OBSERVATIONS

Bodily Pain, Poor Physical Functioning, and Poor Glycemic Control in Adults With Diabetes

In the January issue of *Diabetes Care*, Krein et al. (1) reported that the presence of chronic pain was associated with poor diabetes self-management. Their study was performed in a primarily male veteran population, and glycemic control was not addressed. We examined psychosocial factors associated with poor glycemic control in a largely female population followed in an urban, underserved, primary care medical clinic and found that the presence of pain and poor physical functioning were associated with poor glycemic control.

Medical records of adults with diabetes (n = 236, 76% female, mean age 62 years) were reviewed. Mean HbA_{1c} was 8.1%, and 52.5% had HbA_{1c} levels of <8%. Patients were asked to complete the SF-36 Short Form Survey (2), the Appraisal of Diabetes Scale (ADS) (3), the Diabetes Quality of Life (DQOL) Measure (4), the Problem Areas in Diabetes (PAID) Scale (5), and the patient survey used by the American Diabetes Association for provider recognition. Bivariate analyses were conducted using correlation coefficients for continuous variables and one-way ANOVA to assess differences in means across groups. Alpha was set at 0.05, two-tailed. Odds ratios, 95% CIs, and χ^2 tests for trend were used to compare patients with HbA_{1c} <8% versus ≥8% for various psychosocial measures. This project was approved by the Institutional Review Board for the Protection of Human Subjects at SUNY Upstate Medical University.

HbA_{1c} was negatively associated with the SF-36 Bodily Pain subscale score (P = 0.012). Those patients with HbA_{1c} ≥8.0% were 5.6 times (95% CI 1.3–26.1) as likely to have more pain (as indicated by a low bodily pain subscore <30) compared with patients with less pain (high scores >70). HbA_{1c} was also negatively correlated with physical functioning (SF-36 subscale, P = 0.002), with those having HbA_{1c} ≥8% being 4.5 times (95% CI 1.1–20.3) as likely to have a low physical functioning subscale score (<30) as patients with high scores (>70). Patients with HbA_{1c} ≥8.0% were 3.6 times (95% CI 0.8–18.8) as likely to report poor or fair overall health (American Diabetes Association Provider Recognition Patient Survey, Question 1). HbA_{1c} was not associated with the Mental Health subscales of SF-36, ADS, or DQOL, but those with HbA_{1c} ≥8.0% had higher mean PAID scores (P = 0.034). As previously reported (6), as age increased, several psychosocial indicators improved (PAID total score, P = 0.001; PAID "worry," P < 0.001; PAID "impact," P = 0.026; Mental Composite Score from SF-36, P = 0.005; Mental Health Subscore from SF-36, P = 0.017).

Krein et al. (1) demonstrated that chronic pain limited the ability of patients with diabetes to self-manage their disease. We found that patients who reported more bodily pain, poorer physical functioning, and poorer self-assessment of overall health were more likely to have elevated HbA_{1c} levels. Whether measures to decrease pain and improve physical functioning would help to improve glycemic control is an area for future study.

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Herbal Therapies and Diabetes Among Navajo Indians

In the treatment of chronic diseases like diabetes, many Native Americans value their ability to integrate traditional and western medicine (1). However, there are limited data from clinical trials about the efficacy of herbs, and health care professionals have been concerned that herbal treatments might be harmful or lead patients away from evidence-based therapies and self-monitoring of blood glucose (2).

Traditional medicines, including herbal therapies, are commonly used among the Navajo Indians (3). During a randomized clinical trial on the Navajo Nation, 203 participants recruited between 2001 and 2003 were asked about their use of traditional medicines for diabetes and their blood glucose–monitoring practices. Their most recent A1c values were abstracted from the medical record. The study, Effects of Navajo Interpreters

on Diabetes Outcomes, was overseen by the Navajo Nation and the University of New Mexico institutional review boards.

Of the 203 participants, 195 (96%) responded to the question about herb use. Fifty-eight of the 195 (30%) reported that they used herbs, and some reported use of multiple herbs. Participants described the herbs in the Navajo language according to their own tradition, not according to the species or the common English name, and a Navajo-language expert with an understanding of traditional medicine reviewed and categorized the herbs. The participants identified 27 different plants. Sage was the herb most frequently mentioned (15%), with the frequency for cedar/juniper at 10%.

A total of 19% of the participants used insulin to control their diabetes (21% of the herb users, 19% of nonusers). The mean A1c value was 8.40% in the group using herbs compared with 8.35% in those not using herbs (NS). There were no significant differences in performance ($P = 0.88$) or frequency ($P = 0.44$) of self-monitoring of blood glucose. There was no significant association between herb use and sex ($P = 0.72$), age ($P = 11$), level of education ($P = 0.92$), ability to speak or understand English ($P = 0.15$ and $P = 0.12$, respectively), duration of diabetes ($P = 0.17$), or insulin use ($P = 0.84$). The amount of time to get to the clinic was associated with the use of herbs ($P = 0.02$). Those traveling ≥60 min for health care were more likely to use herbs than those traveling ≤30 min (22 and 41%, respectively).

Our findings support the observations of Kim and Kwok (3), who found that alternative medicine is widely used by different cultural groups for common diseases. Although our sample may not have been representative of all Navajos with diabetes, it is important that the use of traditional herbs in this group of patients was not associated with any measurable adverse interaction with diabetes control as measured by A1c and self-monitoring practices.

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An Unusual Case of Secondary Diabetes due to Surreptitious Nasal Steroid Use

A 54-year-old woman with no family or personal history of diabetes was referred for assessment of fasting hyperglycemia (7.6 mmol/l) and asthenia. Medical history included recurrent stomatopharyngeal candidiasis, rectal ulcerations because of abuse of analgesic suppositories, depression, and chronic sinusitis. On physical examination, she had facial plethora, diffuse bruises, cutaneous fragility, normal weight, and mildly elevated blood pressure (140/90 mmHg). An oral glucose tolerance test (OGTT) showed a 120-min plasma glucose value of 16.2 mmol/l. Homeostasis model assessment suggested decreased insulin sensitivity (67%) with intact β-cell function (106%). HbA_{1c} value was 6.8% (3–6%). Anti-GAD, anti-IA2 antibodies, and microalbuminuria were negative.

There were no compelling clinical features to suggest either routine type 1 or type 2 diabetes. The clinical impression was suggestive of a chronic glucocorticoid excess and an ACTH-independent Cushing's syndrome was confirmed by an abolished circadian cortisol rhythm (444 and 492 nmol/l at 8 and 20 h, respectively), elevated free urinary cortisol excretion (147 μg/day, normal limit <60), a low ACTH concentration (3 pg/ml), and a lack of morning plasma cortisol suppression after both low (355 nmol/l)- and high (467 nmol/l)-dose dexamethasone administration. However, adrenal gland imaging was normal. In this context, the possibility of hidden intake of glucocorticoids was considered. The patient admitted that she had been taking nasal drops containing prednisolone (2.5 mg/ml) at a dose of 30–40 ml per week for at least 5 years to relieve symptoms of chronic sinusitis (mean dose 10–14 mg prednisolone acetate/day). This consumption was surreptitiously continued during evaluation of the hypothalamic-pituitary-adrenal (HPA) axis. After discontinuation of nasal drops, the patient developed secondary adrenal insufficiency (low morning cortisol at 43 nmol/l) and required hydrocortisone treatment. Three months later, a reevaluation showed near normoglycemia (fasting glycemia 4.4 mmol/l, at 120 min of OGTT 7.9 mmol/l) and a normal HPA axis (morning cortisol 364 nmol/l, peak-to-ACTH stimulation 628 nmol/l).

This is the first report of overt Cushing's syndrome induced by hidden chronic nasal prednisolone administration and complicated by diabetes and withdrawal-induced adrenal insufficiency. There are only a few publications concerning cases of Cushing's syndrome induced by intranasal administration of steroids, and these seem to occur particularly in children and adolescents taking betamethasone or dexamethasone drops (1–3). In our case, the high cross-reactivity (171%) of prednisolone in the immunoassay used for cortisol measurement (Elecsys 2010) (4) resulted in falsely high cortisol concentrations, making the evaluation of the HPA axis even more complex.

Physicians should be aware of the deleterious effects of chronic use of intranasal steroids and the risks of their uncontrolled discontinuation.

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Mild, Reversible Pancytopenia Induced by Rosiglitazone

Rosiglitazone, a member of the thiazolidinediones, is a well-established oral antidiabetic agent. It reduces plasma glucose levels and glucose production, increases glucose clearance, and significantly improves insulin sensitivity, pancreatic β-cell function, and cardiovascular risk factors (1). In addition to the potential risk of liver toxicity, thiazolidinediones can cause fluid retention, which can exacerbate congestive heart failure (2). Hematologic effects reported in clinical trials include only small decreases in Hb and hematocrit. A recent report described rosiglitazone-induced protection against myelotoxicity produced by 5-fluorouracil (3). We report a case of mild, reversible pancytopenia during treatment with rosiglitazone for type 2 diabetes.

A 56-year-old physician with a previous history of ischemic heart disease and hypertension developed symptoms of hyperglycemia and glycosuria and was diagnosed with type 2 diabetes. Treatment with 4 mg rosiglitazone per day was added to previous daily treatment with 100 mg acetylsalicilic acid, 80 mg slow-release propranolol, 5 mg amlodipine besylate, 10 mg phenoxybenzamine, and 10 mg simvastatin. The patient was symptom free. At that time, hematologic indexes were Hb 14.4 g/dl, hematocrit 40.5%, white blood cell count 6,700/μl, and platelets 238,000/μl. HbA_{1c} was 10.9%.

During treatment, all hematologic indexes decreased following a dose-dependent pattern with rosiglitazone dose. On 8 mg rosiglitazone per day, Hb decreased to 13 g/dl, hematocrit to 37.8%, white blood cell count to 4,300/μl, and platelets to 169,000/μl. On 12 mg rosiglitazone per day (a dose exceeding the recommended maximal dose), Hb decreased to 12.3 g/dl, hematocrit to 34.9%, white blood cell count to 3,600/μl, and platelets to 138,000/μl. When rosiglitazone was decreased to 4 mg daily, Hb increased to 12.7 g/dl, hematocrit to 35.8%, and white blood cell count to 4,200/μl. Two months after rosiglitazone was stopped and replaced with 1.5 mg repaglinide daily, Hb returned to 13.9 g/dl, hematocrit to 42.2%, white blood cell count to 6,100/μl, and platelets to 157,000/μl.

No other medication was added or changed during this time. No edema or other signs of fluid overload developed during treatment. Currently, the patient is treated with 1.5 mg repaglinide per day, and his diabetes is well controlled.

To date, the only known adverse hematologic effect of rosiglitazone is mild anemia presumed to be secondary to increased plasma volume. Furthermore, a recent report describes a hematologic advantage of rosiglitazone through the proliferation of granulocyte-macrophage colony-forming units associated with its treatment, an effect attributable to its insulin-sensitizing actions (3). The case presented here demonstrates the development of mild, reversible, and dose-related pancytopenia associated with rosiglitazone treatment. This adverse event seems to be a dose-related rather than an idiosyncratic one. The Hb/hematocrit changes are consistent with many other reports and are ascribed to an increased plasma volume, but the white blood cell count and platelet decreases indicate an effect on the bone marrow. Clinicians should be made aware of the possibility of hematologic toxicities occurring with rosiglitazone therapy. Patients should have their erythrocytes, leukocytes, and platelets monitored while on this drug.

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COMMENTS AND RESPONSES

SF-36 and Diabetes Outcome Measures

In a recent issue of *Diabetes Care,* Hill-Briggs et al. (1) found that the Medical Outcomes Study 36-item short form (SF-36) did not improve in a population whose outcome measures (HbA_{1c}, triglycerides, and diastolic blood pressure) showed modest improvement. We found a similar lack of change in the standard SF-36 in a group of patients whose HbA_{1c} levels, measured in a boronate affinity assay in which the upper limit of normal was 6.8%, fell >3.0% from an initial median of 11.9% (2). Hill-Briggs et al. suggested that diabetes-specific questions be either added to the SF-36 or used alone to

evaluate the impact of diabetes interventions on health status and health-related quality of life. We selected the latter by including the following two diabetes-specific questions (developed by Ron Hayes, PhD, Rand Corp., Santa Monica, CA) in our study.

1) During the past months how much did your diabetes cause a problem with each of the following?

- Doing things on the spur-of-the-moment
- The amount of time or inconvenience involved in treating your diabetes
- Maintaining a diet and preparing food
- Having a large appetite for food
- Feeling embarrassed in public while managing your diabetes
- Taking a trip or going on vacation
- Pain or discomfort involved in taking care of your diabetes
- Doing things socially with friends/relatives
- Planning meals or eating out with others
- Your family life, getting along with others
- Having to plan things differently to take care of your diabetes
- Lack of interest in sex or enjoyment of sex

2) Overall, how much of a problem is it to live a normal life and take care of your diabetes?

Responses were given the following discrete scores: very much a problem (0), somewhat of a problem (33), a little bit of a problem (66), not a problem (100), and not applicable. Thus, the higher the score, the more positive the answer. These items were scored in the same manner as the standard SF-36 form. Both of them improved significantly in our population (2), validating the suggestion by Hill-Briggs et al.

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Initiation of Insulin in Patients With Type 2 Diabetes Failing Oral Therapy

Response to Raskin et al. and Janka et al.

We read with interest the two studies conducted by Janka et al. (1) and Raskin et al. (2) and the accompanying editorial (3) regarding the initiation of insulin in patients with type 2 diabetes failing oral agents and noted the apparent discrepancy between the study results. We believe that the data of the two previous trials (1,2) may not be necessarily conflicting. One important factor that contributed to the more favorable HbA_{1c} levels with insulin aspart 70/30 compared with insulin glargine in the study of Raskin et al. was the difference in insulin dosage between the two insulin regimens. Thus, at the end of the study, the mean daily insulin doses were ~50% greater for the insulin aspart 70/30 group than for the glargine group (78.5 and 51.3 units, respectively). The magnitude of difference between the insulin doses remained essentially unchanged when expressed as units by weight (0.82 vs. 0.55 units/kg, respectively). The reasons for this substantial difference in insulin dose were not totally clear, particularly that patient characteristics were well balanced at the study entry, with nearly identical mean body weight, baseline HbA_{1c}, and proportions of patients on metformin and pioglitazone in the two study groups (2). Failure of the investigators in the trial of Raskin et al. to increase the doses of glargine was unlikely attributed to the fear of hypoglycemia, since previous data have consistently shown that the peakless insulin glargine was associated with lower risk of hypoglycemia compared with traditional insulins (4). Moreover, there was enough room to increase glargine doses because the achieved mean fasting plasma glucose was 116 mg/dl, well above the study target of 80–110 mg/dl. The study of Raskin et al. was inevitably unblinded and financially supported by the manufacturer of insulin aspart 70/30. Therefore, the possibility that the investigators in the previous study were more aggressive in increasing the doses of insulin aspart compared with glargine to achieve better glycemic control with aspart could not be excluded. It would have been of interest if Raskin et al. had reported HbA_{1c} values after adjusting for differences in insulin doses between the two insulin regimens.

Another factor that could have contributed to the variable results between the two trials (1,2) was the timing of injecting insulin glargine, which was administered in the morning in the study of Janka et al. (1) and at bedtime in the study of Raskin et al. (2). In one large trial, patients with type 2 diabetes who injected glargine in the morning had lower HbA_{1c} values and lesser frequency of hypoglycemia than subjects who injected similar doses of glargine at bedtime (5).

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Initiation of Insulin in Patients With Type 2 Diabetes Failing Oral Therapy

Response to Raskin et al. and Mikhail and Cope

Our previous publication regarding the initiation of insulin therapy in patients with type 2 diabetes failing oral therapy (1) and the recent study by Raskin et al. (2) has raised interesting discussion (3,4). Raskin et al. reported that glycemic control was better in patients treated with BIAsp 70/30 plus oral antidiabetic agents (OADs) than in those receiving insulin glargine plus OADs (mean end point HbA_{1c} 6.91 vs. 7.41%). In contrast, we demonstrated that glycemic control was better in patients treated with insulin glargine plus OADs compared with 70/30 insulin alone (mean end point HbA_{1c} 7.15 vs. 7.49%). Major discrepancies between the Raskin et al. study and our study exist, including considerably poorer metabolic control at study baseline in the Raskin et al. study (HbA_{1c} 9.8 vs. 8.8%), the use of different OADs, a markedly higher insulin dose at study end (78.5 IU BIAsp 70/30 vs. 28.2 IU in our insulin glargine plus OAD study group), and a dramatic weight gain in the BIAsp 70/30 group (5.4 kg vs. only 1.4 kg in our insulin glargine plus OAD group).

On the surface, it might appear that according to Raskin et al., premix insulin plus OADs were more effective than insulin glargine plus OADs. However, this does not take into account other factors that influence treatment management, including insulin dose, number of daily injections, complexity when monitoring blood glucose, incidence of hypoglycemia, weight gain, and quality of life. Indeed, in both studies, insulin dose and the incidence of hypoglycemia were significantly greater with premix insulin versus insulin glargine. Further analysis has indicated that although the method for identifying hypoglycemia was very different between the two studies, the nearly fivefold higher incidence of hypoglycemia observed in the premixed arm is of major clinical relevance. Aside from the debilitating effect of hypoglycemia on the patient and carers, hypoglycemia has important health economic implications. Additionally, whereas insulin glargine is injected only once daily, premix insulin requires twice-daily administration and blood glucose monitoring two to four times daily, a likely barrier to achieving treatment success, particularly in clinical practice with insulin-naïve patients being initiated to insulin therapy. Furthermore, one might question whether the results obtained by Raskin et al. reflect the true potential of insulin glargine; given the low risk of hypoglycemia observed with insulin glargine, more aggressive titration of this insulin in their study may have achieved a greater decrease in HbA_{1c}.

We believe that one injection of insulin glargine in combination with two OADs is a simple, safe, and effective treatment option for patients with type 2 diabetes with moderately unstable blood glucose control.

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