THE ENDOCRINE SOCIETY

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Risk of Pancreatitis Associated with Certain Diabetes Medications
An Endocrine Society Statement
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A recent study by Singh et al.[(1)], published online in JAMA Internal Medicine on February 25, 2013, suggests that treatment of type 2 diabetes with sitagliptin (Januvia®) – a DPP-4 inhibitor - or exenatide (Byetta®) – a GLP-1 analog - may be associated with an increased risk of developing acute pancreatitis severe enough to require hospitalization, a condition with potentially significant morbidity. Medications such as sitagliptin and exenatide are members of a recently-developed class of glucose-lowering drugs whose mechanism of action is related to a group of hormones normally produced in the GI tract (referred to as incretins) which function to reduce blood sugar.

Singh et al. examined a large administrative U.S. database of 1.1 million persons with Type 2 diabetes mellitus and found a two-fold relative increased risk of acute pancreatitis, after adjusting for confounders and metformin use, in those taking sitagliptin or exenatide as compared with those diabetics not using these medications. However, the crude data indicate that the absolute incidence of acute pancreatitis is quite low in both groups: 2.7 per thousand in the control group not taking the medications as compared to 4.1 per thousand in those on the medications. It should be kept in mind that the patients in this study had other risk factors for pancreatitis and that diabetes itself is associated with an almost two-fold increase in the incidence of acute pancreatitis.

All retrospective database analyses, including that by Singh et al., suffer from common flaws: inability to verify the diagnosis and inability to include data from individual medical records in order to adjust for important confounding factors. In particular, the individual medical records contain key relevant quantitative information that is often not coded into an administrative database. For example, an administrative database like that used by Singh et al. may include a qualitative diagnosis of obesity rather than a quantitative estimate of BMI, as well as a qualitative diagnosis of alcohol abuse rather than a quantitative estimate of alcohol consumption. Similarly, important quantitative information about glycemic control (HbA1C and frequency of hypoglycemia) is not included in Singh's study. Such quantitative information is extremely important in the delicate process of adjusting crude statistical results for confounding clinical factors. Also of concern is that Singh's statistical analysis did not adjust for use of anti-diabetic medications other than metformin nor for duration and severity of diabetes.

Finally, clinical application of these findings would require an assessment not only of hazards of a particular treatment paradigm but also the potential benefits of such a program. Estimation of risk/benefit for one treatment protocol can then be compared with risk/benefit for alternatives in order to select appropriate treatment for each individual patient.

An important but unanswered question is whether or not the morbidity and mortality from incretin-associated pancreatitis is the same as that of other causes of pancreatitis. In particular, it cannot yet be established whether incretin-associated pancreatitis would be associated with an increase incidence of pancreatic cancer similar to that seen in some other causes of acute pancreatitis. Resolving the latter issue will require large scale, prospective, randomized, controlled trials, some of which are on-going. These

studies may also help elucidate the conflict between Singh's finding of increased incidence of acute pancreatitis with these drugs and the four recent retrospective database analyses and 1 meta-analysis cited in Singh's paper which found no such association.

The Endocrine Society believes that patients should be made aware of this potential side effect of incretins and the symptoms of pancreatitis. In addition, we recommend that diabetes care providers consider this possible adverse effect as they balance risk and benefit of particular treatment paradigms, especially in patients with other risk factors for pancreatitis.

The Endocrine Society encourages patients with concerns about this report or about their diabetes treatment to contact their diabetes care provider. Many classes of medications are available that, when combined with healthy eating and physical activity, help achieve and maintain glucose control in type 2 diabetes.

In addition, The Endocrine Society discourages patients with diabetes from stopping medications on their own, without consulting their health care provider, since this can lead to higher levels of blood glucose that may cause serious short-term health problems and, if prolonged, could increase the risk of long term diabetes-related complications.

(1) Singh, S, Chang H-Y, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike Peptide 1-Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Diabetes Mellitus. JAMA Internal Medicine, published online February 25, 2013. DOI: 10.1001/jamainternmed.2013.2720.