Insulin Concerns and Promises

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DIABETES, INSULIN, AND CANCER—At a symposium discussing controversies pertaining to relationships between diabetes and cancer, Jeffrey A. Johnson (Edmonton, Canada) reviewed epidemiologic data, beginning with a meta-analysis showing that diabetes is associated with increased rates of cancers of the pancreas, colon and rectum, bladder, liver, and breast; endometrial cancer; and non-Hodgkin's lymphoma. Prostate cancer rates are decreased, perhaps as a consequence of a subtle form of hypogonadism, but prostate cancer mortality is increased among diabetic men who do develop prostate cancer. Obesity increases the development of cancers as well, to a greater degree with greater levels of obesity, particularly for cancers of the esophagus and thyroid and, among women, cancers of the endometrium, gallbladder, colon, and kidney. Cancer mortality increases by ~50% in both sexes in association with obesity (1). The interesting exception to the generally adverse association of obesity with malignancy is its negative relationship with lung cancer, with cigarette use the presumed confounder by its weight-reducing effect (2).

The mechanism of the relationship between diabetes and cancer has not been defined in clinical studies. Johnson's meta-analysis of trials of glycemic control did not show an effect on the risk of developing malignancy (3). Hyperglycemia was, however, associated with cancer mortality in 10-year studies of >1 million Korean (4) and >500,000 European (5) men and women, with the studies controlling for obesity though possibly reflecting a role of hyperinsulinemia. A role of hyperinsulinemia is further suggested by studies showing association of C-peptide with colorectal cancer risk (6,7). Reduced cancer survival seen in individuals with diabetes (8) may be, at least to an extent, due to diabetes-related diseases other than the malignancy itself (9) or to diabetic individuals having a lower likelihood of undergoing mammography, resulting in presentation with later-stage tumors (10). Lower rates of Pap test screening for cervical cancer have been reported in obese white women (11)—further evidence for the latter explanation.

An important group of studies suggests that sulfonylureas and insulin are associated with greater likelihood of malignancy than that seen with metformin (12,13). Longer duration of insulin treatment is associated with greater likelihood of malignancy (14). Whether there is a specific effect of metformin or a general effect of improved insulin sensitivity is not clear, as greater levels of physical fitness are also associated with lower cancer mortality in diabetic and pre-diabetic individuals (15).

Derek LeRoith (New York, NY) discussed the mechanisms of increased risk of cancer in obesity and in type 2 diabetes, reviewing studies of an insulin-resistant animal model to ask whether the breast cancer progression and increased prominence of metastases associated with hyperinsulinemia were caused by effects at the insulin receptor (IR) or the insulin-like growth factor (IGF)1 receptor. There are two subtypes of the IR. IR-B is the metabolic receptor. IR-A may be stimulated either by insulin or by IGF2 and is found in both fetal tissues and in cancers; IR-A appeared in LeRoith's studies to explain insulin's trophic effects on malignancy. The more aggressive tumor behavior and more rapid rate of growth associated with hyperinsulinemia also may reflect cross-talk between the IR/IGF1R and an oncogene. Treatment strategies blocking the IR reduce tumor growth but worsen hyperinsulinemia, as would be predicted from the model. Another approach is to reduce insulin levels. LeRoith described studies of a β-3 adrenergic receptor agonist decreasing adipose tissue mass; circulating insulin levels decreased with reduction in tumor growth. He concluded that endogenous hyperinsulinemia is an important risk factor for cancer progression, presumably working in conjunction with hyperglycemia, with dyslipidemia, with elevation in levels of a variety of nutrients, and with the proinflammatory state leading to elevations in IGF1, leptin, cytokines, and chemokines and reductions in adiponectin—all occurring as a consequence of insulin resistance. Hyperinsulinemia is, he concluded, one of many factors in the relationship between diabetes and malignancy, but he commented that it appears to explain the intersection of a number of related mechanisms of cancer growth.

John Lachin (Rockville, MD) discussed what he termed "facts and fancies" in the understanding of whether there is a relationship between insulin glargine and cancer. He cited the Polish-born British mathematician Jacob Bronowski, who stated, "All information is imperfect ... [and] errors are inextricably bound up with the nature of human knowledge" (16). The gold standard of medical research is the randomized controlled trial (RCT), which assures that treatment assignment is independent of patient characteristics, eliminating selection bias and confounding and allowing one to infer a causal relationship between the outcome and the experimental variable. In contrast, observational studies have no randomized control subjects and many potential biases of selection and confounding. Such studies are necessary in settings where a RCT is impossible, such as that of cigarette smoking and cancer, but make it difficult to establish causality. Thus, in analyzing such a set of observations, one must endeavor to understand the degree to which an association cannot be explained by other factors. Lachin cited as an example the association between coffee consumption and cancer, which has been shown to be confounded with cigarette smoking because more coffee drinkers smoke. One must in this case use a regression or stratification model, which requires correct model specification and knowledge of all confounders. Adjustment then is used to give the likelihood of adverse outcome if the confounder were imagined to be equally distributed between groups. Lachin pointed out, however, that

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not all covariate imbalances introduce bias, whereas adjustment may itself introduce bias. An important example is as follows: if male-female differences were to be adjusted for body weight, a bias would be introduced skewing the female group to characteristics of heavier women.

Given this background, Lachin asked to what extent the recent epidemiologic study suggesting a relationship between use of insulin glargine and cancer should be considered to have accurately been analyzed. Hemkens et al. (17) identified 127,031 patients exposed for an average of 1.63 years, 95,804 to human insulin and 23,855 to insulin glargine, excluding those using combinations of insulin and those changing insulin. It was not possible in the analysis to distinguish type 1 from type 2 diabetes, body weight was not reported, and the type of malignancy not reported. With no adjustment, it has not been widely realized that there was actually a 16% reduction in risk among individuals receiving insulin glargine. Adjusting for age and sex did not change this. The insulin doses given to the glargine versus human insulin groups, however, were different. When the authors adjusted for the insulin dose administered, they found a suggestion that glargine led to a 14% increase in risk of malignancy.

Lachin explained that the analysis used, the Cox proportional hazards model, is valid only if covariate values for all subjects are obtained prior to the time of the event. The study, however, computed an average insulin dose for each subject over the entire follow-up, including the doses administered after diagnosis of cancer (18). Lachin wondered, how could the dose adjustment lead to a change from 16% less risk to 14% more? A larger number of the glargine-treated individuals must therefore have received lower, and fewer must have received higher, doses of insulin. The risk of cancer increased in the small group of glargine patients receiving doses of >40 units/day. "The pivotal question," Lacher said, "is whether or not the adjustment in insulin dose is statistically appropriate." In multiple RCTs of glargine versus NPH insulin, there are negligible differences in the doses needed to achieve comparable levels of glycemic control. What, then, are reasons for the dose imbalance? It is likely, he suggested, that there were unmeasured patient factors differentially distributed between the groups, leading the glargine-treated patients to require lower insulin doses. If this is the case, it is incorrect to statistically adjust for confounding by insulin dose because it introduces the presumed bias of those between-group differences. Indeed, there were substantial reasons for the dose imbalance. The human insulin patients either received basal insulin alone or a combination of basal/bolus insulin, whereas the glargine-treated patients, by the design of the analysis, only received the basal insulin. As a consequence, 77% of the NPH-treated but 92% of the glargine-treated group received oral agents, suggesting differences in endogenous insulin. Perhaps there were no type 1 diabetic patients in the glargine group but were some in the NPH insulin group. The dataset available did not allow the authors to adjust for such differences. The analysis without dose adjustment, Lachin said, would therefore more accurately reflect the effect of glargine in the population, reflecting either a decrease or, at most, no increase in risk, a finding confirmed by other studies. Lachin further suggested that the glargine-treated patients receiving higher insulin doses were likely to have had the allocation bias of confounding by indication or of imbalances in other important factors, suggesting an issue with cohort selection bias. He concluded that there is no replicated evidence that glargine at any dose is associated with increase in risk of malignancy.

Jay Skyler (Miami, FL) further discussed lessons from what he called "the *Diabetologia* story" of the relationship between insulin glargine and development of malignancy, describing "what that story actually was." Four articles appeared in June 2009 (13,17,19,20), along with an editorial (21). At the same time, the European Association for the Study of Diabetes issued a press release with the inflammatory title "Possible Link Between Insulin Glargine and Cancer Prompts Urgent Call for More Research." Although in the body of the release, patients were urged not to abruptly stop treatment, Skyler wryly pointed out that "it certainly excites patients," particularly with multiple news articles and Web sites, including one with the name "lawsuits.com," creating confusion by suggesting that glargine was in fact shown to have caused cancer.

The sequence related by Edwin Gale, the editor of *Diabetologia*, explained that a study from Germany was submitted first reporting that patients using higher glargine doses were more likely to develop cancer (17) and that the other epidemiologic studies were then carried out at the request of the editors of the journal. Interestingly, in the analysis all-cause mortality was reduced 32% with glargine, a finding not highlighted in the news articles but presumably of interest to individuals taking the medication. This study was then at best difficult to interpret, with large imbalance in the proportion of patients given the highest insulin dose, with a high mean age, and with lack of information on important covariates.

The Swedish database combined seven nationwide registries with >114,000 pots, finding a neutral effect on all cancers, increased breast cancer risk for glargine monotherapy but not for glargine in combination, and, again, a significantly decreased mortality risk with glargine (19). The findings were adjusted for multiple covariates, potentially further lessening reliability.

The Scottish database was a nationwide diabetes registry that similarly failed to show an increased risk of all cancers (20). The study showed a nonsignificant increase in breast cancer, although risk was increased in patients receiving insulin glargine alone, based on six events in one of the two cohorts studied. Skyler noted that in this cohort, there were 18,455 non–glargine treated versus only 411 glargine-treated patients. The authors observed that the "subgroup effects most likely reflect allocation bias (ie, those less healthy in many ways being treated with insulin glargine on its own)." The U.K. THIN database showed that there was increased risk with sulfonylureas and with insulin relative to metformin but that there was no significant increase in risk for insulin glargine either for all cancers or, in particular, for breast cancer (13).

Skyler concluded, "The hypothesis ... generated by the German study ... was flawed." Although the three additional studies concluded that there was no evidence that glargine caused cancer, he observed that this "sure doesn't reflect those news headlines, does it?" There was an additional article in that issue, an analysis of an RCT comparing NPH with glargine for retinopathy with a long-duration follow-up, and there was no significant difference in malignancy (22). A subsequent article from the sanofi-aventis database of 26 randomized trials up to 3 years in duration showed no evidence of cancer (23). "Unsubstantiated, unwarranted, unproven, that's my conclusion," said Skyler.

The Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial is underway, with 12,612 randomized to

glargine versus standard care. A press release from the data-monitoring committee on 5 August 2009 stated that with >50,000 person-years of exposure, there was "no cause for concern" (24). Skyler noted that the randomization is to insulin versus no insulin and may help address the question of whether exogenous insulin has an adverse effect on malignancy and whether the metformin versus insulin comparison is confounded by different characteristics of those receiving the different treatments.

What of the suggestion that glargine has greater IGF-1 receptor binding and greater mitogenicity? Circulating insulin levels after glargine administration are unlikely to reach the levels required to interact with the IGF1R (25). Furthermore, the glargine M1 metabolite is the primary circulating insulin component after injection, and this form has reduced IGF1R affinity.

What, Skyler asked, of the study of insulin-treated patients in Florence suggesting that glargine causes increased malignancy risk (26)? In a study of 1,340 patients with type 2 diabetes starting insulin from 1998–2007, 112 incident cancer cases were compared with 370 matched control subjects. There were no significant differences between case and control subjects in the proportion of patients exposed to each insulin, but case subjects had a mean glargine dose of 0.24 units, whereas control subjects used 0.16 units/kg. Incident cancer was associated with the use of >0.3 units/kg glargine. The case subjects, however, had a higher comorbidity score, had less retinopathy, and had a very high cancer incidence—approximately fivefold greater than in other Tuscany data.

Several studies at the 70th Scientific Sessions of the American Diabetes Association (Orlando, FL) reported further aspects of the potential relationships between diabetes, insulin, and cancer. Chuang et al. (abstract 619) reported statistically similar malignancy rates of 13.3 vs. 16.4% per 1,000 person-years and cancer fatality rates among those with malignancy of 28 vs. 26%, during 2,472 vs. 3,668 person-years' follow-up of diabetic patients receiving insulin glargine versus human insulin, respectively. No differences in cancer risks were found for specific different malignancies. Yehezkel et al. (abstract 620) did report in vitro findings that insulin glargine produced atypical IGF-I receptor internalization and activation of the Akt and Erk pathways in a colon cancer–derived cell line. Dankner et al. (abstract 1144) followed 1,770 nondiabetic men and women, aged 52 years at baseline, from 1980 to 2005. Excluding cancer developing during the first 2 years, results showed that fasting insulin was not significantly associated with total site-specific cancer incidence among the 327 individuals developing cancer, but survival time was 4 years for patients with cancer whose baseline fasting insulin was in the upper quartile, which is one-half that of those in the lower three quartiles, with the highest quartile having a significant 53% increase in total mortality, adjusting for age, sex, and ethnicity. Noto et al. (abstract 1165) performed a meta-analysis of 22,485 cancer cases among 250,479 Japanese individuals, finding that diabetes increased risk 70%, with ~3.5-fold greater risk of hepatocellular and endometrial cancers, and some evidence of increased risk for cancers of the pancreas, stomach, and lungs.

A Consensus Statement from the American Diabetes Association and American Cancer Society confirmed the association between diabetes and malignancy but concluded that it is unclear whether the association is related to hyperglycemia, to insulin resistance, or to common risk factors such as obesity (27). It is also unclear whether the association is influenced by diabetes duration. Potential biological links included the insulin/IGF-1 axis, hyperglycemia, and chronic inflammation. The expert group considered whether diabetes treatments influence risk, offering no recommendation other than that it is appropriate to encourage healthy diet, activity, and weight management.

Should insulin treatment be started early in the natural history of diabetes?

Steven Kahn (Seattle, WA) discussed the concept of insulin treatment at the onset of type 2 diabetes, reviewing "the working hypothesis" that this approach preserves the β-cell, offering the potential to reverse diabetes. A study using insulin to normalize glycemia for 3 weeks carried out more than two decades ago showed subsequent improvement in second-, although not in first-, phase insulin response to intravenous glucose, suggesting improvement in β-cell function (28).

Free fatty acid (FFA) levels are elevated with poor control of diabetes and decline with improved glycemia; both glucose and FFA toxicity may then contribute to abnormal insulin secretion. Kahn discussed the notion of glucose toxicity. There is a hyperbolic relationship between insulin secretion and sensitivity, which can be approximated by analyzing the relationship between the change in insulin divided by the change in glucose following nutrient ingestion, a measure of secretion, and the reciprocal of fasting insulin, a measure of sensitivity. The product of the two is termed the disposition index. In impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) and, to a considerably greater extent, in diabetes, the curve is shifted downward, with lower disposition index (29). There is progressive reduction in the first-phase acute insulin response to glucose as IFG progresses, from nearly normal at a fasting glucose of ~100 mg/dL to less than one-third at ~126 mg/dL (30). Kahn reviewed an early study with 24-h glucose infusion to raise blood glucose levels from 92 to 115 mg/dL, leading to increases in insulin levels but actually with increased insulin sensitivity and an increased second-phase insulin response to intravenous glucose. Very short-term and mild hyperglycemia, then, may not have adverse effect. A subsequent study of hyperglycemia sustained at ~160 and ~225 mg/dL for 3 days using variable glucose infusion showed, however, development both of insulin resistance and, at the higher glucose level, of a progressive decrease in the insulin secretory response (31)—an effect, Kahn commented, that "takes a lot of glucose and [requires] very elevated glucose concentrations." There are no specific human data to show we can reverse this, but administration of phlorizen to 90% pancreatectomized rats, lowering blood glucose by increasing glycosuria, restored both the first- and second-phase insulin secretory responses per residual pancreas mass (32). Kahn noted that such a study can now be carried out in humans using sodium glucose transporter-2 inhibitors.

Kahn next addressed β-cell lipotoxicity. He discussed a study showing decline in the acute insulin response to glucose with increasing FFA levels in relatives of type 2 diabetic individuals (33). Another study showed that 3 days of FFA elevation reduced insulin sensitivity, by decreasing nonoxidative glucose uptake, to levels similar to those of relatives of type 2 diabetic individuals; insulin secretion increased in individuals without a family history of diabetes, however, while decreasing in relatives (34). In contrast, relatives of type 2 diabetic individuals treated

to lower FFA levels for 48 h showed improvement both in insulin sensitivity and in first- and second-phase glucose-induced insulin release (35). Interestingly, although a 24-h glucose infusion given alone improves both insulin secretion and sensitivity, when this is combined with elevations in FFA both insulin sensitivity and β-cell function decrease, suggesting that both glucose and lipotoxicity play roles in the development of diabetes (36).

Kahn reviewed a number of potential mediators of these phenomena. Oxidative stress is strongly associated with hyperglycemia (37) and with elevations in FFA and reduces insulin gene expression, with improvement seen after antioxidant administration (38). Endoplasmic reticulum stress, also referred to as the unfolded protein response, is a complex process increased by FFA. Inflammation is another mediator, with evidence of interleukin-1β expression in type 2 diabetic, but not control islets, induced by incubation with high glucose concentrations (39). Finally, islet amyloid, present in islets of individuals with long-standing type 2 diabetes (40), offers a pathway independent of oxidative stress leading to β-cell damage (41). The ability of insulin to reduce glucose and FFA may protect against these harmful effects. An interesting question is whether insulin may protect the β-cell independent of the glucose- and FFA-lowering effects, as suggested by studies of insulin secretion during infusion of exogenous B28-Asp insulin, which can be immunologically distinguished from endogenous insulin (42).

In this context, studies of initial insulin treatment increasing the proportion of individuals achieving remission of type 2 diabetes suggest a fascinating potential approach (43). Those patients who failed to maintain remission had higher fasting and 2-h glucose and A1C after treatment and took a longer time to achieve euglycemia, suggesting that a greater underlying β-cell defect prevented insulin-induced improvement in β-cell function. Indeed, Kahn pointed out, in the UK Prospective Diabetes Study euglycemia was not achieved and both metformin and rosiglitazone have very different effects from glyburide in leading to more sustained control of glycemia (44). He suggested that the ability of insulin to improve β-cell function is mediated primarily by its ability to reduce glucose and FFA, that failure to maintain glucose control is determined in large part by β-cell function, and that measures decreasing glucolipotoxicity and/or reducing β-cell secretory demand appear to prevent progression of diabetes.

Juliana Chan (Hong Kong, China) further discussed the Asian data on intensive insulin treatment of early diabetes, reviewing evidence that both β-cell dysfunction and visceral obesity are associated with oxidative stress, inflammation, and amylin toxicity and discussing studies of intensive insulin treatment. Despite their lower prevalence of obesity, Asians have higher rates of diabetes than Caucasians (45) and more visceral fat (46). The China Diabetes Survey, an analysis of 46,239 individuals from 14 provinces, showed that 25% had diabetes or prediabetes. Chan reviewed results of a 2007 survey done in Singapore, in which the majority of those with prediabetes had IGT, which she suggested indicates a greater degree of β-cell defect. Reduction in first-phase insulin secretion appears to characterize Japanese individuals with prediabetes (47), with decreased insulin secretion preceding insulin resistance in this group (48). Among Japanese Americans, increased visceral fat and β-cell dysfunction are associated with development of diabetes (49), with increased body weight not required for development of insulin resistance and low BMI with high waist circumference actually appearing to be associated with risk of worse glycemic status as well as with complications such as nephropathy (50). Chan reviewed her study showing structural abnormalities of islets including amyloid infiltration, inflammation, and apoptosis, seen at autopsy of Chinese type 2 diabetic patients (51), and a study showing β-cell structural defects and functional abnormalities in Japanese individuals with diabetes (52).

A study of 136 newly diagnosed Chinese type 2 diabetic individuals demonstrated recovery of β-cell function after 2 weeks of continuous subcutaneous insulin infusion (CSII) (53). A1C decreased from 10 to 8.7%, insulin and C-peptide improved at all points during IVGTT, and circulating lipid and proinsulin levels decreased, suggesting reduced β-cell stress. At 3, 6, and 12 months after withdrawal, approximately 70, 65, and 30% of patients were in drug-free remission, which was associated with greater insulin secretion levels. This group's subsequent study of 382 individuals aged 25–70 years, from nine centers in China and carried out from 2004 to 2006, randomized patients to CSII or multiple dose insulin (MDI), beginning with a 0.5 units/kg insulin dose, or to oral hypoglycemic agent treatment with sulfonylureas and/or metformin, for 2 weeks, with subsequent follow-up on diet and exercise alone (42). Remission at 2 weeks was defined by FBG <112 and 2-h glucose <144 mg/dL, while relapse was defined by levels >126 and 180 mg/dL, respectively. Euglycemia was achieved in 4 days in 97% of those on CSII, in 5.6 days in 95% with MDI, and in 9.3 days in 84% with oral agents at daily insulin doses of 0.68 and 0.74 units/kg and mean gliclazide and metformin doses of 180 and 1,000 mg daily in the respective groups. Hypoglycemia was seen in 31, 28, and 19%, and remission was maintained at 1 year in 51, 45, and 27%, respectively. The acute insulin response improved after insulin treatment, whereas the 1-year decline in β-cell function was greater with oral agents. The likelihood of relapse increased with higher fasting glucose levels.

Several similar studies of intensive insulin treatment have been carried out in Asia in patients with longer duration of type 2 diabetes. In Korea, 34% of 91 type 2 diabetic patients achieved remission with CSII after an average of 54 days of treatment, lasting 14 months; responders had had shorter diabetes duration, higher C-peptide and lower postprandial glucose levels and tended to be more obese and have fewer complications; responders rapidly reduced their insulin requirement (54). In Taiwan, 50 patients were randomized to a 6-month course of MDI or to oral agents after all had a 10–14 day intensive inpatient basal-bolus treatment; A1C levels were 6.3 vs. 7.5%, respectively, at 6 months and 6.8 vs. 7.8% at 12 months (55). Even longer periods of CSII may be useful, with a 30-month study in 15 patients with long-standing diabetes showing improvement in dyslipidemia and reduction in levels of inflammatory markers (56). In the Kumamoto study, 6 years of intensive insulin treatment decreased microvascular complications by 70% in 110 lean Japanese patients (57). Chan concluded that Asians have a dual defect leading to diabetes, with both reduced β-cell reserve and visceral obesity contributing to the diabetes epidemic, and that there is considerable phenotypic and genotypic heterogeneity but that short-term CSII induces diabetes remission and restores β-cell function, particularly in patients with short duration, and that both short- and long-term intensive insulin administration reduces gluco- and lipotoxicity, suggesting the importance of

early diagnosis and initiation of insulin treatment in these populations. Mayer Davidson (Los Angeles, CA), asked, "Is it really worth all the hassles of starting insulin just for 6 to 12 months' remission?" Chan agreed that the cost-effectiveness of this treatment needs to be studied, preferably over a long-term period to determine whether sustained benefit of the intervention can be demonstrated.

Hertzel Gerstein (Hamilton, Ontario, Canada) discussed early insulin treatment of type 2 diabetes, asking, "How early is early?" What, he asked, does a high glucose or A1C mean? At what glucose/A1C levels do problems develop? How are glucose/A1C levels controlled? Do any existing trials provide clues? And, finally, what will we learn from the ongoing ORIGIN trial?

In a meta-analysis of the relationship between fasting glucose concentration and vascular disease, with 8.5 million person-years of follow-up, the level that should be considered normal fasting glucose in terms of vascular risk, even with advanced diabetes, is 90–95 mg/dL (58). "The key to maintaining that normal fasting glucose is the pancreas and its insulin secretion," Gerstein said, implying that "the best test of the β-cell is your glucose level." His meta-analysis of prospective studies showed that IGT is associated with a 2.5-fold higher risk of nonfatal CVD and a 1.5-fold higher risk of mortality and that fasting glucose >110 mg/dL without elevation in 2-h glucose was associated with 20, 28, and 21% increases in risks of myocardial infarction, nonfatal CVD, and mortality, respectively (59). Fasting glucose >100 mg/dL was, adjusted for age, cigarettes, BMI, and blood pressure, associated with 7 and 15% increases in cardiovascular risks in men and in women, respectively (57). "Categories of increased glucose that are clearly not diabetic," Gerstein stated, "carry increased risk," with coronary mortality beginning to increase at fasting glucose levels of ~95 mg/dL. In the 33-year follow-up of the Whitehall study, glucose levels measured 2 h after 50 g oral glucose showed a continuous relationship with coronary mortality beginning at 83 mg/dL; mortality increased 22% for every 18 mg/dL increase up to 200 mg/dL (60), leading to the notion of "a continuum of dysglycemia." Similar analysis with A1C shows an 18% increase in mortality risk for every 1% increase, "extending right into the normal range" as well (61).

Diabetes is typically diagnosed ~5 years after its onset, Gerstein observed. "How," he asked, "do we clinically control glucose levels?" Diet and weight loss, physical activity, metformin, and thiazolidinediones increase the effect of available insulin; sulfonylureas, glinides, incretins, and insulin itself increase the supply of insulin; and α-glucosidase inhibitors, incretins, and pramlintide reduce the need for rapid insulin supplies. All therapies for diabetes, then, can be viewed through the vantage point of mediation by insulin. In the UK Prospective Diabetes Study, newly diagnosed type 2 diabetic patients treated with insulin had a 12% reduction in diabetes-related end points, a 25% reduction in microvascular disease, and 33% reduction in albuminuria at 12 years (62). At follow-up 10 years later, there was still a 24% reduction in microvascular disease and there were 15 and 13% reductions in myocardial infarction and mortality, respectively (63). This, Gerstein said, "supports the hypothesis that there may very well be a place for early insulin use." There is no maximum or minimum insulin dose, it is easily titrated, there are no contraindications or drug interactions, there are easy-to-use insulin delivery devices and preparations, often only one daily dose is needed, and we have 88 years' experience with it. Might excess glucose-lowering cause harm, particularly with hypoglycemia? This may be less frequent when insulin is used early. Questions as to exogenous insulin being atherogenic, as to risk of weight gain, and as to carcinogenicity have been raised. At present, no real evidence exists either for or against these points.

In the ORIGIN trial of individuals aged ≥50 years with evidence of CVD and either IFG/IGT or early diabetes, insulin glargine, given with a fasting glucose target of <95 mg/dL, is being compared with standard approaches to dysglycemia; the trial is being carried out as a 2 × 2 study, with randomization to an omega-3 polyunsaturated fatty acid supplement as well (64). Individuals (n = 12,612) from North and South America, Europe, India, the Asia/Pacific region, and Australia were randomized through December 2005, with results to be reported in 2012. Their mean age was 64 years, 35% are female, 12% smoked cigarettes, and 86% had hypertension, 70% dyslipidemia, 66% prior CVD, and 82% diabetes. Baseline BMI was 29.8 kg/m^2 and A1C 6.5%. The coprimary outcomes are cardiovascular death, nonfatal myocardial infarction, stroke, revascularization, or congestive heart failure. Cognitive function, bone density, continuous glucose monitoring, weight status, and glycemia will be followed as well. Reducing β-cell demand with thiazolidinediones and metformin has greater effect on β-cell failure than sulfonylureas, and in those with prediabetes another outcome being studied is diabetes prevention. "The notion that using insulin early may have benefit," Gerstein concluded, is more than 50 years old, dating to Banting's Nobel lecture in 1935.

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