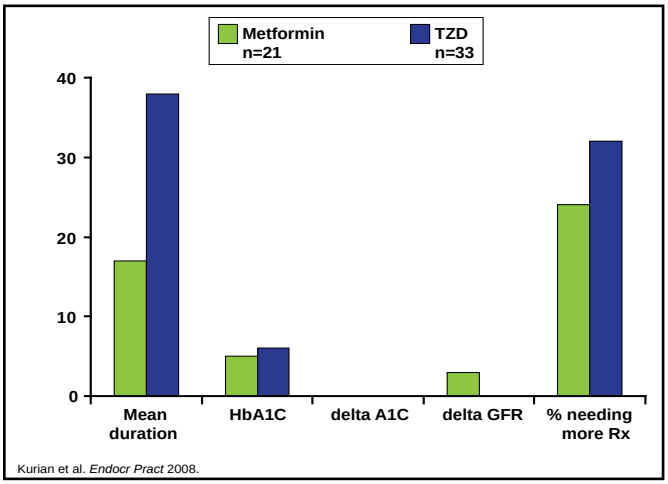
units every 1 to 2 days or a body weight dosing formula. In extremely obese patients, body weight dosing is used. Patients with more moderate hyperglycemia receive education and evaluation, possibly leading to adjustment of their immunosuppressive agents and insulin or oral therapies, as needed.

When using oral antidiabetic agents, metformin is affordable, effective, and well tolerated, with no associated weight gain or hyperglycemia. Although there are little data on its use in the transplant population, it appears safe in patients who do not have renal insufficiency, significant liver disease, or congestive heart failure.

The thiazolidinediones (TZD) appear to be safe for use in patients with chronic kidney disease; however, they should be used cautiously in patients with liver dysfunction. It is important to note that cardiovascular risk that is associated with TZD use is unclear, and TZD therapy may increase the risk of fractures and may result in weight gain and edema.

A retrospective study that addressed the duration and efficacy of TZDs versus metformin in transplant patients found that while HbA1C levels were similar between the two groups, patients who were on TZDs had a greater duration of glycemic control (Figure 1). However, they ultimately needed further treatment as the study progressed. Additionally, metformin demonstrated a greater effect on glomerular filtration rate (GFR) levels, raising concerns about its use in patients with renal disease [Kurian B et al. *Endocr Pract* 2008].

Figure 1. Metformin Versus TZD in Renal Transplant Recipients.



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Secretagogues are also effective in NODAT patients, but these compounds require more frequent dosing and are metabolized via CYP3A4, raising concerns regarding drug interactions. There are little data on other oral hyperglycemic options in this population.

In conclusion, it is clear that more research is needed as to the best approach to prevent and treat NODAT. Greater collaborations between diabetologists and transplant physicians are required to ensure the delivery of optimum care.

Noninsulin Antidiabetic Agents: Typical and Atypical Effects

The incretin mimemics—dipeptidyl peptidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 (GLP-1) receptor agonists—stimulate insulin secretion and inhibit glucagon secretion to stabilize serum glucose levels. They provide blood glucose reductions that are similar to other antidiabetic drugs, with no associated weight gain and, in the case of the GLP-1 agonists, some weight loss [Drucker DJ, Nauck MA. *Lancet* 2006; Russell-Jones D. *Int J Clin Pract* 2010].

There is also some evidence from animal and human models that these compounds may provide β-cell preservation. In animal studies, they have been shown to increase neogenesis from islet precursor cells, induce β-cell replication from mature β-cells, prevent apoptosis in toxic environments, determine insulin biosynthesis that results in greater β-cell mass, improve β-cell functional status, and increase recruitment of dormant cells that do not respond to high glucose levels, thus increasing the actively recruiting β-cell mass [Brubaker PL, Drucker DJ. *Endocrinology* 2004; Holz GG, Kuhtreiber WM, Habener JF. *Nature* 1993].

In human studies, patients who received the DPP-4 inhibitor sitagliptin demonstrated a reduced proinsulin: insulin ratio, indicating greater processing of proinsulin to insulin and evidence of healthier β-cells [Riche DM et al. *Am J Med Sci* 2009].

In addition, 3-year results in patients who received exenatide or glargine insulin found increased insulin sensitivity in the exenatide patients over baseline but no change from baseline in the insulin group. Whether the weight loss from exenatide or some other mechanism of action is responsible for the improved insulin sensitivity remains to be determined [Bunck MC. Abstract #848, EASD 2010. Stockholm, Sweden].

Pancreatitis and Incretin Mimetics

A concern has been raised about the risk of severe pancreatitis in patients who take exenatide. These cases

were reported as part of postmarketing surveys, although none were seen during clinical trials.

Studies have found that pancreatitis is significantly more prevalent in people with diabetes, with the risk related to traditional risk factors for the disease, including alcohol intake, obesity, hypertriglyceridemia, gallstones, and the use of certain antihypertensive drugs. An evaluation of a claims-based database that contained more than 40,000 individuals who received either exenatide or sitagliptin, matched against an equal number of patients who received metformin or glyburide initiators, found a relative risk of 1.0 (95% CI, 0.6 to 1.7, exenatide; 95% CI, 0.5 to 2.0, sitagliptin), providing no evidence of a direct association between the drugs and pancreatitis [Dore DD et al. *Curr Med Res Opin* 2009].

Incretin Mimemics and C-Cell Abnormalities

Concern has also been raised about the drug liraglutide, after animal studies found a slightly higher risk of C-cell abnormalities and C-cell medullary thyroid carcinoma, a cancer that is very rare in humans. However, further studies found significant differences in C-cell response to GLP-1 receptor agonist stimulation compared with human C-cell response. Specifically, rat C-cells demonstrated far greater calcitonin release and adenylate cyclase activation than human cells, in which no immediate response was seen after GLP-1 receptor activation [Knudsen B et al. *Endocrinology* 2010]. No cases of medullary thyroid carcinoma have been reported in humans who have taken liraglutide, and it is unlikely that any direct association between this rare form of cancer and the GLP-1 receptor agonist will be found.

Incretin Mimetics and Cardiovascular Effects

Studies that have been conducted in dogs, rats, and pigs using exenatide and liraglutide have found far smaller areas of necrotic tissue following induced myocardial infarction (MI) on animals who received exenatide or liraglutide at the time of MI [Timmers L et al. *J Am Coll Cardiol* 2009; Sauve M et al. *Diabetes* 2008; Bose AK et al. *Diabetes* 2005].

Although large human studies are pending, a small pilot study, involving 5 patients with type 2 diabetes and 5 without who arrived in the emergency department with acute MI and low left ventricular ejection fraction, found that those who were randomized to a 72-hour infusion of a GLP-1 receptor agonist demonstrated significantly improved left ventricular ejection fraction, global wall motion score indexes, and regional wall motion score indexes compared with controls ($p<0.01$ for all) [Nikolaidis LA et al. *Circulation* 2004].

There is also some evidence that the DPP-4 inhibitors may significantly reduce cardiovascular events in patients with diabetes compared with sulfonylureas [Filozof C & Gautier JF. *Diabet Med* 2010; Ferrannini E et al. *Diabetes Obes Metab* 2009]. This conclusion, however, is based on small numbers of events in studies that aimed at demonstrating improved glycemic control. Larger trials are needed to better characterize the benefits and risks of incretin-based antidiabetic medications with regard to cardiovascular outcome.

The Future of Antidiabetic Drug Development: GPR40-Selective Agonist TAK-875

GPR40 is a G-protein-coupled receptor that is highly expressed in pancreatic β-cells and is involved in free fatty acid-induced insulin secretion. TAK-875 is a GPR40-selective agonist that improves glucose control in type 2 diabetic animal models by stimulating glucose-dependent insulin secretion. In a study that was presented by Hiroaki Yahiro, Takeda Pharmaceuticals, Osaka, Japan, researchers examined the effects of the compound on insulin and glucagon secretion and on intracellular calcium (Ca^{2+}) in pancreatic β- and α-cells from human and rat islets.

The islets were isolated through collagenase digestion. Radioimmunoassay was used to measure secreted insulin and glucagon. The human islets were derived from normal subjects aged 33 to 57 years.

In static incubation, TAK-875 augmented insulin secretion from rat and human islets at high (16 mmol/L) but not low (1 mmol/L) glucose.

An islet perfusion experiment was conducted to determine the glucose-dependent insulinotropic action of TAK-875. The compound enhanced both first- and second-phase insulin secretion at high glucose but had no effect at low glucose. It demonstrated comparable expression with a GLP-1 agonist and a sulfonylurea, enhancing glucose-dependent insulin secretion as much as GLP-1 in the static incubation experiment.

In both rat and human islets, TAK-875 had no effect on glucagon secretion, regardless of glucose dosing. Calcium measurements in intact rat and human islets showed that TAK-875 enhanced glucose-induced calcium in β-cells, while