Update on Insulin Therapy for Type 2 Diabetes

Thomas Donner and Miguel Muñoz

Division of Endocrinology and Metabolism, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287

Type 2 diabetes is characterized by insulin resistance and impaired insulin secretion at diagnosis and by progressive β-cell dysfunction over time. Insulin therapy is thus frequently required during the course of the disease to maintain glycemic control and prevent diabetes complications. Insulin should be initiated when alternative antihyperglycemic agents have failed or when symptomatic or marked hyperglycemia is present. Recent studies demonstrate that the addition of basal, prandial, basal/bolus, or premixed insulins to existing antihyperglycemic regimens effectively lowers glycosylated hemoglobin (HbA_{1c}). The long-acting insulin analogs cause less nocturnal hypoglycemia than bedtime NPH, with comparable HbA_{1c} reductions. Insulin detemir confers a weight advantage over glargine or NPH. Rapid-acting insulin analogs control postprandial hyperglycemia more effectively than regular insulin and modestly lower HbA_{1c}. For selected patients with severe insulin resistance, U-500 is a less expensive and potentially more effective alternative to U-100 insulin. Adverse effects of insulin, including weight gain and hypoglycemia, can be minimized by initial use of basal insulins in combination with metformin, incretin mimetics, or dipeptidyl-peptidase-IV inhibitors. Although *in vitro* studies suggest that hyperinsulinemia may promote tumorigenesis, no currently available insulin has been shown to increase cancer rates. Targeting near-normal glucose levels in insulin-treated patients should be reserved for those of younger age with a longer life expectancy, a shorter duration of diabetes, and little or no end-organ complications. A higher HbA_{1c} target of 7–8% is more appropriate for patients less likely to benefit from intensive control and in those at high risk for severe hypoglycemia. **(*J Clin Endocrinol Metab* 97: 1405–1413, 2012)**

Type 2 diabetes (T2DM) currently affects 8.3% of Americans (1). Incidence rates of T2DM are rising among children, representing one third of all new diabetes cases in the 10- to 19-yr age group. Among those aged 65 and older, diabetes prevalence rises to 26.9%. Diabetes remains the leading cause of end stage renal disease and blindness among adults in the United States and is the leading cause of nontraumatic amputations. Earlier and more frequent cardiovascular events are the cause of death in 70–80% of patients. These factors contribute to a 2-fold higher mortality rate among patients with diabetes relative to age-matched controls. Because the development of microvascular diabetes complications can be greatly reduced by improved glycemic control, early, aggressive, and sustained diabetes management is needed. Insulin deficiency is a central pathogenic factor in the development of hyperglycemia and is typically progressive during the course of the disease. More profound insulin deficiency leads to failure of single or combination non-insulin antihyperglycemic agents. How insulin therapy is best introduced and safely administered to maintain glycemic control in T2DM patients is the focus of this review.

The Case for Tight Glycemic Control Using Insulin in T2DM

Aggressive insulin or sulfonylurea therapy in T2DM patients in the UK Prospective Diabetes Study (UKPDS) and insulin therapy in the Kumamoto study significantly re-

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Abbreviations: DPP-IV, Dipeptidyl-peptidase-IV; FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin; IGF1R, IGF-I receptor; NPH, neutral protamine Hagedorn; SH, severe hypoglycemia; T2DM, type 2 diabetes.

duced the development or progression of microvascular complications by 17% (retinopathy, UKPDS) to 100% (macroalbuminuria, Kumamoto) after 8–10 yr of follow-up (2, 3). These early trial results made intensive glycemic management a cornerstone of T2DM patient care. Among intensively controlled patients in the VADT (Veterans Affairs Diabetes Trial), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), and ACCORD (Action to Control Cardiovascular Risk in Diabetes), 41–90% required insulin therapy *vs.* 24–74% in the standard control groups (4–6). Intensive control led to reductions in the incidence of nephropathy in all three trials and in some measures of retinopathy and neuropathy in ACCORD when compared with standard control after 3.5 to 5.6 yr of mean follow-up [mean achieved glycosylated hemoglobin (HbA_{1c}), 6.4–6.9 *vs.* 7.0–8.4%]. Greater weight gain and more frequent hypoglycemia were seen among intensively treated patients in all three trials. Nonsignificant reductions in cardiovascular events of 6, 10, and 12% were seen with intensive diabetes control when compared with standard control in ADVANCE, ACCORD, and VADT respectively. Ten years after cessation of randomized interventions in the UKPDS, significant reductions in myocardial infarctions (15%) and in all-cause mortality (13%) were observed among patients initially assigned to intensive medical management (2). An increased mortality rate was observed in ACCORD after 3.5 yr of intensive therapy when patients were targeted to an HbA_{1c} of less than 6.0%—73% of whom received insulin. Intensively treated patients in ACCORD who had not had a cardiovascular event before randomization or whose baseline HbA_{1c} was no greater than 8% had fewer fatal and nonfatal cardiovascular events than those receiving standard therapy (5), suggesting that certain subgroups of patients may derive a cardiovascular benefit from intensive diabetes management. Studies to date have not shown whether exogenous insulin has uniquely beneficial or harmful effects on cardiovascular outcomes when compared with other antihyperglycemic agents. The ORIGIN (Outcome Reduction with Initial Glargine Intervention) Trial is evaluating whether glargine-mediated normoglycemia can reduce cardiovascular events in 10,000 subjects at high risk for vascular disease with impaired fasting glucose, impaired glucose tolerance, or early T2DM (7). Results from ORIGIN are due in June, 2012.

Insulin Deficiency in the Pathogenesis of T2DM

T2DM is characterized by insulin resistance and impaired pancreatic β-cell function at diagnosis and progressive β-cell dysfunction over time. Genes identified as predisposing to diabetes predominantly diminish basal or glucose-stimulated insulin secretion or β-cell mass. Glucotoxicity, lipotoxicity, increased islet amyloid polypeptide accumulation, and excessive inflammatory cytokines have been identified as likely pathogenic mechanisms leading to β-cell failure in T2DM (8). Collectively, these cause decreased first-phase and, later, second-phase insulin secretion, accelerated β-cell apoptosis, and reduced β-cell mass. The UKPDS found an approximate 50% reduction in estimated β-cell function at diagnosis, based on homeostatic model assessment-B calculations, and a progressive decline in insulin secretion over the next 6 yr (9). A decline in β-cell function was seen, irrespective of the antihyperglycemic agents used, and correlated closely with the degree of glycemic deterioration. Antihyperglycemic medication requirements thereby predictably increase with longer duration of T2DM.

Insulin in T2DM

Currently in the United States, 12% of T2DM patients take insulin only, whereas 14% take both insulin and oral medication (1). The progressive loss of β-cell function in patients with T2DM often leads to decreased effectiveness and eventual failure of non-insulin antihyperglycemic therapy alone. The VADT, ADVANCE, and ACCORD trials demonstrate an increasing need for insulin therapy among patients with longer-standing T2DM subjected to lower HbA_{1c} targets (Table 1). Addition of insulin to existing antihyperglycemic agents helps restore glycemic control. Differential effects on weight, fluid retention, and hypoglycemia risk after starting insulin will be influenced by existing antihyperglycemic therapies in the individual patient. Table 2

TABLE 1. Insulin requirements in T2DM: disease duration and HbA_{1c} target

Study (Ref.)	Baseline age (yr)	T2DM duration (yr)	HbA_{1c} target (%)		% Requiring insulin at end of study	
			Standard	Intensive	Standard	Intensive
VADT (4)	60.4	11.5	<9.0	<6.0	74	90
ACCORD (5)	62.2	10.0	<7.0–7.9	<6.0	58	73
ADVANCE (6)	66.0	7.9	Local standard	<6.5	24	41

TABLE 2. Effects of insulin regimen on outcomes

First author, year (Ref.)	Intervention	Control	No. of subjects	Study duration	% HbA_{1c} reduction	Weight change (kg)	Adverse events	Additional outcomes
Rosenstock, 2008 (11)	Detemir + oral agents	Glargine + oral agents	582	12 months	−1.5 *vs.* −1.5	+2.7 *vs.* +3.5	Hypoglycemia, 5.8 *vs.* 6.2 episodes/patient/yr; major, 2 *vs.* 3%	HbA_{1c} ≤7.0% without hypoglycemia, 33 *vs.* 35%; mean daily dose, 0.78 *vs.* 0.44 IU/kg
Holman, 2009 (12)	Detemir + oral agents	Biphasic insulin aspart or prandial aspart + oral agents	708	36 months	−1.2 *vs.* −1.3 *vs.* −1.2	+3.6 *vs.* +5.7 *vs.* +6.4	Hypoglycemia, 2.7 *vs.* 3.8 *vs.* 5.7 episodes/patient/yr; major, 0.9 *vs.* 2.6 *vs.* 2.1%/yr	HbA_{1c} ≤6.5%, 43.2 *vs.* 31.9 *vs.* 44.7%
Raskin, 2009 (16)	Biphasic insulin BIAsp 30 + MET + PIO	MET + PIO	200	34 wk	−1.5 *vs.* −0.2	+4.6 *vs.* +0.8	Hypoglycemia, 8.3 *vs.* 0.1 episodes/patient/yr	HbA_{1c} <7%, 76 *vs.* 24%; HbA_{1c} <6.5%, 59 *vs.* 12%
Davidson, 2010 (17)	U-500 regular insulin	U-100 insulins	11	Mean, 26 months	−2.4 (last value)	+4.2	1 severe hypoglycemic event	Total units/kg, 3.2 *vs.* 3.3
Arnolds, 2010 (27)	EXE + MET + glargine	MET + glargine	48	4 wk	−1.9 *vs.* −1.2	−0.9 *vs.* 0	Hypoglycemia, 1.7 *vs.* 1.6 events/subject/yr (NS); total adverse events, 47 (62.5%) *vs.* 10 (25%)	AUCBG 0–6 h, 606 *vs.* 728 mg/dl/h
Buse, 2011 (28)	EXE + basal insulin	Basal insulin	259	30 wk	−1.7 *vs.* −1.0	−1.8 *vs.* +1.0	Study withdrawal rate, 9 *vs.* 1%; hypoglycemia, 25 *vs.* 29% (NS)	HbA_{1c} ≤7%, 60 *vs.* 35%; HbA_{1c} ≤6.5%, 40 *vs.* 12%; change in insulin dose, +13 *vs.* +20 U
Hollander, 2008 (29)	Detemir + aspart	Glargine + aspart	319	12 months	−1.5 *vs.* −1.7	+2.8 *vs.* +3.8	Major hypoglycemia, 4.7 *vs.* 5.7%	
Buse, 2011 (30)	Glargine	Lispro 75/25	1818	6 months	−1.4 *vs.* −1.6	+3.7 *vs.* +5.4	Hypoglycemia, 45.3 *vs.* 49.9%	SH, 2.9 *vs.* 4.2% (NS)
Charbonnel, 2010 (31)	PIO + insulin therapy	Insulin therapy	1760	34 wk	−1 *vs.* −0.4	+4.2 *vs.* −0.1	Peripheral edema, 31 *vs.* 18%; hypoglycemia, 42 *vs.* 29%	% Discontinued insulin, 8.6 *vs.* 1.7%; % insulin dose change, −9 *vs.* + 17.5%; HbA_{1c} <7%, 41.7 *vs.* 24.3%
Hollander, 2011 (32)	SITA + detemir	SITA ± SU	217	26 wk	−0.8 to −0.3	−1.7 *vs.* −0.8	Hypoglycemia, 1.3 *vs.* 1.7 (NS) episodes/patient/yr	Lowering of fasting plasma glucose, −54.3 to −33.8 mg/dl; HbA_{1c} <7%, 45 *vs.* 24%

PIO, Pioglitazone; MET, metformin; BIAsp 30, biphasic insulin aspart 30/70; SITA, sitagliptin; SU, sulfonylurea; EXE, exenatide; NS, not significant; AUCBG, blood glucose area under the curve.

summarizes the findings of recent studies that compare insulin regimens or insulin added to antihyperglycemic agents.

Insulin remains the most potent antihyperglycemic agent available for uncontrolled T2DM patients. It can significantly improve diabetes control when added to other antihyperglycemic agents, given as once-daily basal insulin or via combinations of basal and rapid-acting (prandial) insulins, based on the individual patient's glycemic profile and degree of desired control. Its use is indicated when signs of severe insulin deficiency are present, including ketosis, uncontrolled diabetes despite use of multiple non-insulin antihyperglycemic agents, or symptomatic hyperglycemia with weight loss, polyuria, and polydipsia. Insulin initiation is indicated when fasting plasma glucose (FPG) levels are frequently above 250 mg/dl, random glucose levels are consistently above 300 mg/dl, or the HbA_{1c} is above 10% (10). Insulin should also be considered whenever the HbA_{1c} is above 8.5%, when patients are already on one or more antihyperglycemic agents, to achieve more effective control. Basal insulin, either bedtime neutral protamine Hagedorn (NPH) or once daily glargine or detemir, is effective when added to oral agents starting at a dose of 10 U daily or 0.2 U/kg (10). In patients uncontrolled on oral agents with a baseline HbA_{1c} of 7.0–10.0%, basal insulin lowers HbA_{1c} 1.2–1.5% (11, 12). Such treat-to-target studies have patients titrate basal insulin dosages up every 2–3 d by 1–4 U based on treatment target algorithms to achieve FPG levels in the 70- to 126-mg/dl range. Studies targeting a FPG of less than 108 mg/dl achieve modestly better success in achieving an HbA_{1c} of less than 7% (63.2 *vs.* 52%) than those targeting a FPG of less than 126 mg/dl, with mildly higher rates of hypoglycemia (11, 12).

The pharmacokinetics of currently available insulins are listed in Table 3. Intermediate-acting NPH insulin may be given to T2DM patients at bedtime to control fasting hyperglycemia, with or without a morning injection to control daytime glycemia. Long-acting insulin analogs glargine and detemir may be dosed once daily in the morning or evening. Addition of morning basal insulin may be added to an evening dose when fasting, but not predinner, glucose levels are at target levels (12, 13). The proteolytic cleavage of protamine occurs at inconsistent rates leading to considerable inter- and intrapatient variability in ab-

TABLE 3. Characteristics of currently available insulins

Insulin	Onset of action (h)	Peak action (h)	Duration (h)	Comments
NPH	1–3	4.0–10	10–20	Greater nocturnal hypoglycemia risk c/w other basal insulins
Glargine	2–4	No peak	20–24	Daily dosing
Detemir	2	No peak	16–24	1–2 times daily dosing
Lispro 75/25	0.25–0.5	5.8 (1.3–12)	12–24	Better postprandial control with more hypoglycemia than basal insulins
Lispro 50/50	c/w lispro	1.0	c/w lispro 75/25	When used TID, acts as a basal/bolus regimen
Aspart 70/30	0.17–0.33	2.4 ± 0.8	12–24	Better postprandial control with more hypoglycemia than basal insulins
Regular	0.5–1	2.0–3.0	5–8	More postprandial hypoglycemia than rapid-acting analogs
Lispro, aspart, glulisine	0.1–0.25	0.5–1.5	3–5	Can dose closer to meal and with better postprandial control c/w regular insulin
U-500 Regular	0.5–0.75	3.5–8.5	6 to >10	Greatly reduces volume of insulin required

Data abstracted from package inserts. Times are approximate only. Large variations between and within persons may be noted. Pharmacodynamics/kinetics are also dose-dependent. c/w, Comparable with; TID, three times daily.

sorption rates with NPH and greater degrees of nocturnal hypoglycemia when compared with the long-acting insulin analogs (14).

When compared with human regular insulin, the rapid-acting insulin analogs aspart, glulisine, and lispro are more rapidly absorbed and have an earlier peak and shorter duration of action, owing to more rapid degradation to insulin monomers. A meta-analysis of rapid-acting analogs demonstrated better postprandial glycemic control and a mean 0.4% lower HbA_{1c} when compared with human regular insulin, but with no reduction in severe hypoglycemia (SH) as is seen in type 1 diabetes patients (15). Rapid-acting analogs should be added to basal insulin when fasting glucose levels are under control but HbA_{1c} levels stay above goal or when measured postprandial glucose levels run consistently over 180 mg/dl. Starting doses of 10% of the total basal insulin dose before each meal but no more than 4–6 U was successfully used in the Treating To Target in Type 2 Diabetes (4-T) study (12). No clinically meaningful differences in pharmacodynamics, glycemia, or other clinical outcomes have been demonstrated between the three rapid-acting insulin analogs.

Premixed NPH and regular insulin as well as rapid-acting insulin analogs mixed with their intermediate-acting protamine suspension provide dual fasting and postprandial glycemic control with fewer injections. The addition of premixed insulins to patients who have failed oral antihyperglycemic therapy lowers HbA_{1c} while increasing rates of hypoglycemia. In a recent trial, biphasic insulin aspart 30/70 (BIAsp 30) was added to optimized metformin and pioglitazone therapy in subjects with uncontrolled T2DM (16). Twice-daily dosing was titrated to a prebreakfast and predinner plasma glucose target of 80–110 mg/dl. As compared with metformin plus pioglitazone alone, addition of aspart 70/30 led to a 1.3% greater reduction in HbA_{1c} and a 3.8 kg greater weight gain, whereas hypoglycemia rates increased from 0.1 to 8.3 episodes per patient year.

In the 4-T trial, patients unsuccessfully controlled on maximally tolerated dosages of metformin and a sulfonylurea were randomized to addition of biphasic insulin (aspart 30 twice daily), prandial insulin (aspart three times daily), or basal insulin (once or twice daily detemir) targeting glucose levels of 72–108 mg/dl before meals and 90–126 mg/dl 2 h after meals (12). After 3 yr, the mean HbA_{1c} reductions from baseline were similar, 1.3% in the biphasic group, 1.4% in the prandial group, and 1.2% in the basal group. More patients achieved HbA_{1c} levels of less than 7% in the prandial group (67.4%) or the basal group (63.2%) than in the biphasic group (49.4%). There was less weight gain in the basal group (3.6 kg) than in either the biphasic group (5.7 kg) or the prandial group (6.4 kg). Rates of hypoglycemia were lower in the basal group than in the biphasic or prandial groups (2.7, 3.8, and 5.7 episodes per patient per year, respectively). During the trial, a second type of insulin was added in response to HbA_{1c} concentrations persistently above 6.5% in 67.7–81.6% of patients. The results of the 4-T study support the initial addition of basal insulin to oral antihyperglycemic agents among uncontrolled patients with T2DM and the addition of rapid-acting prandial insulin in those still not achieving desired control. The majority of patients initially treated with basal insulin achieved glycemic control with lower rates of hypoglycemia and less weight gain than those in either the biphasic group or the prandial group.

U-500 regular insulin has a pharmacokinetic profile similar to NPH. It more effectively controls hyperglycemia

at a lower cost per unit of insulin than U-100 insulins in severely insulin-resistant patients. Uncontrolled T2DM patients who required more than 200 U of insulin daily were changed to U-500 insulin dosed before breakfast and dinner (17). U-500 insulin doses were titrated to attain target premeal glucose levels of 70–130 mg/dl. Six of 11 patients with HbA_{1c} levels over 7.5% and preprandial glucose concentrations in the target range had to have premeal lispro added to attain postprandial glucose levels of less than 160 mg/dl. Mean baseline HbA_{1c} levels fell from 9.9 to 7.1% with a mean 4.2-kg weight gain. Continuous insulin infusion using external pumps has not been shown to improve glycemic control or reduce hypoglycemia when compared with multiple insulin injections in patients with T2DM (18).

Attainment of glycemic targets using insulin remains difficult. In a recent review of 48 randomized clinical trials using insulin in T2DM patients with a mean baseline HbA_{1c} of 8.7%, only 40–54% achieved an HbA_{1c} of less than 7% (19). Home insulin titration algorithms based on treat-to-target studies have been proposed, but their effectiveness in helping patients attain the treatment success seen in clinical trials has not been studied.

Insulin-Induced Hypoglycemia

Hypoglycemia is a frequent and rarely fatal complication of insulin therapy, and it remains a major barrier to achieving glycemic control in patients with T2DM. The incidence of overall and severe hypoglycemia (requiring third-party assistance) in patients with T2DM receiving insulin is similar to that of type 1 diabetes and higher than that seen in patients on oral antihyperglycemic agents. A longer duration of diabetes places patients at increasing risk for hypoglycemia, correlating with declining endogenous insulin secretion and a greater dependence on exogenous insulin replacement.

Other risk factors for hypoglycemia among insulin-treated patients include renal insufficiency, older age, and lower HbA_{1c}. In ACCORD, each 1-yr increment in baseline age was associated with a 3% increase in the risk for SH (20). Hypoglycemic unawareness, a well-established risk factor for SH, is more common among patients age 65 yr or greater. This appears due in part to blunted autonomic and neuroglycopenic symptoms in the elderly when compared with middle-aged T2DM patients (21). In ADVANCE, those with cognitive dysfunction had a 2.1-fold greater risk of SH (22). Avoidance of hypoglycemia therefore takes on an even greater importance in the elderly population, given the greater prevalence of cardiovascular disease, cognitive dysfunction, and higher risk of falls and fractures.

Patients with T2DM who have had SH are at increased risk of death regardless of the intensity of their glycemic control. Hypoglycemia may lead to increased mortality due to a proarrhythmic effect mediated by sympathoadrenal activation and/or hypokalemia, or from cardiac repolarization. The stimulatory effects of hypoglycemia increase heart rate, systolic blood pressure, myocardial contractility, and cardiac output, which may adversely affect those with T2DM who frequently have underlying coronary artery disease. In subjects with T2DM and coronary artery disease, glucose levels below 70 mg/dl have been shown to cause ischemic electrocardiogram changes during continuous glucose and electrocardiogram monitoring (23).

In the VADT, ADVANCE, and ACCORD trials, intensive therapy leading to a mean HbA_{1c} of 6.3–6.9% (*vs.* 7.0–8.5% in the standard control group) resulted in SH among 2.7–21.2% of subjects, compared with 1.5–9.9% in the standard therapy group (4–6). Patients in ACCORD who experienced a severe hypoglycemic event were found to have a higher mortality rate (24). However, SH was not temporally associated with mortality, and those in the intensively treated group who experienced SH had lower mortality rates. The data suggest that patients having SH identify a higher risk, more frail population at an increased risk of death from other causes who should consequently be followed more carefully.

The rates of hypoglycemia in recent clinical trials adding basal insulin alone or in combination with bolus insulin to preexisting antihyperglycemic agents are summarized in Table 2. Similar HbA_{1c} reductions and comparable rates of overall or nocturnal hypoglycemia were observed when either glargine or detemir was added to oral agents in uncontrolled patients and doses of insulin were titrated to attain a FPG of less than 108 mg/dl (11). Adding prandial lispro to antihyperglycemic agents in uncontrolled T2DM patients led to more frequent hypoglycemia when compared with glargine (24.0 *vs.* 5.2 events per patient per year), despite attaining similar HbA_{1c} levels at study end (6.8 *vs.* 7.0%) (25).

Glycemic control improves with little extra hypoglycemia when either glucagon-like peptide-1 analogs or dipeptidyl-peptidase-IV (DPP-IV) inhibitors are added to glargine insulin. A 30-wk study randomized 259 adult patients with uncontrolled T2DM to twice daily exenatide or placebo (26). At study entry, subjects were receiving at least 20 U of daily insulin glargine alone or in combination with metformin or pioglitazone. Basal insulin therapy was titrated to a target FPG below 100 mg/dl in both groups. A 0.69% greater HbA_{1c} reduction was seen in the exenatide group as com-

pared with placebo, and weight decreased by 1.8 kg with exenatide and increased by 1.0 kg with placebo. No differences in minor hypoglycemic events were seen (25 *vs.* 29%). Arnolds *et al.* (27) randomized 48 subjects with T2DM uncontrolled on insulin glargine and metformin to exenatide, sitagliptin, or the continuation of glargine and metformin alone. In all groups, glargine was titrated to a FPG no greater than 100 mg/dl. Greater HbA_{1c} reductions were seen in the adjunctive exenatide and sitagliptin groups compared with glargine and metformin alone (−1.9, −1.5, and −1.2%, respectively). An HbA_{1c} of less than 7% was attained in 80.0, 87.5, and 62.5% of patients. No major hypoglycemic episode occurred in any of the three groups. Mild hypoglycemia occurred at rates of 10, 3.3, and 1.6 events per subject year in the exenatide adjunctive, sitagliptin adjunctive, and metformin/glargine groups, respectively. Body weight decreased 0.9 kg in the adjunctive exenatide group and was stable in the other two groups. Buse *et al.* (28) studied the effects of adding exenatide or placebo to uncontrolled T2DM patients treated with glargine, metformin, and/or pioglitazone. The addition of exenatide reduced HbA_{1c} to 6.6 *vs.* 7.5% in the optimized glargine group, with comparably low hypoglycemia rates.

Insulin-Induced Weight Gain

Although insulin therapy is associated with modest weight gain when added to uncontrolled T2DM patients, the degree of weight gain may vary by the type of insulin given (Table 2). When added to existing oral therapy, once or twice daily insulin detemir led to less weight gain as compared with glargine among study completers (3.0 *vs.* 3.9 kg) despite similar end-trial glycemic control (11). Less weight gain was seen with detemir than glargine as a basal-bolus regimen with insulin aspart, despite comparable glycemic control (13, 29). A recent meta-analysis of trials comparing NPH with glargine showed less nocturnal hypoglycemia and greater weight gain with glargine insulin, with comparable HbA_{1c} lowering (14). The etiology of lower weight gain with detemir when compared with NPH or glargine is unknown. Basal insulin added to oral antihyperglycemic agents leads to less weight gain than either biphasic insulin aspart or prandial aspart insulin, despite similar 3-yr HbA_{1c} reductions (12). When compared with adding daily insulin glargine to oral antihyperglycemic agents in uncontrolled T2DM patients, adjunctive lispro mix 75/25 led to a modestly better HbA_{1c} reduction (1.6 *vs.* 1.4%), but at the expense of a 1.7 kg greater weight gain (30).

Variable effects on weight are seen when insulin is combined with thiazolidinediones, sulfonylureas, DPP-IV inhibitors or glucagon-like peptide-1 agonists. Insulin-treated T2DM patients uncontrolled on antihyperglycemic agents randomized to pioglitazone had a 0.6% greater HbA_{1c} reduction when compared with placebo treatment (31), but had more peripheral edema (31 *vs.* 18%), weight gain (+4.2 *vs.* −0.1 kg), and hypoglycemia (42 *vs.* 29%). The addition of insulin detemir together with sitagliptin to uncontrolled T2DM subjects on oral antihyperglycemic agents resulted in a 0.55% greater HbA_{1c} reduction with a similar, insignificant weight loss when compared with sitagliptin ± sulfonylurea (32). Studies consistently show that exenatide added to insulin-requiring T2DM patients reduces weight while improving glycemic control (26–28).

Barriers to Insulin Therapy

Physicians and their patients with T2DM are often resistant to starting insulin therapy, which may delay appropriate initiation of insulin by many years. Medical providers weigh concerns over the time needed to initiate and titrate insulin dosages, the physical and intellectual capabilities of their patients, and insulin-induced hypoglycemia and weight gain. Patients commonly perceive their need for insulin as a failure to control their disease and negotiate for longer trials of lifestyle modification. Educating patients about the progressive nature of the disease, the common need for insulin with longer duration of diabetes, the alleviation of symptoms of uncontrolled diabetes, and the prevention of diabetes complications with tighter glycemic control may all help gain patient acceptance of insulin therapy. Once insulin is started, intentional insulin omission is common and correlates with poor glycemic control. A study of 502 adults with diabetes found that a majority intentionally missed insulin injections, and that older age, lower income and education, pain, and embarrassment were risk factors among T2DM patients for insulin omission (33). Identification of the cause of insulin omission among individual patients may help providers better tailor strategies that address barriers to insulin adherence.

Exogenous Insulin and Malignancy

T2DM is a well-established risk factor for numerous malignancies including cancer of the breast, pancreas, colorectum, liver, kidney, and endometrium and non-Hodgkin lymphoma. Mortality rates are also higher among cancer patients with comorbid diabetes and among patients with T2DM who use insulin. *In vitro* studies demonstrating mitogenic effects of insulin at high concentrations and carcinogenic effects of insulin binding to the IGF-I receptor (IGF1R), suggest that hyperinsulinemia may promote tu-

morigenesis. It is unknown whether exogenous insulin increases cancer risk. Insulin glargine has been the most studied insulin, due to early *in vitro* studies showing increased mitogenic potency and a 6- to 8-fold increase in IGF1R binding. However, glargine is rapidly degraded to metabolites M1 and M2. The predominant metabolite, M1, has been shown to have a 0.4-fold binding affinity to the IGF1R compared with human insulin. A recent review by Müssig *et al.* (34) of large epidemiological studies did not support an increased risk of malignancy among glargine-treated patients when compared with other insulin therapies. Whether increased use of antihyperglycemic agents that can reduce exogenous insulin requirements and decrease hyperinsulinemia will lower cancer rates in T2DM is unknown.

New Insulin Formulations

Newer long- and short-acting insulin analogs are in development to provide even more physiological insulin alternatives. Insulin degludec is an ultra-long-acting basal analog that forms multihexamers after sc injection, from which insulin monomers slowly dissociate into circulation. This leads to a half-life of more than 24 h. In a 16-wk trial of once daily or three times a week degludec titrated to a fasting glucose target of 72–108 mg/dl, similar HbA_{1c} reductions and low rates of hypoglycemia were seen when compared with once daily glargine (35).

Linjeta (formerly VIAject) is an ultrafast-acting human insulin formulation containing EDTA and citric acid. These additives lead to more rapid hexameric insulin dissociation into insulin monomers after sc injection and a more rapid increase and faster decline in insulin levels. The time to half maximal activity of Linjeta was found to be 33 min, 18 min faster than insulin lispro and 33 min faster than regular human insulin (36). Linjeta holds promise to reduce postprandial hyperglycemia and late postprandial hypoglycemia and has been shown to lessen postprandial oxidative stress and improve endothelial function in patients with T2DM (37).

Applications for Food and Drug Administration approval of biosimilar insulins may appear after patent protections on current insulin analogs begin to expire, starting with Humalog (insulin lispro) in 2013. Approval of biosimilar insulins will face great challenges in the United States, given the narrow therapeutic window of insulin. Biosimilar insulins will need to demonstrate consistent insulin action, dosing accuracy of the delivery device, safety, and tolerability of insulins whose manufacturing and formulation may differ from the original biopharmaceutical product (38).

Goals of Therapy for Insulin-Treated T2DM Patients

Large, randomized clinical trials have shown that glycemic lowering to a HbA_1 of 7% or less reduces microvascular complications in both new- and later-onset patients with T2DM (3, 4, 6, 39). Forty-one to 100% of subjects in the intensively controlled groups were treated with insulin during these trials. In the UKPDS, cardiovascular risk reductions became significant only after an additional 10 yr of extended follow-up of patients who had been intensively controlled with sulfonylureas or insulin (2).

Studies reviewed in this update suggest that glycemic targets should be individualized in patients on insulin. Because complications from moderate hyperglycemia typically take decades to develop, insulin therapy targeting near-normal glucose levels should be reserved for those who are likely to benefit the most—those of younger age with a longer life expectancy, with a shorter duration of diabetes, and with little or no end-organ complications. In such patients, the 2012 American Diabetes Association (ADA) guidelines recommending an HbA_{1c} level of 7% or less, preprandial plasma glucose levels of 70–130 mg/dl, and 2-h postprandial glucose levels of less than 180 mg/dl are appropriate. The ADA supports raising glycemic targets in those less likely to benefit from intensive control or in those at higher risk for SH. These include patients who are elderly and those with advanced diabetic, microvascular or macrovascular complications or other significant comorbidities, poor functional status, short life expectancy, or a prior history of SH. An HbA_{1c} target of 7–8% is more appropriate in such patients. Ismail-Beigi *et al.* (40) have recently published a framework that helps individualize glycemic targets based on these criteria. Recent trials also suggest that for most patients with uncontrolled T2DM, combination therapy with a basal insulin, rather than prandial or premixed insulins, and nonsulfonylurea agents (metformin, DPP-IV inhibitors, incretin mimetics) will lead to effective glycemic control without unacceptable degrees of consequent hypoglycemia or weight gain.

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Address all correspondence and requests for reprints to: Thomas Donner, M.D., Johns Hopkins University, 601 North Caroline Street, Suite 2008, Baltimore, Maryland 21287. E-mail: Tdonner1@jhmi.edu.

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