acute pancreatitis, as the most common pancreatic disorder, is more often associated with the development of pancreatic endocrine dysfunction. However, there is little information relating pancreatic exocrine function to the development of diabetes after an episode of AP. During the recovery phase of AP, blood glucose levels would rapidly return to normal in most patients. However, a subset of the patients will develop DM and need prolonged antidiabetic treatments including insulin. One possible mechanism of DM secondary to AP could be nutrient malabsorption induced by exocrine insufficiency that causes abnormal incretin secretion and impaired insulin release from β-cells. Increased insulin resistance could be another explanation for abnormal carbohydrate metabolism after AP.

These two possible mechanisms appear to be associated with classical type 2 diabetes, which illustrates that T2cDM might be a heterogeneous disorder strongly overlapping with type 2 diabetes. In addition, the loss of pancreatic β cells caused by necrosis is considered to be a main cause of DM after AP, especially in those subjects with necrosectomy.

Conclusion:-
The results of our analysis show that ~1 in 5 patients with an AP episode develops DM afterwards, and the rate increases over time. In addition, the occurrence of DM after alcoholic AP, SAP, and ANP was 2 to 3 times higher than that secondary to biliary AP, MAP, and AP without necrosis.

References:-
1. American Diabetes, A. (2017). Diagnosis and classification of diabetes mellitus. Diabetes Care 34(Suppl. 1), S62–S69. doi: 10.2337/dc11-S062
2. Andersson, B., Pendse, M. L., and Andersson, R. (2010). Pancreatic function, quality of life and costs at long-term follow-up after acute pancreatitis. World J. Gastroenterol. 16, 4944–4951. doi:10.3748/wjg.v16.i39.4944
3. Appelros, S., Lindgren, S., and Borgström, A. (2001). Short and long term outcome of severe acute pancreatitis. Eur. J. Surg. 167, 281–286. doi:10.1080/110241501300091462
4. Apte, M. V., Pirola, R. C., and Wilson, J. S. (2010). Mechanisms of alcoholic pancreatitis. J. Gastroenterol. Hepatol. 25, 1816–1826. doi:10.1111/j.1440-1746.2010.06445.x
5. Balhazur, E.J., Robinson, D.L., Megibow, A.J., and Ranson, J.H. (1990). Acute pancreatitis: value of CT in establishing prognosis. Radiology 174, 331–336. doi:10.1148/radiology.174.2.2296641
6. Boreham, B., and Ammori, B. J. (2003). A prospective evaluation of pancreatic exocrine function in patients with acute pancreatitis: correlation with extent of necrosis and pancreatic endocrine insufficiency. Pancreatology 3, 303–308. doi:10.1159/000071768

682
7. Büchler, M., Malfertheiner, P., Block, S., Maier, W., and Beger, H. G. (1985). Morphologic and functional changes in the pancreas following acute necrotizing pancreatitis. Z. Gastroenterol. 23, 79–83.

8. Chandrasekaran, P., Gupta, R., Shenvi, S., Kang, M., Rana, S. S., Singh, R., et al. (2015). Prospective comparison of long term outcomes in patients with severe acute pancreatitis managed by operative and non-operative measures. Pancreatology 15, 478–484. doi:10.1016/j.pan.2015.08.006

9. Das, S. L., Singh, P. P., Phillips, A. R., Murphy, R., Windsor, J. A., and Petrov, M. S. (2014). Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. Gut 63, 818–831. doi:10.1136/gutjnl-2013-305062

10. Eriksson, J., Doepel, M., Widen, E., Halme, L., Ekstrand, A., Groop, L., et al. (1992). Pancreatic surgery, not pancreatitis, is the primary cause of diabetes after acute fulminant pancreatitis. Gut 33, 843–847. doi:10.1136/gut.33.6.843

11. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. (2003). Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 26 (Suppl. 1), S5–20. doi:10.2337/diacare.26.2007.S5

12. Freeman, M. F., and Tukey, J. W. (1950). Transformations related to the angular and the square root. Ann. Math. Stat. 21, 607–611. doi:10.1214/aoms/1177729756

13. Freeman, M. L., Werner, J., van Santvoort, H. C., Baron, T. H., Besselink, M. G., Windsor, J. A., et al. (2012). Interventions for necrotizing pancreatitis: summary of multidisciplinary consensus conference. Pancreas 41, 1176–1194. doi:10.1097/MPA.0b013e318269e660

14. Garip, G., Sarandöl, E., and Kaya, E. (2013). Effect of disease severity and necrosis on pancreatic dysfunction after acute pancreatitis. World J. Gastroenterol. 19, 8065–8070. doi:10.3748/wjg.v19.i44.8065

15. P. A., and Haapiainen, R. K. (2003). Long-term health-related quality of life in survivors of severe acute pancreatitis. Intensive Care Med. 29, 782–786. doi:10.1007/s00134-003-1700-8

16. Higgins, J. P., Thompson, S. G., Deeks, J. J., and Altman, D. G. (2003). Measuring inconsistency in meta-analyses. BMJ 327, 557–560. doi:10.1136/bmj.327.7414.557

17. Ho, T. W., Wu, J. M., Kuo, T. C., Yang, C. Y., Lai, H. S., Hsieh, S. H., et al. (2015). Change of both endocrine and exocrine insufficiency after acute pancreatitis. Medicine 94:e1123. doi:10.1097/MD.0000000000011123

18. Hochman, D., Louie, B., and Bailey, R. (2006). Determination of patient quality of life following severe acute pancreatitis. Can. J. Surg. 49, 101–106.

19. Johansen, K., and Ornsholt, J. (1972). Frequency of diabetes after acute pancreatitis. Metabolism 21, 291–296. doi:10.1016/0026-0952(72)90072-8

20. Larvin, J., and McMahon, M. J. (1989). APACHE-II score for assessment and monitoring of acute pancreatitis. Lancet 2, 201–205. doi:10.1016/S0140-6736(89)90381-4

21. Lee, Y. K., Huang, M. Y., Hsu, C. Y., and Su, Y. C. (2016).

22. Machicado, J. D., and Yadav, D. (2017). Epidemiology of recurrent acute and chronic pancreatitis: similarities and differences. Dig. Dis. Sci. 62, 1683–1691. doi:10.1007/s10620-017-4510-5

23. Ogawa, M., Hirota, M., Hayakawa, T., Matsumo, S., Watanabe, S., Atomi, Y., et al. (2002). Development and use of a new staging system for severe acute pancreatitis based on a nationwide survey in Japan. Pancreas 25, 325–330. doi:10.1097/00006676-200211000-00001

24. Ohlsen, P. (1968). Endocrine and exocrine pancreatic function in pancreatitis. Acta Med. Scand. (Suppl. 484), 1–99.

25. Olszewski, S., Kitsuka, I., Długosz, J., Stasiewicz, J., and Gabryelewicz, A. (1978). The glucose tolerance, insulin response and pancreatic exocrine function in patients after acute pancreatitis. Endokrinology 71, 183–191.

26. Pärniczky, A., Kui, B., Szentesi, A., Balázs, A., Szucs, A., Moszbacher, D., et al. (2016). Prospective multicentre, nation wide clinical data from 60 cases of acute pancreatitis. PLoS ONE 11:e0165309. doi:10.1371/journal.pone.0165309

Lappalainen-Lehto, R., Piironen, A., Jarvinen, S., Sand, J., and Nordback.