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Insulin Therapy for Reducing Cardiovascular Risk in Patients with Type 2 Diabetes

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Twenty-four percent of the adult American population have the metabolic syndrome. Although somewhat counterintuitive, carefully regulated treatment with insulin has been shown to reduce insulin resistance and may also retard the development of cardiovascular disease by preventing chronic hyperglycemia, a condition that synergistically contributes to many proatherogenic pathways, including glycoxidation, the polyol pathway, advanced glycation end products, interference with normal metabolic pathways, and stimulation of protein kinase C-β and proinflammatory pathways. This article describes some of the physiologic changes that occur when hyperglycemia and insulin resistance develop in patients with type 2 diabetes and discusses therapies, including insulin, that normalize glucose and reduce insulin resistance, thereby potentially reducing cardiovascular risk. Clinical Cornerstone® Supplement 4.

Cardiovascular disease (CVD) accounts for 80% of deaths among patients with type 2 diabetes (1). Recent evidence suggests that insulin resistance, which may lead to hyperglycemia, hypertension, lipid abnormalities (hypertriglyceridemia; small, dense low-density lipoproteins [LDL], and low levels of high-density lipoproteins [HDL]), and thrombotic disorders, contributes to CVD. The downstream effects of insulin resistance stimulate the hormonal growth response that leads to atherosclerosis and CVD. Therefore, diminishing insulin resistance is key to minimizing cardiovascular risk in patients with type 2 diabetes.

KEY POINT

Insulin therapy is not associated with cardiovascular risk. Treatment with insulin improves glycemic control and hyperglycemia, thereby reducing cardiovascular risk.

HYPERGLYCEMIA

As shown in the United Kingdom Prospective Diabetes Study (UKPDS) (2), hyperglycemia, which can be manifested by either elevated hemoglobin A1C concentration or fasting plasma glucose (FPG) or both, is one of the major contributors to vascular disease in patients with type 2 diabetes. Patients with diabetes are 2 to 4 times more likely to develop coronary artery disease (CAD) than the general population (3); mortality attributable to CAD is 3 times higher in patients with type 2 diabetes than in those with normal glucose tolerance and 2 times higher in individuals with impaired glucose tolerance (3). A number of prospective studies demonstrate the relationship between CVD and elevated FPG, postprandial plasma glucose, and/or A1C levels in patients with type 2 diabetes. Kuusisto et al (4), in a study of Finnish patients with type 2 diabetes, evaluated the effect of glycemic control (by A1C levels) on the risk of coronary heart disease (CHD) events. Patients with an A1C concentration ≥7% had a 3 times greater risk for a CHD event than patients with an A1C

concentration <7%. In addition, in those patients with a duration of diabetes for at least 6 years, A1C concentration ≥7% doubled the CHD event rate compared with those with an A1C concentration of <7%, indicating an integrated time/dose effect of glucose exposure.

In the San Antonio Heart Study (5), investigators determined the adjusted risk ratios for cardiovascular mortality based on FPG concentration in patients with type 2 diabetes. Those with FPG ≥207 mg/dL were found to have a 4.7-fold greater risk of cardiovascular mortality than patients with FPG levels <144 mg/dL and a 2.8-fold greater risk than those having an FPG level between 144 and 207 mg/dL. These findings emphasize the importance of maintaining glycemic control to reduce the risk of CHD events and cardiovascular mortality in patients with type 2 diabetes.

Hyperglycemia is generally a late manifestation of long-standing insulin resistance and the inability of the beta cells to produce adequate insulin in a timely manner. By the time the 2-hour postglucose challenge is >200 mg/dL, beta cell function has decreased by 50%. By the time preprandial plasma glucose is >140 mg/dL, beta cell function has decreased by 80% (6). Since a postprandial increase in blood sugar is the first apparent glucose abnormality, and diabetes is usually not diagnosed until the fasting blood sugar becomes elevated, both insulin resistance and beta cell defect are well established by the time of diagnosis in most cases (6).

HYPERINSULINEMIA

Although epidemiologic studies of people without diabetes have shown a correlation between insulin levels and CVD, the reason these individuals have hyperinsulinemia is because they have insulin resistance. If they were not insulin resistant, they would have hypoglycemia in response to the increased insulinemia. It is the insulin resistance that contributes to CVD. Hyperinsulinemia is merely a physiologic response to the insulin resistance. Insulin resistance leads to hypertension, hypercoagulability, elevated levels of triglycerides, decreased levels of HDL-cholesterol (HDL-C), and increased levels of small, dense LDL particles. Dysregulation of these factors contributes to atherogenesis and resultant cardiovascular events (7).

The Quebec Cardiovascular Study (8) prospectively investigated the risk of developing ischemic heart disease based on quartiles of fasting insulin levels. This study of 2103 males showed a clear stepwise stratification of relative risk versus insulin level. Relative risk was 1.0 in the first quartile, almost 3.0 in the second quartile (P <0.05), almost 6.0 in the third quartile (P <0.001), and 8.0 in the fourth quartile (P <0.0001). Lamarche et al (9) performed a study on 85 pairs of ischemic heart disease patients (nondiabetic and controls) assessing the degree to which fasting blood glucose and other factors (apolipoprotein B levels) contribute to an increased risk for cardiovascular events. Apart from traditional risk factors for CVD (high LDL-C, elevated triglyceride levels, and low HDL-C levels), the greatest predictor of ischemic heart disease was elevated fasting insulin concentration (an indicator of insulin resistance), which was associated with a 5.5-fold increase in risk (P <0.001). The other variables studied provided ~ half the predictive value.

EFFECTS OF DIABETES THERAPY ON CARDIOVASCULAR RISK FACTORS

Many of the proatherogenic factors thought to be associated with hyperinsulinism are actually a consequence of the insulin-resistant state. For example, elevated triglyceride and proatherogenic lipid levels often decrease substantially as insulin resistance is ameliorated by exercise, weight loss, and/or treatment with metformin or thiazolidinediones. Lipid levels also decrease with adequate insulinization (ie, insulin therapy). When basal and postprandial metabolism improve, lipolysis is inhibited and excessive glycation of lipoproteins is decreased (10). Metformin and the thiazolidinediones both increase insulin sensitivity and decrease lipolysis, thereby decreasing free fatty acid concentrations and lessening hypertriglyceridemia. Elevated concentrations of plasminogen activator inhibitor–1 (PAI-1), which inhibits breakdown of fibrin clots, are associated with insulin resistance and also with an increased risk of CVD,

including myocardial infarction (MI) (11). Treatment with insulin sensitizers such as metformin and the thiazolidinediones has been shown to decrease levels of PAI-1 (12).

Patients with type 2 diabetes have been shown to have impaired endothelium-dependent flow-mediated dilation of the arteries. Treatment with thiazolidinediones improves blood flow response significantly while decreasing endogenous insulin levels in response to glucose (by increasing insulin sensitivity), leading to an improvement in endothelial cell function (13). In one study, troglitazone (although not now marketed) was found to significantly and dramatically improve coronary blood flow in response to acetylcholine administration (P <0.01) (14). In patients with diabetes who had vasospastic angina, treatment with troglitazone decreased the number of anginal episodes per patient per month from 72 before medication to 14 after medication (P = 0.04), while flow-mediated dilation, as measured by lumen diameter of the brachial artery, increased significantly (P = 0.03) (15). Rosiglitazone has also been shown to increase brachial artery vasodilation in response to acetylcholine. Both troglitazone and pioglitazone have been shown to decrease carotid intimal medial thickness in type 2 diabetes. There is also evidence that insulin therapy can have a positive effect on cardiac outcome. Long-term (3.5 years) insulin treatment with the insulin analog insulin glargine improved both endothelial-dependent and -independent vasodilation (16), significantly increasing blood flow during infusions of either acetylcholine or sodium nitroprusside or both (17).

In the UKPDS the metformin-treated intensive-therapy group had a significant reduction in macrovascular events (39% reduction for MI, 41% for stroke, and 42% for diabetes-related deaths), despite no difference in blood sugar compared with the sulfonylurea treated group (18). However, the reduction in MI was 5-fold greater than predicted from glucose lowering, implying that additional vascular benefits were probably due to increased insulin sensitivity, which lowered free fatty acids, procoagulants, and cytokines, among other effects. The ability of metformin to quench glycation of protein and thereby reduce glycoxidation may also play a part in vascular protection.

Intensive Insulin Therapy

In patients experiencing an acute coronary event, administering adequate amounts of insulin to overcome insulin resistance and normalize blood glucose levels improves clinical outcomes and lowers mortality (19). The Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (20) is considered the landmark investigation demonstrating improved clinical outcomes resulting from control of hyperglycemia in patients with acute MI. In this study, 620 hyperglycemic patients with acute MI (13% of whom were not known to have diabetes on admission) were randomized to receive intensive insulin therapy (n = 306) or routine diabetic care with insulin administered at the discretion of the patients' physicians (n = 314). Intensive insulin therapy involved continuous infusion of insulin for at least 24 hours, starting within 48 hours of admission, and multiple daily subcutaneous insulin injections for at least 3 months following discharge. Prior to randomization, patients were stratified according to risk: patients who were >70 years, had a history of MI or congestive heart failure, or who were receiving digitalis at the time of admission were considered to be at high risk. All other patients were considered to be at low risk.

At 3.4 years of follow-up, mortality was 33% in patients who received intensive insulin therapy and 44% in those who received routine diabetic care. The absolute difference in mortality of 11% equates to 1 life saved for every 9 patients treated with intensive insulin therapy. Other independent predictors of mortality used in this study included blood glucose levels and A1C on admission. The most pronounced reduction in mortality was observed in patients not previously treated with insulin and with low predicted cardiovascular risk. In this subgroup, mortality was 18% in patients who received intensive insulin therapy and 33% in those who received routine diabetic care. Here the absolute difference in mortality was 15% and the relative risk reduction associated with intensive insulin therapy was ~50%.

The use of intensive insulin therapy in critically ill surgical intensive care unit (ICU) patients undergoing mechanical ventilation was investigated by van den Berghe and colleagues (21). A total of 1548 patients were randomized to receive intensive insulin therapy to maintain fasting blood glucose concentrations between 80 and 110 mg/dL (n = 765) or conventional treatment with infusions of insulin administered when the blood glucose concentration exceeded 215 mg/dL and titrated to maintain fasting glucose concentrations between 180 and 200 mg/dL (n = 783). On admission, 13% of patients in each group had a history of diabetes, with 5% of those in the intensive therapy group and 4% in the conventional treatment group being insulin dependent. On admission to the ICU, 75% of the patients had blood glucose concentrations >110 mg/dL and 12% had blood glucose concentrations >200 mg/dL. After treatment, mean fasting blood glucose concentrations were 103 ± 19 mg/dL in the intensive therapy group and 153 ± 33 mg/dL in the conventional therapy group. Among patients in the conventional care group, only 39% received insulin (eg, glucose exceeded 215 mg/dL at some time).

Mortality in the ICU was 4.6% in patients in the intensive therapy group and 8.0% in the conventional therapy group (P <0.04). In-hospital mortality was 7.2% in the intensive therapy group and 10.9% in the conventional therapy group. Among patients who remained in the ICU >5 days, mortality was 10.6% in the intensive group and 20.2% in the conventional therapy group (P = 0.005).

Intensive Therapy with Insulin Analogs

The rapid-acting insulin analogs lispro and aspart and, more recently, the basal analog insulin glargine, can improve glucose metabolism by supplying more physiologic insulin action throughout the day compared with regular- and intermediate-acting insulins (neutral protamine Hagedorn [NPH] or lente) with a significantly lower incidence of hyperglycemia or hypoglycemia. Lispro and aspart insulins are used to control postprandial glucose levels and are considered "bolus" insulins, designed to mimic normal physiologic insulin output in response to meals, as contrasted with "basal" insulin. Basal insulin supplies ~50% of a patient's total daily insulin need through the normal pancreas in a constant manner throughout 24 hours of each day. This process maintains blood glucose control while fasting and between meals and is necessary for other important physiologic processes separate from glucose control, such as wound healing, muscle building, tissue repair, lipid metabolism, and regulation of hemostasis and vascular responsivity.

In the past, attempts to mimic normal basal insulinization were frequently made by the administration of twice-daily NPH or lente insulin, or once- or twice-daily ultralente insulin. Although these insulins have been used as "basal" insulins, each has a pronounced peak of biologic action and wide inter- and intrapatient variability in absorption kinetics, which frequently leads to hypo- or hyperglycemia. This has been markedly decreased by the newer insulin analogs (22).

A more physiologic basal insulin profile is achieved with the new insulin analog insulin glargine (23). It provides 24-hour basal insulinization in most individuals and is intended to be titrated to achieve fasting blood sugars in the range of 80 to 110 mg/dL (23). When used in patients with some degree of endogenous insulin secretory ability, adequate basal insulin treatment reduces glucotoxicity by controlling fasting and premeal glucoses, allowing the beta cells to supply all or part of the needed meal-related first- and second-phase insulin secretion.

In several recent studies of insulin glargine, the analog produced significantly less hypoglycemia than NPH insulin in patients with type 1 or type 2 diabetes (24,28). Of particular note, the incidence of nocturnal hypoglycemia was significantly decreased with the use of insulin glargine (P <0.02). Further, studies have indicated an improvement in mean fasting blood sugar levels with insulin glargine compared with NPH insulin (25) and improved A1C levels (26,27). Since fasting glucose levels, 2-hour postprandial glucose levels, and A1C levels all correlate with macrovascular disease morbidity and mortality, it will be interesting to see the effects of long-term treatment with

TABLE I. FORCED WEEKLY INSULIN TITRATION ALGORITHM FOR GLARGINE OR NEUTRAL PROTAMINE HAGEDORN

Start with 10 IU/day bedtime basal insulin dose and adjust weekly

Self-monitored FPG (mg/dL) for 2 consecutive days with no episodes of severe hypoglycemia or FPG ≤72 mg/dL	Increase of insulin dosage (IU/day)
≥180 mg/dL	8
140–180 mg/dL	6
120–140 mg/dL	4
100–120 mg/dL	2

Treat to Target FPG ≤100 mg/dL

Small decreases (2–4 IU/day per adjustment) in dose are allowed in instances of self-monitored plasma glucose <56 mg/dL or the occurrence of severe hypoglycemic episode. FPG = fasting plasma glucose. Adapted with permission (28).

TABLE II. ALGORITHM FOR INSULIN GLARGINE ONLY

- Begin with 10 units at bedtime. If fasting blood glucose (FBG) is >200 increase by 2 to 3 units daily until FBG gets below 200.
- If FBG is >150 increase by 2 units daily until FBG gets below 150.
- If FBG is >120 increase by 1 unit daily until FBG gets below 120.
- If FBG is >100 increase by 1 unit every 2 to 7 days until FBG is usually under 100.
- If any BG falls below 70 during the night or on awakening, decrease by 2 units (but look for other causes of hypoglycemia, ie, alcohol intake or unaccustomed or prolonged exercise).
- If any daytime blood glucose falls below 65, first consider what other drugs the patient may be taking that could cause the low glucose (ie, sulfonylureas) and decrease them if appropriate.
- If no other apparent cause of the low glucose, then either decrease the basal glargine dose by 2 units or switch the dose to morning (ie, skip the dose one night and start the same dose the following morning and every morning thereafter at the same time).
- Morning doses have been found to often work better to improve control but glargine should always be started at bedtime and titrated to control the FBG initially.

the more physiologic insulin analogs regarding cardiovascular outcomes.

KEY POINT

New insulin analog insulin glargine provides a near-normal physiologic basal insulin profile.

INITIATING INSULIN THERAPY

Insulin therapy can improve glycemic control and limit hyperglycemia, reduce insulin resistance caused by glucotoxicity, and improve lipid levels. Algorithms for initiating insulin therapy are shown in **Tables I** (28) and **II**. An insulin algorithm for type 2 diabetes mellitus in children and adults is also available at http:www.tdh.state.tx.us/diabetes/healthcare/standards.htm. The goal of therapy should be to limit hyperglycemia, keeping FPG <100 mg/dL and 2-hour postprandial plasma glucose levels to <140 mg/dL if possible, without unacceptable hypoglycemia. The American Diabetes Association recommends targeting A1C to <7% while the American Association of Clinical Endocrinology and the International Diabetes Federation recommend targeting A1C to <6.5%.

SUMMARY

CVD remains the leading cause of death among patients with type 2 diabetes. Factors that increase cardiovascular risk include hyperglycemia, hypertension, lipid abnormalities, thrombotic disorders, and insulin resistance. All contributing factors should be addressed and control of these factors maximized through lifestyle modification and pharmacotherapy. Well-regulated insulin therapy can decrease cardiovascular risk in the acute care setting and decrease insulin resistance. New insulin analogs have been shown to physiologically improve glucose metabolism. Adequate insulinization to overcome insulin resistance at the cellular level to normalize lipids, coagulation factors, vascular reactivity, and inflammatory cytokines, especially when used in conjunction with the oral insulin sensitizers, promises the potential of reducing the risk of CVD in patients with type 2 diabetes.

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