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William M. Steinberg
George Washington University

Michael A. Nauck

Bernard Zinman

Gilbert H. Daniels

Richard Bergenstal

See next page for additional authors

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Authors

William M. Steinberg, Michael A. Nauck, Bernard Zinman, Gilbert H. Daniels, Richard Bergenstal, Johannes F.E. Mann, Lasse Steen Ravn, Alan C. Moses, Mette Stockner, Florian M.M. Baeres, Steven P. Marso, and John B. Buse

ORIGINAL ARTICLE

LEADER 3—Lipase and Amylase Activity in Subjects With Type 2 Diabetes

Baseline Data From Over 9000 Subjects in the LEADER Trial

William M. Steinberg, MD, Michael A. Nauck, MD,† Bernard Zinman, MD,‡ Gilbert H. Daniels, MD,§ Richard M. Bergenstal, MD,‖ Johannes F.E. Mann, MD,¶ Lasse Steen Ravn, MD, PhD,# Alan C. Moses, MD,# Mette Stockner, MD,# Florian M.M. Baeres, MD,# Steven P. Marso, MD,** and John B. Buse, MD, PhD††
on behalf of the LEADER Trial investigators*

Objectives: This report from the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial describes baseline lipase and amylase activity in type 2 diabetic subjects without acute pancreatitis symptoms before randomization to the glucagonlike peptide analog liraglutide or placebo.

Methods: The LEADER is an international randomized placebo-controlled trial evaluating the cardiovascular safety of liraglutide in 9340 type 2 diabetic patients at high cardiovascular risk. Fasting lipase and amylase activity was assessed at baseline, before receiving liraglutide or placebo, using a commercial assay (Roche) with upper limit of normal values of 63 U/L for lipase and 100 U/L for amylase.

Results: Either or both enzymes were above the upper limit of normal in 22.7% of subjects; 16.6% (n = 1540) had an elevated lipase level (including 1.2% >3-fold elevated), and 11.8% (n = 1094) had an elevated amylase level (including 0.2% >3-fold elevated). In multivariable regression models, severely reduced kidney function was associated with the largest effect on increasing activity of both. However, even among subjects with normal kidney function, 12.2% and 7.7% had elevated lipase and amylase levels.

Conclusions: In this large study of type 2 diabetic patients, nearly 25% had elevated lipase or amylase levels without symptoms of acute pancreatitis. The clinician must take these data into account when evaluating abdominal symptoms in type 2 diabetic patients.

Key Words: pancreatitis, lipase, amylase, type 2 diabetes

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Subjects with type 2 diabetes are at increased risk of developing acute pancreatitis.[1,2] Analyses from insurance claims databases

estimate the incidence rate of acute pancreatitis in the diabetes population to be from 0.54 to 5.6 cases per 1000 patient-years.[3,4] These figures have been attributed to an increase in gallstone disease, hypertriglyceridemia, and obesity, whereas drugs used to treat type 2 diabetes may represent another factor potentially causing an increase in acute pancreatitis.

Glucagonlike peptide (GLP-1) receptor agonists and dipeptidyl peptidase (DPP-4) inhibitors (incretin-based therapies) are useful agents in the treatment of type 2 diabetes. In a few case reports, pharmacoepidemiologic studies,[5–8] and adverse event reports from the US Food and Drug Administration,[9] an association between these drugs and acute pancreatitis has been suggested. However, other studies have not found a similar association.[3,10–12]

Because of the questions raised about pancreatitis, current studies using incretin-based therapies have measured serial amylase and lipase activity at baseline and on therapy. Several studies have reported elevated lipase and amylase activity at baseline in a substantial minority of subjects with type 2 diabetes.[13–18] Lipase activity has also been shown to rise after initiating use of liraglutide, a GLP-1 analog, in subjects with type 2 diabetes or obesity without diabetes.[19] In an obese population without diabetes, lipase activity returned to baseline levels when liraglutide was stopped.[19]

Lipase and amylase activity is crucial to the diagnosis of acute pancreatitis.[20] According to the updated Atlanta classification,[20] 2 of the following 3 features are required: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back), (2) serum lipase (or amylase) activity at least 3 times greater than the upper limit of normal (ULN), and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography and less commonly magnetic resonance imaging or transabdominal ultrasonography. Therefore, it is important to further define the influence of type 2 diabetes on these enzymes. The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial includes over 9000 subjects with type 2 diabetes who are randomized to receive liraglutide or placebo. The purpose of the current study is to assess baseline amylase and lipase activity in the LEADER population. We believe that this is the largest study of lipase and amylase activity in subjects with type 2 diabetes.

MATERIALS AND METHODS

Subjects and Study Design

The LEADER trial is an international double-blind placebo-controlled trial currently evaluating the cardiovascular safety of liraglutide (www.clinicaltrials.gov; NCT01179048). There are 9340 subjects with type 2 diabetes at high risk for cardiovascular events (with or without existing cardiovascular disease) enrolled at 410 centers worldwide and randomized 1:1 to liraglutide or placebo. Subjects will be followed for a minimum of 3.5 years.

Baseline characteristics of subjects enrolled in LEADER have been described elsewhere.[21] Briefly, subjects with type 2 diabetes and elevated cardiovascular risk who were either drug-naive or treated with 1 or more antihyperglycemic drugs were screened. Subjects treated with GLP-1 receptor agonists or DPP-4 inhibitors were excluded. Medical history, including history of pancreatitis and/or gallstone disease, was obtained. Enrollment of subjects with severely reduced estimated glomerular filtration rate (eGFR <30 mL/min per 1.73 m^2) was limited to a maximum of 220, whereas no similar limit was applied to subjects with moderately reduced eGFR (30–60 mL/min per 1.73 m^2). After a 2-week run-in phase, subjects were randomized in double-blind

fashion to receive either liraglutide (0.6 mg up to a maximum dose of 1.8 mg) once daily or equivalent placebo as an add-on to their baseline treatment. After randomization, study visits occur at months 1, 3, and 6 and every 6 months thereafter until termination of the trial. Subjects are followed for up to 5 years. Secondary and safety end points include, among others, the incidence of acute pancreatitis, acute gallstone disease, and changes in serum lipase and amylase. Enrollment commenced in September 2010 and was completed in April 2012. Each enrolling center's institutional review board approved the study.

Lipase and Amylase Screening and Monitoring

Lipase and amylase activity is measured at baseline and months 6 and 12. Assessments are to be repeated annually (for up to 5 years) until termination of the trial, with a final measurement at the end of treatment. Serum pancreatic lipase and total amylase activity is measured in the fasting state in all subjects using an enzymatic colorimetric assay (Roche Diagnostics, Mannheim, Germany) performed by a central laboratory (ICON PLC, Dublin, Ireland). None of the subjects had symptoms suggesting acute pancreatitis at the time of baseline blood drawing. The ULN for this assay is set at 63 U/L for lipase and 100 U/L for amylase. Neither limit is adjusted for subjects with type 2 diabetes. Per protocol, more frequent measurements of lipase and amylase activity are to be conducted locally in cases of persistent severe abdominal pain leading to a suspicion of acute pancreatitis.

Statistical Analysis

The distribution of both lipase and amylase values was right-skewed; therefore a logarithmic transformation was applied before analysis. Explanatory factors were prespecified and included sex, age, body mass index (BMI), smoking status, race, duration of diabetes, glycemic control (HbA1c), diabetes pretreatment, eGFR (modified diet in renal disease formula), autoimmune disease, thyroid disease, lipid levels, and use of certain medications (proton pump inhibitors, β-blockers, H2 receptor antagonists, and glucocorticoids). A multivariable linear normal analysis of covariance model was created, with the logarithmically transformed lipase and amylase values as dependent variables. The effect of each covariate was first derived on the log scale and then exponentially transformed to obtain an interpretation as relative activity of lipase and amylase. Effects of each factor are therefore adjusted to the set of all other factors and expressed in relative terms, with an effect equal to 1.0 representing "neutral" (also expressed as percent change = 0%). All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

All authors had access to the study data and reviewed and approved the final article.

RESULTS

Baseline characteristics of the LEADER population stratified by sex are presented in Table 1. No subjects had symptoms of pancreatitis at baseline, and lipase activity was available in 99.3% of all subjects (n = 9273). The distribution of lipase values is depicted in Figure 1A. Mean (SD) and median (interquartile range) values were 47.5 (43.7) U/L and 38.3 (28.2–53.9) U/L, respectively. Baseline amylase was available in 99.7% of all subjects (n = 9309), with mean (SD) and median values of 66.2 (36.3) and 59.0 (44.0–79.0) U/L, respectively (Fig. 1B). There were 9273 subjects with both valid amylase and lipase values.

Among all subjects with available baseline data for both enzymes, 16.6% (n = 1540) and 11.8% (n = 1094), respectively, had lipase and amylase activity above the ULN. Measurements greater

TABLE 1. Baseline Demographics

	Total (N = 9340)	Female (n = 3337)	Male (n = 6003)
Age, y	64.3 (7.2); 64.0	64.4 (7.2); 64.0	64.2 (7.3); 64.0
Body weight, kg	91.8 (21.0); 89.9	84.7 (19.5); 82.4	95.7 (20.8); 93.2
BMI, kg/m^2	32.5 (6.3); 31.7	33.6 (6.8); 32.8	31.9 (5.9); 31.2
HbA1c, %	8.7 (1.5); 8.3	8.8 (1.6); 8.4	8.6 (1.5); 8.2
Diabetes duration, y	12.7 (8.0); 11.3	13.3 (8.3); 11.8	12.4 (7.8); 11.1
Blood pressure, mm Hg			
Systolic	137.7 (18.6); 137.0	139.1 (19.2); 138.0	136.9 (18.2); 136.0
Diastolic	77.9 (10.5); 78.5	78.1 (10.7); 79.0	77.8 (10.3); 78.5
Heart rate, beats per minute	73.2 (11.4); 72.0	74.4 (10.9); 74.0	72.5 (11.6); 72.0
eGFR, mL/min per 1.73 m^2			
<30	177 (1.9)	76 (2.3)	101 (1.7)
30–59	1854 (19.9)	700 (21.0)	1154 (19.2)
60–89	3860 (41.3)	1353 (40.5)	2507 (41.8)
≥90	3447 (36.9)	1207 (36.2)	2240 (37.3)
Glucose lowering treatment			
Diet or no treatment	504 (5.4)	128 (5.3)	376 (5.5)
Insulin alone	665 (7.1)	279 (8.4)	386 (6.4)
Oral glucose lowering*	4931 (52.8)	1687 (50.6)	3244 (54.0)
Oral glucose lowering + insulin	3240 (34.7)	1195 (35.8)	2045 (34.1)
Prior cardiovascular disease	7592 (81.3)	2544 (76.2)	5048 (84.1)
No. oral antihyperglycemic medications used			
1	1917 (20.5)	679 (20.3)	1238 (20.6)
2	2686 (28.8)	914 (27.4)	1772 (29.5)
>2	328 (3.5)	94 (2.8)	234 (3.9)
Smoking			
Current	1130 (12.1)	281 (8.4)	849 (14.1)
Previous	4337 (46.4)	926 (27.7)	3411 (56.8)
Never	3873 (41.5)	2130 (63.8)	1743 (29.0)

   Data shown are mean (SD); median for continuous variables and n (%) for groupings.
   *Not used in combination with insulin.

than 3 times the ULN for lipase were seen in 1.2% of subjects and 0.2% for amylase (Figs. 1A, B; Table 2).

    Results of the same multivariable regression model performed separately for lipase and amylase are presented in Table 3A and B.

Severely reduced eGFR (<30 mL/min per 1.73 m^2, corresponding to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative chronic kidney disease [CKD] stage 4–5) was associated with the largest effect on increasing lipase and amylase
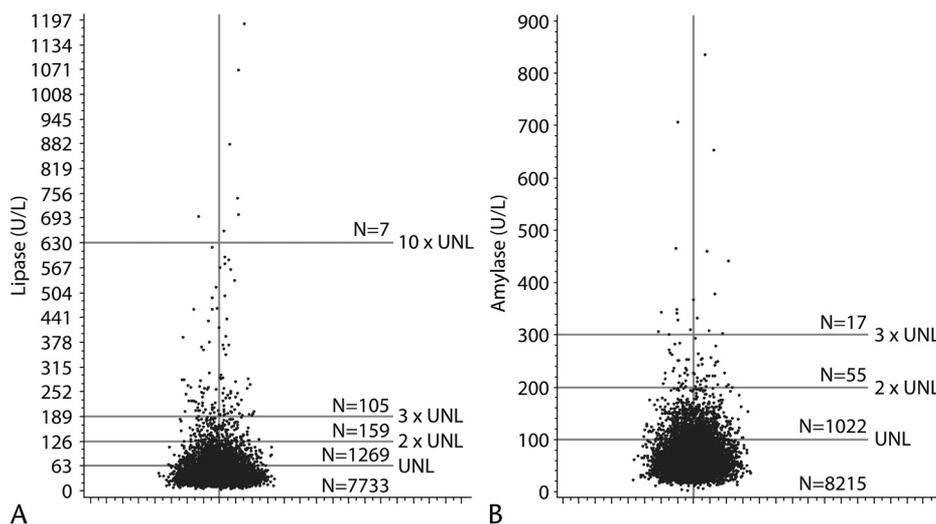

FIGURE 1. Distribution of (A) lipase and (B) amylase values in all randomized subjects. Horizontal lines (from lowest to highest value on y-axis) denote 1, 2, 3, and 10 times ULN values.

TABLE 2. Distribution of Baseline Lipase and Amylase Values by eGFR (mL/min per 1.73 m^2) in Subjects With Known eGFR, Lipase, and Amylase Measures (n = 9271)

A. Lipase, U/L		
eGFR	>ULN	>3× ULN
<30 (n = 177)	35.03	1.69
30–59 (n = 1840)	24.02	1.25
60–89 (n = 3837)	16.13	1.49
≥90 (n = 3417)	12.17	0.85
Total (n = 9271)	16.60	1.21
ULN = 63 U/L		
B. Amylase		
eGFR	>ULN	>3× ULN
<30 (n = 177)	26.55	0.57
30–59 (n = 1840)	18.70	0.16
60–89 (n = 3837)	11.31	0.26
≥90 (n = 3417)	7.72	0.06
Total (n = 9271)	11.75	0.17
ULN = 100 U/L		

Data are presented as percent.

activity. There were no effects on either lipase or amylase activity from history of CVD, thyroid disease, autoimmune disease, pancreatitis, or gallstones; diabetes duration; or glucocorticoid use. Several characteristics unrelated to eGFR were associated with smaller but statistically significant changes in serum lipase and amylase activity. For lipase, Asian race, higher HbA1c, higher serum triglyceride concentrations, presence of diabetic nephropathy, and treatment with oral antihyperglycemic drugs were associated with increasing activity, whereas female sex, black race, increasing age, higher BMI, use of proton pump inhibitors, higher serum low density lipoprotein (LDL) cholesterol concentrations, and insulin treatment were associated with decreasing activity. For amylase, Asian and black races, higher serum high density lipoprotein (HDL) cholesterol concentrations, and presence of diabetic nephropathy were associated with increasing activity, whereas female sex, history of smoking, increasing age, increasing BMI, increasing HbA1c, history of cholecystitis, gallstone disease, and use of β-blockers, H2 receptor antagonists, and proton pump inhibitors were associated with decreasing activity.

The distribution of baseline lipase and amylase values by eGFR in subjects with known values for eGFR, lipase, and amylase (n = 9271) is shown in Table 2. There was an association between progressive eGFR reductions and elevations in both (either >ULN or >3× ULN). However, a majority of the 177 subjects with eGFR less than 30 mL/min per 1.73 m^2 (corresponding to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative CKD stage 4–5) had normal lipase (65%) and normal amylase (73%) activity. Of those subjects with normal eGFR (≥90 mL/min per 1.73 m^2), 12.2% had elevated lipase and 7.7% had elevated amylase activity.

Table 4 analyzes subjects with normal or elevated levels of activity in both, one enzyme, or the other. Among subjects with elevations in either enzyme (22.7%), approximately one quarter had elevated amylase level with normal lipase, approximately one half had elevated lipase level with normal amylase, and approximately one quarter had both elevated lipase and amylase levels.

Table 5 reviews data compiled in recent publications evaluating baseline lipase and amylase in subjects with type 2 diabetes, either unrelated to GLP-1 receptor agonists or DPP-4 inhibitor therapy or before randomization to GLP-1 receptor agonists or DPP-4 inhibitors. The present study contains the largest cohort, whereas the proportions of type 2 diabetes subjects with elevated activity in either enzyme are consistent with previous work.

DISCUSSION

In this report of baseline data from the LEADER trial, nearly one quarter (22.7%) of subjects with type 2 diabetes had elevated levels of lipase and/or amylase activity above ULN. The proportions of subjects with elevated serum lipase (16.6%) and amylase (11.8%) activity were consistent with findings from previous reports in type 2 diabetes,[14–17] and elevations above 3 times the ULN were seen in 1.2% of subjects for lipase and 0.2% for amylase. To our knowledge, this is the largest study (N = 9340) of lipase and amylase activity in a population of type 2 diabetes mellitus. Logistic regression indicated that worsening eGFR was the most prominent factor influencing lipase and amylase activity. An eGFR less than 30 mL/min per 1.73 m^2 (corresponding to CKD stage 4–5) was associated with higher serum lipase and amylase activity and greater proportions of subjects with elevations in either enzyme, findings recognized in other studies.[22] However, of those subjects with normal renal function (eGFR ≥90 mL/min per 1.73 m^2), 12.2% had elevated levels of lipase and 7.7% had elevated levels of amylase activity. Other factors shown to have a smaller impact on either increasing or decreasing lipase or amylase activity included certain drugs (proton pump inhibitors, insulin, and oral antihyperglycemics), BMI, HbA1c level, age, and race. Risk factors, known to be associated with pancreatitis, such as a history of pancreatitis or gallstones, did not seem to affect baseline activity of either lipase or amylase. Other environmental factors such as alcohol intake and smoking have been described as risk factors for the development of pancreatitis.[23] Although a history of alcohol consumption was not systematically collected for the present population, smoking was analyzed and did not have an independent effect on pancreatic enzyme activity.

It is unclear why lipase and amylase activity is elevated in a significant portion of subjects with type 2 diabetes. To understand these findings, the complex physiologic nature of these biochemical markers requires comment. It is known that there are many sources of amylase and lipase in the human body. Amylase exists

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TABLE 3. Multivariable Log-Linear Regression Models Performed Separately for Lipase and Amylase*

	Effect	95% Confidence Limits	*P*	Percentage Change
A. Lipase				
eGFR, per 10 mL/min per 1.73 m²				
<30	1.540	1.413–1.678	<0.0001	54.0
30–59	1.287	1.243–1.334	<0.0001	28.7
60–89	1.121	1.093–1.150	<0.0001	12.1
≥90†	1.000			
Sex				
Female	0.955	0.931–0.980	0.0005	−4.5
Male†	1.000			
Smoking	0.972	0.939–1.006	0.1052	−2.8
Race				
Asian	1.018	0.979–1.059	0.3659	1.8
Black	0.951	0.913–0.991	0.0178	−4.9
Other	1.026	0.972–1.084	0.3487	2.6
White†	1.000			
Prior cardiovascular disease				
No	1.011	0.979–1.044	0.5227	1.1
Yes†	1.000	—	—	—
Age, per 10-year increment	0.942	0.925–0.958	<0.0001	−5.8
BMI, per 10-kg/m² increment	0.942	0.924–0.960	<0.0001	−5.8
HbA1c, per % increment	1.018	1.011–1.026	<0.0001	1.8
Diabetes duration, per year increment	0.999	0.998–1.001	0.2006	−0.1
Autoimmune disorder	1.040	0.974–1.111	0.2417	4.0
Thyroid disease	0.971	0.940–1.003	0.0792	−2.9
β-Blocker use	1.015	0.991–1.039	0.2189	1.5
H2 receptor antagonist use	0.980	0.921–1.043	0.5254	−2.0
Proton pump inhibitor use	0.896	0.871–0.921	<0.0001	−10.4
Glucocorticoid use	0.947	0.883–1.017	0.1346	−5.3
LDL cholesterol, per mmol/L increment	0.967	0.955–0.979	<0.0001	−3.3
HDL cholesterol, per mmol/L increment	1.018	0.978–1.059	0.3933	1.8
Triglycerides, per mmol/L increment	1.048	1.033–1.063	<0.0001	4.8
History of pancreatitis	1.000	0.932–1.073	0.9940	−0.0
History of cholecystitis	0.965	0.921–1.012	0.1397	−3.5
History of diabetic nephropathy	1.040	1.014–1.066	0.0025	4.0
History of gallstones	1.032	0.995–1.071	0.0938	3.2
Diabetes pretreatment				
Insulin + oral antihyperglycemics	1.024	0.972–1.078	0.3776	2.4
Insulin only	0.869	0.816–0.926	<0.0001	−13.1
Oral antihyperglycemics only	1.114	1.059–1.171	<0.0001	11.4
None/diet†	1.000	—	—	—
B. Amylase				
eGFR, per 10 mL/min per 1.73 m²				
<30	1.466	1.368–1.572	<0.0001	46.6
30–59	1.261	1.225–1.297	<0.0001	26.1
60–89	1.114	1.091–1.137	<0.0001	11.4
≥90†	1.000			
Sex				
Female	0.891	0.873–0.910	<0.0001	−10.9
Male†	1.000			
Smoking	0.968	0.941–0.995	0.0201	−3.2
Race				
Asian	1.158	1.122–1.196	<0.0001	15.8
Black	1.358	1.314–1.404	<0.0001	35.8

(continued on next page)

TABLE 3. *(Continued)*

	Effect	95% Confidence Limits	*P*	Percentage Change
B. Amylase				
Race				
Other	1.168	1.118–1.221	<0.0001	16.8
White[†]	1.000			
Prior cardiovascular disease				
No	0.989	0.964–1.015	0.4094	−1.1
Yes[†]	1.000	—	—	—
Age, per 10-year increment	0.981	0.967–0.995	0.0071	−1.9
BMI, per 10-kg/m^2 increment	0.853	0.840–0.866	<0.0001	−14.7
HbA1c, per % increment	0.984	0.978–0.990	<0.0001	−1.6
Diabetes duration, per year increment	1.000	0.999–1.001	0.7723	0.0
Autoimmune disorder	1.012	0.959–1.067	0.6742	1.2
Thyroid disease	0.980	0.955–1.006	0.1390	−2.0
β-Blocker use	0.967	0.949–0.985	0.0005	−3.3
H2 receptor antagonist use	0.945	0.899–0.994	0.0283	−5.5
Proton pump inhibitor use	0.934	0.913–0.955	<0.0001	−6.6
Glucocorticoid use	0.976	0.921–1.033	0.4004	−2.4
LDL cholesterol, per mmol/L increment	0.988	0.978–0.998	0.0201	−1.2
HDL cholesterol, per mmol/L increment	1.079	1.045–1.115	<0.0001	7.9
Triglycerides, per mmol/L increment	0.994	0.983–1.006	0.3214	−0.6
History of pancreatitis	0.970	0.916–1.027	0.2923	−3.0
History of choleosystitis	0.937	0.902–0.974	0.0009	−6.3
History of diabetic nephropathy	1.044	1.023–1.066	<0.0001	4.4
History of gallstones	1.006	0.976–1.036	0.7160	0.6
Diabetes pretreatment				
Insulin + oral antihyperglycemics	1.033	0.991–1.077	0.1245	3.3
Insulin only	0.966	0.918–1.017	0.1848	−3.4
Oral antihyperglycemics only	1.040	0.998–1.083	0.0591	4.0
None/diet[†]	1.000			

*Effective number of subjects contributing to analysis: n = 8824 (no missing values allowed).

[†]Reference.

in 2 isoenzyme forms: p-amylase (mostly originating from the pancreas) and s-amylase (mostly originating from the salivary glands). However, other sources in the body can contain various mixtures of both forms, including the fallopian tubes, thyroid, small intestine, liver, placenta, testis, skeletal muscle, and spleen, as well as various tumors.[24–29] In the asymptomatic subject, serum amylase is made up of a mixture of p-amylase (approximately 40%) and s-amylase (approximately 60%). In acute pancreatitis,

the predominant isoenzyme in the serum is p-amylase. However, p-amylase level has been reported to be markedly elevated in other nonpancreatic acute conditions such as ovarian cyst rupture.[30] Several types of lipase are also present in the human body, including gastric, pancreatic, hepatic, endothelial, and muscle.[31–33] The pancreas itself contain several different lipases, including pancreatic triglyceride lipase, pancreatic lipase-related proteins 1 and 2, carboxyl ester lipase, and phospholipase A2.[34] It is generally

TABLE 4. Distribution of Lipase and Amylase Activity According to eGFR (mL/min per 1.73 m^2)

	Lipase Normal, Amylase Normal	Lipase Normal, Amylase >ULN	Amylase Normal, Lipase >ULN	Amylase >ULN, Lipase >ULN
eGFR				
<30 (n = 177)	95 (53.7)	20 (11.3)	35 (19.8)	27 (15.3)
30–59 (n = 1840)	1221 (66.4)	177 (9.6)	275 (15.0)	167 (9.1)
60–89 (n = 3837)	2998 (78.1)	220 (5.7)	405 (10.6)	214 (5.6)
≥90 (n = 3417)	2852 (83.5)	149 (4.4)	301 (8.8)	115 (3.4)
Total (n = 9271)	7166 (77.3)	566 (6.1)	1016 (11.0)	523 (5.6)

Data are presented as n (%).

*ULN = 63 U/L

[†]ULN = 100 U/L

TABLE 5. Other Studies Reporting Elevated Lipase and Amylase Levels in Subjects With Type 2 Diabetes

	Lipase		Amylase	
	>ULN	>3× ULN	>ULN	>3× ULN
Lando et al[15] (n = 33)	18.0	NR	3.0	NR
Bastyr et al[17] (n = 440)	13.0	NR	5.0	NR
Malloy et al[16] (n = 514)	13.0	1.0	6.0	0.5
Steinberg et al[18] (n = 987)	20.4	2.1	8.5	0.1
Exenatide LAR[13]	11.4*	NR	4.8[†]	NR
LEADER (present study) (n = 9273)	16.6	1.2	11.7	0.17

Data are presented as percent of the total population, ULN.
*Subjects with lipase measurements (n = 2153).
[†]Subjects with amylase measurements (n = 1199).
NR, not recorded.

assumed that basal serum lipase is of pancreatic origin. However, the actual proportion of basal serum lipase from other sources is unknown. The lipase assay in LEADER uses colipase and bile salts and hence is thought to be specific for pancreatic lipase activity. However, some experts question whether these assays can truly distinguish pancreatic from nonpancreatic lipases (personal communication: Mark Lowe, MD, PhD, vice-chairman and professor of pediatrics at University of Pittsburgh School of Medicine).

Lipase and amylase are synthesized in the pancreatic acinar cell, packaged in zymogen granules, and thought to reach the blood stream by leakage of these enzymes from the basal lateral membrane of the acinus into the surrounding capillaries or via the pancreatic lymph with drainage through the thoracic duct.[31,35] Secretory studies in animals and humans demonstrate an effect of a high-carbohydrate or high-fat diet on the composition of amylase and lipase in these granules.[36,37] However, it is unknown whether fasting or food consumption has an effect on levels of serum activity for either enzyme. Amylase is filtered by the renal glomerulus and excreted into urine where it can be measured. Lipase is also filtered at the glomerulus but almost completely reabsorbed by the renal tubules, leaving negligible amounts of lipase in the urine.[38–40] Rat studies suggest that amylase, and particularly lipase, is degraded by the renal tubules; however, there are no data on this process in humans.[40]

Given the limited knowledge on the origins and excretion/degradation of serum amylase and lipase, there are several possible explanations for elevated activity in the diabetic population. Our data confirm prior observations that reduced eGFR raises serum lipase and amylase activity. Possible mechanisms include reduced glomerular filtration, a change in tubular reabsorption, degradation of the enzymes, or all of these factors. It should be noted, however, that reduced eGFR does not affect both enzymes equally. In the group with eGFR less than 30 mL/min per 1.73 m^2 (CKD stage 4–5), amylase activity alone was elevated in 11%, lipase activity alone was elevated in 19.8%, and both were elevated in 15.3% (Table 4). Neither these findings nor our finding that more than one half of the subjects with eGFR less than 30 mL/min per 1.73 m^2 had normal lipase and amylase activity can be explained on the basis of known mechanisms.

It is unclear what is driving elevated lipase and amylase activity unrelated to kidney function (12% and 7% of the entire cohort, respectively). Subclinical pancreatic inflammation may be one explanation. Prior studies suggest that subclinical chronic pancreatitis may be increased in subjects with type 2 diabetes. In an asymptomatic diabetes population, Hardt and colleagues[41]

showed that 35% (compared with 18% in controls) of subjects with diabetes had a low fecal elastase concentration, which is thought to be a marker of pancreatic insufficiency or chronic pancreatitis. One autopsy study revealed that subjects with diabetes had a greater level of pancreatic fibrosis and evidence of chronic pancreatitis than controls.[42] However, if pancreatic inflammation explained the enzyme elevations, it might be expected that lipase and amylase activity would be elevated to a similar degree. Nevertheless, our data, as well as that from others,[13–18] indicate that lipase activity elevations predominate over amylase in the percentage of subjects affected. In addition, amylase activity is elevated about 25% of the time without an elevation in lipase (Table 4).

Because amylase and lipase come from other potential sites (gastric, hepatic, endothelial, muscle), it is possible that these serum enzymes in diabetes may originate in areas other than the pancreas. It is also possible that diabetes—or the drugs that subjects with type 2 diabetes take—may cause changes in the secretion or excretion/degradation of these enzymes by the kidney that may also lead to elevations. An increased glucose concentration, as found in poorly controlled diabetes or ketoacidosis, has previously been reported to affect enzyme activity[43]; however, this finding in relation to HbA1c could not be confirmed.[16] In our population, a higher HbA1c was related to higher lipase but lower amylase activity. The impact of confounding risk factors that may be present and more common in a type 2 diabetes population, such as cholelithiasis or hypertriglyceridemia, also does not provide a clear picture. Although some of these factors showed significant associations due to the large sample size in LEADER, the effect sizes were small and presented no consistent trend (eg, HbA1c).

The present study is strengthened by its robust sample size, consisting of the largest study to date of lipase and amylase in a type 2 diabetes population. On the other hand, LEADER specifically enrolled subjects at high cardiovascular risk, potentially limiting the generalizability of our findings. However, there is no reason to expect that cardiovascular disease per se would change pancreatic enzyme activity. Furthermore, similar elevations in lipase and amylase were noted in other studies that did not specifically include subjects at high cardiovascular risk.[15,16,18] Our study measured total amylase and not pancreatic (p-) amylase; thus different findings may have resulted from use of this assay. Others have in fact measured p-amylase in subjects with diabetes and found that 6% had an elevation, approximately one half that of our results.[16]

In conclusion, our study shows that among subjects with type 2 diabetes, 16.6% had elevated lipase (including 1.2% that

have a greater than 3-fold elevation) and 11.8% had elevated amylase activity (0.2% >3-fold elevated). Although it may be the single most important parameter responsible for some of the elevations, reduced kidney function is not responsible for most. Other significant causes remain unknown. Because pancreatic enzyme elevations (especially a 3-fold elevation) are crucial for the diagnosis of acute pancreatitis (along with significant upper abdominal pain and positive imaging with computed tomography, magnetic resonance imaging, or abdominal ultrasound),[16] it is important for the gastroenterologist to be aware of the pitfalls of these laboratory studies in subjects with diabetes. In addition, certain antidiabetic drugs such as GLP-1 receptor agonists may raise pancreatic enzymes above baseline, further confusing the enzyme picture.[16] Therefore, it is important for the clinician to pay extra attention to clinical symptoms and imaging in the diabetic population when considering the diagnosis of acute pancreatitis.

REFERENCES

1. Noel RA, Braun DK, Patterson RE, et al. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. *Diabetes Care*. 2009;32:834–838.

2. Girman CJ, Kou TD, Cai B, et al. Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. *Diabetes Obes Metab*. 2010;12:766–771.

3. Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care*. 2010;33:2349–2354.

4. Gonzalez-Perez A, Schlienger RG, Rodriguez LA. Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study. *Diabetes Care*. 2010;33:2580–2585.

5. Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. *Diabetes Care*. 2006;29:471.

6. Lee PH, Stockton MD, Franks AS. Acute pancreatitis associated with liraglutide. *Ann Pharmacother*. 2011;45:e22.

7. Tripathy NR, Basha S, Jain R, et al. Exenatide and acute pancreatitis. *J Assoc Physicians India*. 2008;56:987–988.

8. Singh S, Chang HY, Richards TM, et al. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. *JAMA Intern Med*. 2013;173(7):534–539.

9. Elashoff M, Matveyenko AV, Gier B, et al. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1–based therapies. *Gastroenterology*. 2011;141:150–156.

10. Dore DD, Seeger JD, Arnold Chan K. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin*. 2009;25:1019–1027.

11. Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. *Diabetes Res Clin Pract*. 2012;98:271–284.

12. Dore DD, Bloomgren GL, Wenten M, et al. A cohort study of acute pancreatitis in relation to exenatide use. *Diabetes Obes Metab*. 2011;13:559–566.

13. Exenatide LAR New Drug Application Clinical Review. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000MedR.pdf. Accessed November 19, 2013.

14. DeVries JH, Bain SC, Rodbard HW, et al. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. *Diabetes Care*. 2012;35:1446–1454.

15. Lando HM, Alattar M, Dua AP. Elevated amylase and lipase levels in patients using glucagonlike peptide-1 receptor agonists or dipeptidyl-peptidase-4 inhibitors in the outpatient setting. *Endocr Pract*. 2012;18:472–477.

16. Malloy J, Gurney K, Shan K, et al. Increased variability and abnormalities in pancreatic enzyme concentrations in otherwise asymptomatic subjects with type 2 diabetes. *Diabetes Metab Syndr Obes*. 2012;5:419–424.

17. Bastyr EJ, Barkin J, Botros FT, et al. High incidence of elevated lipase and amylase in type 2 diabetes patients (T2DM) (abstract). *Pancreas*. 2009;38:980.

18. Steinberg WM, Rosenstock J, DeVries JH, et al. Elevated serum lipase activity in adults with type 2 diabetes and no gastrointestinal symptoms (abstract). *Gastroenterology*. 2012;142(suppl 1):S93–S94.

19. Steinberg WM, DeVries JH, Wadden TA, et al. Longitudinal monitoring of lipase and amylase in adults with type 2 diabetes and obesity: evidence from two phase 3 randomized clinical trials with once daily GLP-1 analog liraglutide. *Gastroenterology*. 2012;142(suppl 1):S850–S851.

20. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111.

21. Marso SP, Poulter NR, Nissen SE, et al. Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. *Am Heart J*. 2013;166:823–830 e825.

22. Kimmel PL, Tenner S, Habwe VQ, et al. Trypsinogen and other pancreatic enzymes in patients with renal disease: a comparison of high-efficiency hemodialysis and continuous ambulatory peritoneal dialysis. *Pancreas*. 1995;10:325–330.

23. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013;144:1252–1261.

24. Green CL. Identification of alpha-amylase as a secretion of the human fallopian tube and tubelike epithelium of müllerian and mesonephric duct origin. *Am J Obstet Gynecol*. 1957;73:402–408.

25. Berk JE, Shimamura J, Fridhandler L. Tumor-associated hyperamylasemia. *Am J Gastroenterol*. 1977;68:572–577.

26. Whitten RO, Chandler WL, Thomas MG, et al. Survey of alpha-amylase activity and isoamylases in autopsy tissue. *Clin Chem*. 1988;34:1552–1555.

27. Apple F, Benson P, Preese L, et al. Lipase and pancreatic amylase activities in tissues and in patients with hyperamylasemia. *Am J Clin Pathol*. 1991;96:610–614.

28. Shimamura J, Fridhandler L, Berk JE. Does human pancreas contain salivary-type isoamylase? *Gut*. 1975;16:1006–1009.

29. Fridhandler L, Berk JE, Ueda M. Isolation and measurement of pancreatic amylase in human serum and urine. *Clin Chem*. 1972;18:1493–1497.

30. Sinha S, Khan H, Timms PM, et al. Pancreatic-type hyperamylasemia and hyperlipasemia secondary to ruptured ovarian cyst: a case report and review of the literature. *J Emerg Med*. 2010;38:463–466.

31. Tietz NW, Shuey DF. Lipase in serum—the elusive enzyme: an overview. *Clin Chem*. 1993;39:746–756.

32. Jocken JW, Moro C, Goossens GH, et al. Skeletal muscle lipase content and activity in obesity and type 2 diabetes. *J Clin Endocrinol Metab*. 2010;95:5449–5453.

33. Langin D, Dicker A, Tavernier G, et al. Adipocyte lipases and defect of lipolysis in human obesity. *Diabetes*. 2005;54:3190–3197.

34. Whitcomb DC, Lowe ME. Human pancreatic digestive enzymes. *Dig Dis Sci*. 2007;52:1–17.

35. Wanke M. Pathogenese und morphologisches Bild akuter Pankreaserkrankungen. In: Forell MM, ed. *Pankreas. Hdb Inn Med, 5. Aufl, Bd 3, Teil 6*. Berlin-Heidelberg-New York: Springer; 1976:S520–S615.

36. Boivin M, Lanspa SJ, Zinsmeister AR, et al. Are diets associated with different rates of human interdigestive and postprandial pancreatic enzyme secretion? *Gastroenterology*. 1990;99:1763–1771.

37. Ricketts J, Brannon PM. Amount and type of dietary fat regulate pancreatic lipase gene expression in rats. *J Nutr*. 1994;124:1166–1171.

38. Junge W, Malyusz M, Ehrens HJ. The role of the kidney in the elimination of pancreatic lipase and amylase from blood. *J Clin Chem Clin Biochem*. 1985;23:387–392.

39. Moller-Peterson J, Dati F. Renal handling of pancreatic lipase. *Clin Chem*. 1984;30:343–344.

40. Malyusz M, Wrigge P, Caliebe D, et al. Renal handling of ^{125}I-labelled homologous pancreatic lipase and amylase in the rat. *J Clin Chem Clin Biochem*. 1988;26:611–615.

41. Hardt PD, Hauenschild A, Jaeger C, et al. High prevalence of steatorrhea in 101 diabetic patients likely to suffer from exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations: a prospective multicenter study. *Dig Dis Sci*. 2003;48:1688–1692.

42. Lazarus SS, Volk BW. Pancreas in maturity-onset diabetes. Pathogenetic considerations. *Arch Pathol*. 1961;71:44–59.

43. Butler AE, Campbell-Thompson M, Gurlo T, et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes*. 2013;62: 2595–2604.