Diabetes or Diabetes Drugs: A Cause for Acute Pancreatitis

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1. Introduction

About a decade ago, a question was raised about glyburide, a widely used sulfonylurea, as a possible cause for acute pancreatitis (Blomgren). Since then, several systemic reviews reveal the incidence of acute pancreatitis in patients with type 2 diabetes 1.5 to 3-fold increase risk compared to non-diabetic subjects in each of 3 large health data bases (Noel, Garg, Girman). Five years after the concern was raised about glyburide and soon after the first of the incretin based, exenatide, had gained a significant market share, reports of pancreatitis again began to surface. This was followed by a similar concern when the first in class of the next new class of diabetes agents, the dipeptyl depeditidase-4 inhibitor (DPP-4 inhibitor), sitagliptin had achieved a significant market share. Exenatide is a glucagon like peptide one (GLP-1) agonist and DPP-4 inhibitors increase to action of endogenous GLP-1 by slowing the degradation of endogenous GLP-1, as well of other gut derived hormones, so a common etiology was implied. Examination of two different insurance data bases, again reveal no real increase over other agents used to treat type 2 diabetes. Review of the incidence of acute pancreatitis from the adverse event data from the clinical trials of the two GLP-1 agonists and the three DPP-4 inhibitors available currently on the US market reveals similar rates of acute pancreatitis with each agent and with the comparators during blinded clinical trials, providing more evidence that it is the disease state, not the agent causing the increase in incidence.

This chapter will cover the wide variety of drugs that have been associated with acute pancreatitis as well as the studies that substantiate increase in acute pancreatitis in type 2 diabetes. The rate of acute pancreatits in incretin based agents and other agents as mentioned above seems the same as the rate in the population of type 2 diabetic as a whole. The rates of acute pancreatitis from clinical trial data of the five agents available in the US and the comparators afford the best prospective data on this subject.

2. Background

In 2002 Blomgren reported the association of acute pancreatitis with obesity and glyburide therapy in type 2 diabetic subjects (Blomgren). The first of a new class of incretin-mimetic agents, exendatide (Byetta) was introduced for the treatment of diabetes in 2005 and by 2006 the first report of acute pancreatitis was made by Denker (Denker) and soon others began to immerge. In 2007, the first of the dipeptyl depeditidase-4 (DPP-4) inhibitors (Januvia)

entered the US market and by 2009 there were 88 reports of acute pancreatitis in patients treated with this agent (FDA). These agents shared a common pathway in improving metabolic control in diabetes by increasing the occupancy of GLP-1 receptors. The incretin-mimetic agents are synthetic agonists for the gut hormone, glucagon like peptide 1 (GLP-1)receptors, and the DPP-4 inhibitors extend the action of endogenous incretin hormones including GLP-1 and also gastric inhibitory peptide (GIP) as well other gut derived hormones by delaying their degradation. Perhaps, the fact that the pathway involved with each of these new types of agents has the potential to affect the gastrointestinal tract, there was concern that this might be responsible for precipitating acute pancreatitis.

Acute pancreatitis in the general population appears to be increasing in Western countries with 70–80% attributed to alcohol or gallstones but at least 20% has no clear etiology. Diabetic comorbidities of hypertriglyceridemia and obesity may increase their risk for acute pancreatitis. New etiologies continue to be described as evidenced by the report by Frulloni and colleagues of an autoimmune pancreatitis identified by a novel antibody directed at an epitope homologous to a protein from *Helicobacter pylori* (Frulloni). Type 2 diabetes is associated with obesity and hyperlipidemia, each of which has been considered a risk factor for pancreatitis (Trivedi, Blomgren). It is estimated that 2-5% of cases of acute pancreatitis are drug-induced. Many drugs have been associated with acute pancreatitis, yet these include drugs from varied classes, with very different modes of action and metabolic degradation pathways without any uniform explanation. Only alcohol, which both stimulates exocrine pancreatic secretion and contraction of the outlet sphincter (of Oddi) can be explained. In a 2005 review, Trivedi reported that, of the top 100 prescribed drugs in the United States, 44 have been associated with acute pancreatitis (Trivedi). These include over-the-counter agents such as acetaminophen, common antibiotics such as trimethoprim/sulfamethoxazole and erythromycin, commonly used agents such as furosamide, glucocortiods, statins, angiotensin conversion inhibitors as well as agents used to treat human immunodeficiency virus acquired immunodeficiency syndrome, and oncologic agents. No clear pathophysiologic basis connects the various agents.

3. Diabetes and acute pancreatitis

The association of diabetes and acute pancreatitis was noticed at least a century ago and reported by Korte (Korte). His data was included in a large review by Shumacker along with many of Shumacker's own observations (Shumacker). Korte's observation preceded any pharmacologic agents for diabetes and at a time of Schumacker's reports, only insulin was available to treat diabetes. While the emphasis of Shumacker's paper appears to be acute pancreatitis causing diabetes, he does report some patients who were known to have diabetes prior to the episode of acute pancreatitis. Schumacker also noted cholelithiasis and/or cholecystitis in patients with acute pancreatitis. Gall bladder disease is known to be increased in diabetes as well as a cause for acute pancreatitis (Pagliarulo). K. Warren made a similar case for pancreatitis causing diabetes in five cases (Warren 1950). However, S. Warren reported acute pancreatitis in 12 patients 6 months to 13 years after the diagnosis of diabetes in a pathology text dealing with pathology of diabetes (Warren 1952). Root reported 5 cases of acute pncreatitis with diabetes, four of which were shown at autopsy to have fatty livers, which suggests type 2 diabetes with accompanying insulin resistance (Root). Bossak's report seemed to be the first to emphasize acute pancreatitis complicating diabetes mellitus rather than causing diabetes (Bossak,). She noted 3 cases of acute

pancreatitis in hospitalized patients with previously diagnosed diabetes which prompted an examination of the records of 103 patients admitted to Mount Sinai Hospital, New York City between 1936 and 1954. She found 5 more cases of acute pancreatitis in patients with pre-existing diabetes. Again, these observations were made in an era prior to any anti-diabetic therapies other than insulin. As more recent reports of acute pancreatitis have been published in association with agents used to treat diabetes, the earlier association of acute pancreatitis in the diabetic patient has not been acknowledged. Since these early twentieth century reports have been primarily in the way of case reports of acute pancreatitis in subjects with diabetes on a particular agent used in the treatment of diabetes or its comorbidities. Drugs such as metformin, ACE inhibitors and statins have been reported. The only series is that by Blomgren suggesting glyburide could increase the risk of acute pancreatitis and the relationship of that agent and the other agents has been primarily circumstantial (Balani, Blomgren, Jeandidier, Singh). The most common etiologies of acute pancreatitis accounting for 70-80% of cases are alcohol and gallstones. Chapman reported in 1996 a higher prevalence of gallstone disease based on ultrasound examination or report of cholecystectomy in diabetics (32.7%) compared to controls (20.8%, $p<0.001$) (Chapman, 1996). The difference was even greater for females were prevalence was 41.8% for female diabetic compared to controls 23.1% ($p<0.001$).

Drug Class	Agents
Cardiovascular	
ACE Inhibitors	Captopril, Enalopril, Lisinopril, Ramipril
Angiotensin Receptor Blocker	Losartan
Centrally acting	Metyldopa
Loop diuretic	Furosemide
Thiazide diuretic	Chlorothiazide, hydrocholthiazide
HMG-CoA reductase inhibitors	Simvastatin, pravastatin, fluvastatin, atrovastatin, rosuvastatin
Fibrate	Benzafibrate
Antidiabetic	Metformin, glyburide, exenatide, sitagliptin

Table 1. Common Agents used in treating diabetic patients with reports of acute pancreatitis

The increased prevalence of gall bladder disease in subjects with diabetes has been addressed more recently in the medical literature than the association with acute pancreatitis. In 1990 Haffner reported an increased incidence of gallbladder disease in non-insulin dependent diabetes mellitus (NIDDM, now referred to as type 2 diabetes) patients compared to those without diabetes in San Antonio Heart Study (Haffner). The relative risk was 1.6, 95% CI 1.08-2.37. There was an even greater risk in Mexican-American women compared to non Hispanic white women where the relative risk was 2.21, 95% CI 1.50-3.28. The San Antonio Heart Study was a landmark study that early on identified the insulin resistance with an increased risk for cardiovascular disease. The increased risk for gallbladder disease as well as cardiovascular disease in this population known to have resistance to insulin suggests that insulin resistance might be the common thread. Jorgensen failed to find an increased prevalence of gall stones in diabetic subjects in a Danish population after adjusting for obesity in a population not known for insulin resistance (Jorgensen). Chapman, in contrast, found an increased risk for gallstones

in female diabetic subjects in New Zealand but no statistically increase in male diabetics after controlling for other know risk factors of BMI, HDL cholesterol, and TG, common comorbidities associated with type 2 diabetes (Chapman, 1996). Chapman reported increased gallbladder volume in type 2 diabetic subjects even without stones not seen in type 1 diabetics (Chapman 1998). It has been suggested that this reflects stasis or poor gallbladder emptying that could predispose to stone formation. Ruhl examined 5,653 adults as part of the third Unites States National Health and Nutrition Examination Survey (NHANES 1988-1994) a cross section of the US population, using ultrasound examinations, fasting glucose and insulin levels in a population not known to have diabetes (Ruhl). After controlling for other known risks for gall bladder disease, she found that women with undiagnosed diabetes (fasting blood glucose above 126 mg/dl (>7 mmole/L)) were at an almost 2-fold risk for gall stones (1.91, 95% CI 1.29-2.83). This risk increased as the fasting serum insulin increased comparing the highest to lowest quintiles. She suggested that it was the insulin resistance rather than diabetes that accounted for the increase in gall bladder disease even though this relationship was not seen in those who only had impaired fasting glucose (fasting glucose 110-125 mg/dl (6.1-6.9 mmole/L)). Boland reported gallbladder disease severe enough to lead to hospitalization in the Atherosclerosis Risk in Communities (ARIC) study of 3.8 per thousand person years increasing with an increase in BMI (Boland 2002). She also noted association to hyperinsulinemia, low HDL, hypertriglyceridemia and hormone replacement in diabetic women. Noel examined a US insurance data base for comorbidities of type 2 diabetes, acute pancreatitis and gall bladder disease and found relative risk for gall bladder disease to be quite similar to the investigators above (Noel). Girman examined health records covering 2003- 2007 from the General Practice Research Database (GPRD) in the UK and found rates that were not dissimilar (Girman). It is not a great leap to infer that increased rates of acute pancreatitis relate to the greater risk for gall bladder disease, a known risk factor for acute pancreatitis as suggested by Pagliarulo (Pagliarulo).

Author	Population	RR	95% CI	P value
Haffner	San Antonio Heart Study (all)	1.6	1.08-2.37	
	Mexican American vs Non Hispanic Women	2.21	1.50-3.82	
Jorgensen	Denmark	NS		
Chapman	New Zealand Women DM vs Non DM	1.8		<.001
	Women Type 2 DM vs Non DM	2.10		<0.001
	Women Type 1 DM vs Non DM	1.57		<0.05
	Men Type 2 DM vs Non DM	1.83		<0.05
	Men Type 1 vs Non DM	0.86		ns
Ruhl	USA Women DM vs Non DM	1.91	1.29-2.83	
Noel	US Type 2 DM vs Non DM	1.91	1.81-1.99	
Girman	UK Type 2 DM vs Non DM Adjusted	1.49	1.31-1.70	

Table 2. Risk of gall bladder disease in diabetic subjects.

The examine more directly the relative risk for acute pancreatitis in subjects with type 2 diabetes three separate large health data bases, two in the USA and one in United Kingdom, have been examined. Noel reported a 2.83 fold risk of acute pancreatitis as well as 1.91 fold risk for biliary tract disease in type 2 diabetic members by examining a large US health care

claims database covering more than 100,000 person-years over the period from 1999-2005, a period predating GLP-1 or DPP4 therapies (Noel). Garg and Girman each examined other large health databases, Garg a US database and Girman one from the UK (Garg, Girman). Garg reports a 2.1 (95 % CI: 1.7-2.5) fold increase in acute pancreatitis in type 2 patients. Girman examined data from the (GPRD) found that 0.2% of type 2 diabetic subjects experienced acute pancreatitis from 2003 to 2007. Girman reports a similar increased risk for acute pancreatitis in type 2 diabetes of 2.89 (95% CI: 2.56-3.27) but after correction for age, gender and obesity the relative risk was 1.49 (95% CI:1.31-1.70). Only Girman made adjustment for obesity.

It is likely that the increase in acute pancreatitis in type 2 diabetic subjects is secondary to the gallbladder dysfunction. The increase in gallbladder disease is attributed to the secretion of lithogenic bile in the setting of obesity, insulin resistance and dyslipidemia. Which of these is primary is not known but studies by Grundy of bile composition in Pima Indian women, a group known to have a high risk for both type 2 diabetes and gallbladder disease, demonstrated an increase secretion of cholesterol and a reduced secretion of bile salts compared to non-stone forming Caucasian women and compared to Pima Indian men (Grundy, Sampliner). Lithogenic bile develops in the setting of inadequate bile salts or phospholipids to maintain cholesterol in solution (Dowling). Stones or sludge form due to supersaturation with cholesterol. Patients can have symptoms of gallbladder dysfunction even when no stones are present, a situation known as acalculous gallbladder disease presumably from this sludge (Fink-Bennett). The relationship of gallbladder disease risk to lipid metabolism in highlighted by Boland's finding in the ARIC study that Apo E4/E4 genotype subjects had a reduced risk to be hospitalized for gallbladder disease compared to all the other genotypes (Boland 2006). Apo E regulate metabolism of triglyceride rich lipid particles. The enzyme CYP7A1 appears to be key to the regulation of cholesterol conversion to bile salts (Pandak). CYP7A1 is regulated by LXR *alpha*, the nuclear oxysterol receptor liver X receptor *alpha* (Goodwin) and that regulation is complex but it has been shown that LXR alpha null mice feed a high cholesterol diet accumulate cholesterol in the liver and eventually die of liver failure. The relationship to insulin resistance and type 2 diabetes has yet to be elucidated but this may be a model for non-alcoholic liver disease seen with increasing frequency in obese type 2 diabetic subjects with dyslipidemia.

4. Diabetes and incretin-based antidiabetic therapies

The association acute pancreatitis with diabetes and with exenatide and sitagliptin usage has been examined systematically by Dore as well as Garg (Dore, Garg). Dore examined similar large health data base covering 2005 to 2008 and was able to compare the risk of acute pancreatitis in over 27,000 exenatide users and matched metformin or glyburide users and found the relative risk for acute pancreatitis was 1.0 (95% CI: 0.6-1.7). He compared over 16,000 sitagliptin users with matched metformin or glyburide users and found the relative risk for acute pancreatitis to be 1.0 (95% CI 0.5-2.0). Garg examined another large US health claims database of 786,656 patients and found the incidence of acute pancreatitis to be 1.9 per 1000 patients years in non-diabetic control group compared to 5.6 per 1000 patient years in the diabetic control group. Exenatide users incidence for pancreatitis was 5.7 and for sitagliptin users 5.6 cases per 1000 patient years. This data is retrospective.

Is there any prospective data that is relevant to this subject? If we examine the adverse event reporting from the clinical trials that lead to approval of incretin based therapies, we see very

similar incidence rates. These were fairly large trials with balanced patient demographics and fairly complete data collection as these event were undoubtedly Severe Adverse Events (SARs) requiring extensive follow-up reporting to the FDA. **Exenatide:** Examination of the clinical trial data deposited with the FDA shows that in the exenatide development program, six cases of acute pancreatitis were observed in about 3,489 subject-years of exposure (1.7 per 1,000 subject-years), compared with one case in about 336 subject-years with placebo (3.0 per 1,000 subject-years) and one case in about 497 subject-years (2.0 per 1,000 subject-years) with insulin (FDA.gov/Drugs/DrugSafey)**. Liraglutide:** The second GLP-1 agonist to market, showed a similar risk of acute pancreatitis, with seven cases in 3,900 patients receiving liraglutide compared with one case in a patient taking comparator diabetes agents. Liraglutide incidence was similar to that seen in exenatide clinical trials but the control goup had fewer than expected, suggesting an ascertainment bias or that comparison groups might have been underreported. **Sitagliptin.** The pooled analysis of controlled clinical trials revealed incidence rates to be (0.8 events vs. 1.0 events per 1000 patient-years for comparators. **Saxagliptin** the second DPP-4 inhibitor to reach the US market**.** reported an incidence of acute pancreatitis of 0.2% in 3,422 patients receiving saxagliptin and 0.2% in 1,066 controls in mostly shorter termed trials. **Linagliptin**, the most recent addition to the US DPP-4 inhibitor agents showed 0.2% incidence of acute pancreatitis (1 case in 538 person years and 0 in 433 patient-years in the comparators). The risk of acute pancreatitis in each of these trials is similar to that found by Noel, Garg and Girman during periods predating most of these agents (Noel, Garg, Girman). Despite this reassuring data, the FDA requires warnings for each product and continues post-marketing surveillance for acute pancreatitis. As new antidiabetic agents enter the market and their use becomes common, we expect similar rates of acute pancreatitis to be reported, just as was reported in by Blomgren in 2002 for glyburide as it was reaching peak popularity (Blomgren).
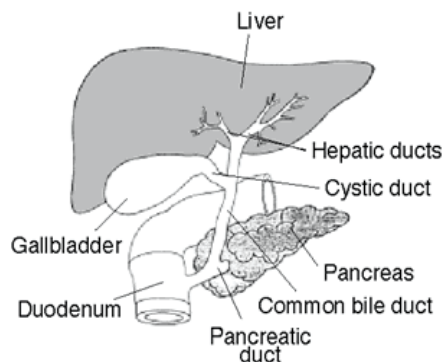

Fig. 1. Pathophysiology of gallbladder disease and acute Pancreatitis in type 2 diabetes. Liver produces lithogenic bile that forms stones or sludge. The occlusion of the common bile duct obstructs the pancreatic duct leading to acute pancreatitis.

5. Discussion

The medical literature over the past century reflects an increase in gallblader disease and acute pancreatitis in patients with diabetes, particularly those with type 2 diabetes. These patients are often obese, with dyslipidemia. The association of dyslipidemia with lithogenic

bile may be the explanation for the increased incidence of gallbladder disease in type 2 diabetic subjects and this is the likely explanation for the increase in acute pancreatitis as illustrated in Figure 1. If any agent would be predicted to be associated with an increase in gallbladder disease and acute pancreatitis, it might be colesevelam, a bile sequesterant with glucose lowering action, due to the loss of bile salts but no reports of an increase in acute pancreatitis with this agent have immerged. It is unlikely that any one class of medications used to treat diabetes has significantly altered this risk. It would be helpful if the risk for acute pancreatitis associated with type 2 diabetes were more generally known so that as each new agent is not accused of causing the problem when it achieves a significant level or use.

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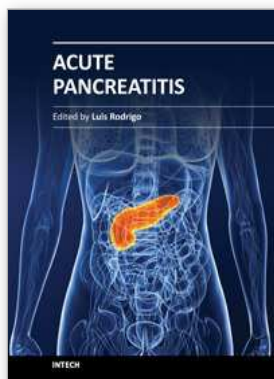
Acute Pancreatitis

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Acute Pancreatitis (AP) in approximately 80% of cases, occurs as a secondary complication related to gallstone disease and alcohol misuse. However there are several other different causes that produce it such as metabolism, genetics, autoimmunity, post-ERCP, and trauma for example... This disease is commonly associated with the sudden onset of upper abdominal pain that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10-25% of AP episodes are classified as severe. This leads to an associated mortality rate of 7-30% that has not changed in recent years. Treatment is conservative and generally performed by experienced teams often in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has a significant prognostic importance. Necrosis, hemorrhage, and infection convey up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudo-aneurysm formation, or venous thrombosis, increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

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