In the study, 17 patients (14 males and 3 females) with obesity (body mass index of 30 kg/m$^2$ to 50 kg/m$^2$) and type 2 diabetes were implanted with the EndoBarrier for 24 weeks. Patients were evaluated to assess levels of HbA1C, glucose, insulin, GLP-1, and PYY prior to and at 24 weeks after endoscopic implantation through blood draws that were conducted during meal tolerance tests using a 500-kcal test meter. The aim of the study was to investigate mechanisms that underlie diabetic improvement after duodenal exclusion by duodenal-jejunal bypass treatment.

Treatment with the EndoBarrier resulted in a rapid and sustained increase in insulin sensitivity, increased levels of both PYY and GLP-1, 1 week postplacement, reduction in mean HbA1C levels of 1.4% (from 8.4% at baseline to 7.0%), normalization of glucagon response, mean excess weight loss of 29.8%, and elimination of or reduction in use of antidiabetic medications in 16 of 17 participants.

"Our data show that treatment with the EndoBarrier affects key hormones involved in insulin sensitivity, glucose metabolism, and satiety, similar to the impact of gastric bypass, and these changes allow for rapid and sustained improvement in patients with type 2 diabetes," said Prof. de Jonge. "In addition, we found that patients maintained diabetic improvements at the end of the follow-up period, 1 week postremoval. These are important findings in understanding how the EndoBarrier works to treat type 2 diabetes."

The intestine is an important metabolic organ that has gained attention in recent years for the newly identified role that it plays in the pathophysiology of various metabolic diseases, including obesity, insulin resistance, and diabetes. Recent insights regarding the role of enteroendocrine hormones, such as GIP, GLP-1, and PYY, in metabolic diseases, as well as the emerging role of the gut microbial community and gastric bypass surgeries in modulating metabolic function and dysfunction, have sparked a wave of interest in understanding the mechanisms that are involved in an effort to identify new therapeutics and novel regulators of metabolism [Bradley WD et al. *Arch Physiol Biochem* 2011].

Gut hormones contribute to glycemic control, the regulation of food intake, and weight loss. Previous research has demonstrated that bariatric surgery in obese patients with type 2 diabetes has immediate effects and improvements in glycemic control and that these effects may be due to changes in gut hormones [Blackburn GL et al. *Obesity* 2009]. The EndoBarrier, a liner that fits inside a section of the intestine, mimics many of the effects of gastric bypass but without the surgery.

## NAFLD: CV Risk Regardless of Hyperglycemia or Obesity

*Written by Rita Buckley*

The prevalence of nonalcoholic fatty liver disease (NAFLD) has been estimated to be between 20% and 30% in the general population, but this value is much higher (approximately 70% to 80%) in individuals with type 2 diabetes. Increasing recognition of NAFLD and its strong relationship with metabolic syndrome has stimulated an interest in its possible role in the development of cardiovascular disease (CVD) [Targher G et al. *Diabetologia* 2008]. Christopher Byrne, MB, PhD, University of Southampton and Southampton University Hospitals Trust Southampton, UK, and colleagues presented findings from a small retrospective study on the relation between NAFLD progression and risk of CVD, especially in patients with diabetes.

The study of 112 patients with biopsy-proven NAFLD used the Kleiner score, a histological measure of NAFLD severity [Kleiner D et al. *Hepatology* 2005]. Kleiner scores assess the degree of steatosis, lobular inflammation, hepatocyte "ballooning," and fibrosis, with higher scores indicating more severe liver disease. The primary aim of the study was to see if this histopathological marker correlated with cardiovascular (CV) risk and if scores were higher in people who were already known to have a high CV risk (eg, those with diabetes).

Inclusion criteria included participant age >18 years; biopsy-proven NAFLD with associated Kleiner score; no preexisting underlying liver disorders (eg, alcoholic liver disease, autoimmune hepatitis, primary biliary cirrhosis), and lifetime weekly alcohol consumption that excluded harmful levels of consumption (<35 units [women] and <50 units [men]). The mean age of the study cohort was 48 years, and the mean Kleiner score was 5.3. Thirty-two subjects (31%) had diabetes. The median Framingham Risk Score (FRS) was 13.20% (16.20), and the median QRISK score was 7.85% (16.73). The mean body mass index (BMI) of participants was 34.33±5.91 kg/m$^2$.

Kleiner scores showed a high association with both CV risk models—FRS (95% CI, 1.1164 to 3.226; p<0.001; Figure 1) and QRISK2 (95% CI, 1.109 to 2.631; p<0.001; Figure 2). They were also higher in the subgroup with diabetes compared with participants without the disease (6.4±2.0 vs 4.7±2.1, respectively). The Kleiner score was associated with HbA1C (95% CI, 0.080 to 0.725; p=0.015), and diabetes was independently associated with Kleiner score (p=0.04).

**Figure 1. Kleiner Score is Associated with FRS.**

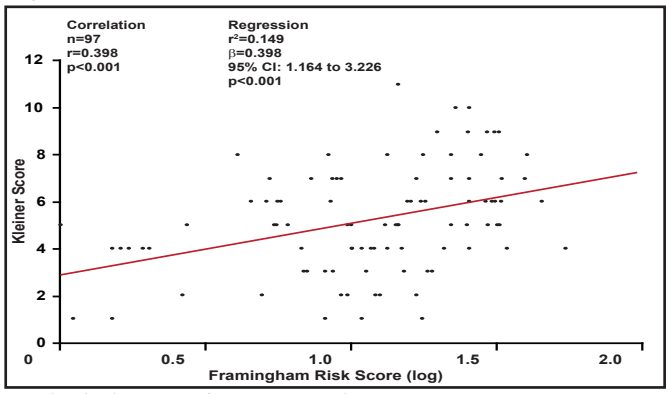


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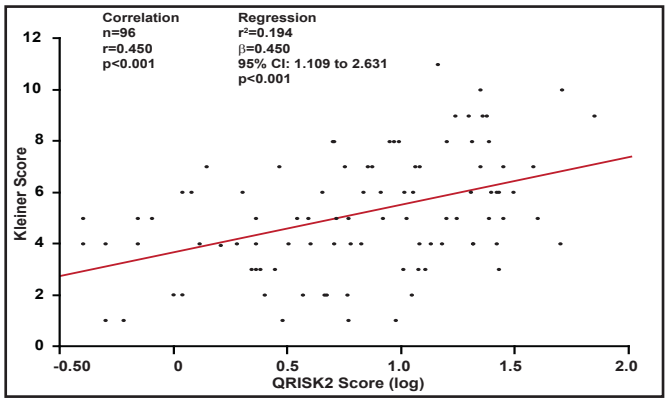
**Figure 2. Kleiner Score is Associated with QRISK2.**

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The authors found a moderately strong association between a gold standard measure of NAFLD disease severity (Kleiner score) and two estimates of 10-year CVD risk scores. The relationships were independent of markers of glucose control (or diabetes) and obesity. Kleiner score was higher in people with diabetes, and diabetes was also independently associated with Kleiner score. Measures of body fat (BMI and truncal fat) were not strongly associated with Kleiner scores.

These findings are consistent with and provide further insight into understanding data from several epidemiological studies that have shown that NAFLD, especially in its more severe forms, is linked to an increased risk of CVD, independent of underlying cardiometabolic risk factors. The data from Prof. Byrne and colleagues suggest that NAFLD is not merely a marker of CVD but may also be actively involved in its pathogenesis, via a worsening of CV risk factors that occurs in more severe forms of NAFLD. "We need more prospective studies to see what markers may be used to help stratify who requires a diagnostic liver biopsy to diagnose the severity of NAFLD and how best to manage people who have NAFLD," said Prof. Byrne.

## Efficacy and Safety of Once-Weekly Exenatide Versus Daily Liraglutide in Subjects with T2DM (DURATION-6)

*Written by Rita Buckley*

The Safety and Efficacy of Exenatide Once Weekly Versus Liraglutide in Subjects with Type 2 Diabetes [DURATION-6; NCT01029886] trial did not meet the prespecified primary endpoint that once-weekly injections of exenatide were noninferior to daily injections of liraglutide in reducing HbA1C in type 2 diabetes mellitus (T2DM) patients who were treated with lifestyle modification and oral antihyperglycemic medications. John Buse, MD, PhD, University of North Carolina, Chapel Hill, North Carolina, USA, presented results of the trial.

DURATION-6 was an international, multicenter, open-label, randomized trial that was designed to compare injections of once-weekly exenatide, a glucagon-like peptide (GLP-1) receptor agonist, to once-daily liraglutide with regard to glycemic control, body weight, and safety in patients with T2DM. The primary outcome of the study was the change in HbA1C from baseline to treatment endpoint. Noninferiority was concluded if the upper limit of the confidence interval for the treatment difference in change from baseline HbA1C (exenatide - liraglutide) was <0.25%.

Inclusion criteria included a diagnosis of T2DM; suboptimal glycemic control, as evidenced by an HbA1C measurement at the study start of 7.1% to 11.0%; a body mass index ≤45 kg/m$^2$; lifestyle modification (diet and exercise) and treatment with one of the following single oral antihyperglycemic agents or a combination of them, administered at maximum tolerated dose: metformin, sulfonylureas, metformin plus a sulfonylurea, or metformin plus pioglitazone.

Patients were recruited from 19 countries. Average study participant age was 57 years, and approximately 55% was male. The duration of diabetes since diagnosis was approximately 9 years. In addition to the patients' baseline medication of oral antidiabetic drugs, subjects were randomized to receive 2 mg exenatide once weekly (n=461) and a standard-dose titration of liraglutide, beginning at 0.6 mg and ending at 1.8 mg by Week 4 of the study (n=450). The 10-week safety follow-up was performed after the 26-week study.

The mean reduction in HbA1C for patients who were on the once-weekly dosing schedule of exenatide was 1.28% compared with 1.48% in patients who received liraglutide at 1.8 mg daily (p<0.002).