

# Design Flaws in the Study of Distinguishing Diabetes Associated With Chronic Pancreatitis and Type 2 Diabetes Mellitus

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We read with great interest the recent published study on distinguishing diabetes mellitus associated with chronic pancreatitis (CP-DM) and type 2 diabetes mellitus (T2DM) based on the genetic risk score (1), and we found that the study design should be improved.

First, the author mistook patients with diabetes mellitus (DM) and recurrent acute pancreatitis (RAP) for CP-DM. In fact, RAP is a disease different from chronic pancreatitis (CP). RAP is defined as a syndrome of multiple distinct acute inflammatory response originated from the pancreas in individuals with 2 or more episodes of acute pancreatitis, separated by at least 3 months (2). It is reported that RAP was featured with increasing frequency of monocyte chemoattractant protein 1 G allele and cystic fibrosis transmembrane conductance regulator gene mutation, whereas CP had no statistical association with these gene mutations (3). A meta-analysis revealed that 36% RAP could progress to CP (4). Thus, patients with DM and RAP should not be enrolled in the CP-DM group because they may have different mechanisms for DM.

Second, patient selection bias could lead to the inaccuracy of this study. Patients with CP were selected from the North American Pancreatitis Study 2 (NAPS2). There were 1,195 patients with CP and 569 patients with RAP in NAPS2 studies published in 2016 (5) in which 930 patients with CP and 579 patients with RAP had undergone genome-wide genotyping (6). However, only 734 patients with CP and 438 patients with RAP were enrolled in the present study. Why were not all patients with CP undergone genome-wide genotyping included in the present study? Was there patient selection bias? What is more? Follow-up data for patients were never reported in series studies involving NAPS2, and patients with pancreatic cancer were not excluded. For most researches concerning CP, patients diagnosed with pancreatic cancer within 2 years after CP diagnosis were excluded, and some studies even used 5 years to avoid misdiagnosis. Therefore, patient selection bias may exist in this study.

Third, the conclusion that “CP-DM may be a subtype of T2DM” is inappropriate. CP-DM is considered as DM caused by CP in this study, which is actually post-pancreatitis diabetes mellitus (PPDM). PPDM belongs to diabetes of the exocrine pancreas, which is independent from and cannot coexist with other types of diabetes (7). Moreover, not all cases of diabetes in patients with CP should be regarded as PPDM. Thus, the CP-DM group is actually composed of patients with PPDM and patients with T2DM as a comorbidity of CP.

Mix of PPDM and T2DM in the CP-DM group weakened the difference in the genetic risk score between CP-DM and T2DM. Although the author tried to exclude patients with T2DM in the CP-DM group by removing patients with preexisting diabetes (diagnosed 2 years before CP), patients with family history, or overweight or obese patients from the CP-DM group separately, the analysis was insufficient. Patients with the aforementioned features should be excluded simultaneously in analysis.

In conclusion, the aforementioned study design flaws may cause inaccuracy of the results and conclusion.

## CONFLICTS OF INTEREST

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