OBSERVATIONS

The Role of Platelet-Activating Factor in Pathogenesis of Type 1 Diabetes

Platelet-activating factor (PAF) is a phospholipid mediator that exhibits diverse and potent effects on many cell types (1). PAF is a potent mediator of hypersensitivity and inflammatory reactions (2). Type 1 diabetes is caused by autoimmune destruction of the β-cells in the pancreas, which is initiated years before the clinical presentation of disease (3). In recent-onset type 1 diabetes and in animal models of autoimmune diabetes, a characteristic pathological finding in the islets of Langerhans is the accumulation of mononuclear cells and β-cell death (insulitis) (4,5). In this study, we investigated the role of PAF as an inflammatory mediator in pathogenesis of type 1 diabetes, which is a chronic inflammatory process.

Serum PAF levels of 38 type 1 diabetic patients and 22 healthy children with an age range of 5–15 years were evaluated by a high-performance liquid chromatography method. Statistical analysis was performed by the nonparametric Kruskall-Wallis and Mann-Whitney *U* tests. Average serum PAF levels of patients and healthy children were measured to be 445.11 ± 55.79 and 198.0 ± 80.0 pg/ml, respectively. Serum PAF levels of the patient group were significantly higher than those of the healthy children ($P < 0.01$). The patients were divided into three groups according to the duration of diabetes as newly diagnosed, 3 months to 5 years, and >5 years. Average serum PAF levels in these groups were 757.8 ± 82.2, 307.3 ± 27.1, and 387.0 ± 57.9 pg/ml, respectively. In the newly diagnosed patient group, serum PAF levels were found to be significantly higher than those of the other groups ($P < 0.01$). There was no significant difference in serum PAF levels between the group with diabetes duration of 3 months to 5 years and that with diabetes duration >5 years ($P > 0.01$).

Serum PAF levels of patients with type 1 diabetes were significantly higher than the healthy group. When patients were divided into the three groups according to duration of diabetes, the highest levels were observed in patients with newly diagnosed diabetes. These results may indicate that PAF plays a role in the development of type 1 diabetes. There are few reports on this issue. In an experimental study about the role of PAF in the development of type 1 diabetes, it was detected that administration of recombinant PAF-acetyl hydrolase, which inactivates PAF to rats, caused a decrease in insulitis (6). Another experimental study reported that the PAF synthesis capacity of polymorphonuclear leukocytes was increased in diabetic rats (7).

There is also clinical research that reports an increased serum level of PAF in type 1 diabetes. However, in these studies, increased levels of PAF were attributed to the ongoing hyperglycemia and were thought to accentuate the development of micro- and macrovascular complications (8,9). In our study, high levels of PAF detected in patients who had diabetes for a long duration when compared with the healthy group might be associated with vascular complications.

In conclusion, PAF levels are increased in children with type 1 diabetes. This increment was higher in children with new-onset diabetes and may be important in the etiopathogenesis of type 1 diabetes. Further research supporting the use of PAF antagonists in patients with new-onset diabetes is required.

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Spontaneous Diabetic Myonecrosis

Diabetic muscle infarction is an unusual complication of late-stage diabetes. The first case was reported in 1965 by Angervall and Stener (1). There have been <100 cases reported since then (4). Clinical presentation is an acute atraumatic painful swelling of the affected muscle and a palpable mass. Diabetic muscle infarction has predilection for the quadriceps and thigh muscles and is found in diabetic subjects with established nephropathy and retinopathy (2).

We report a case of spontaneous quadriceps necrosis in a type 2 diabetic patient on hemodialysis. A 59-year-old woman had a type 2 diabetes history of >20 years and unsatisfactory glycemic

control despite insulin therapy. This condition was complicated by proliferative retinopathy, neuropathy, and nephropathy. In 2003, the patient progressed to end-stage renal disease and required hemodialysis. Her serum creatinine level was 5.7 mEq/l (normal value 0.5–1.3). Other medical problems included hypertension, heart failure with pulmonary hypertension, and moderate myocardial depression. Coronary vessels were normal by catheterism.

The patient was admitted for a painful swelling of her left anterior thigh for 7 days. There was no history of recent trauma or muscular injection. On physical examination, she showed a localized swelling and heating of the left thigh. Her body temperature was 37.3°C. Laboratory findings included a normal leukocyte count at 10,000 cells/mcl (normal value 5,000–10,000), with 84.6% (55–65) neutrophils; creatine kinase at 313.5 IU/l (32–162); alkaline phosphatase at 424 IU/l (40–190); fibrinogen at 468 mg/dl (150–350); lactate dehydrogenase at 327 IU/l (150–450); Na^+ at 126.5 mEq/l (135–145); and K^+ at 5.7 mEq/l (3.5–5.0).

A Doppler ultrasound of her left inferior limb excluded a deep venous thrombosis and revealed minimal atheromatosis. Magnetic resonance imaging demonstrated edema and pronounced swelling of the left rectus femoris in T2-weighted sequences that suggested a muscular necrosis. The contralateral thigh was normal.

The differential diagnoses, i.e., deep venous thrombosis, thromboflebitis, fracture, pyomiositis, necrotizant fascitis, myositis or dermatomyositis, and connective tissue tumor, were excluded by the clinical presentation, together with the ultrasound and magnetic resonance imaging. A diagnosis of diabetic muscle necrosis was made. Symptomatic treatment, bed rest, and analgesia were continued, and the pain improved in a period of 3–4 weeks.

According to the literature, diabetic muscle infarction is more frequent in long-standing diabetic women (~15 years), with an average age at presentation of 43 years and multiple end-organ diabetes complications, retinopathy, neuropathy, nephropathy in peritonal dialysis or hemodialysis, and gastroenteropathy (3). It has predilection for the quadriceps (62%), hip adductors (13%), hamstrings (8%), and hip flexors (2%) (4). Myonecrosis, although typically involving the thigh, can extend to the calf (5). Curiously, muscle enzymes could be normal or marginally elevated.

The pathogenesis of this disease is unclear. Several hypotheses have been suggested. Muscle infarction could be caused by atherosclerosis and diabetic microangiopathy. Other hypotheses discuss an alteration in the coagulation-fibrinolisis system as the cause of diabetic muscle infarction, as described by Palmer and Greco (6) in two patients with this disease and antiphospholipid syndrome. Gargiulo et al. (7) indicated the role of antiphospholipid antibodies in the progession of diabetes complications.

In summary, diabetic myonecrosis should be suspected in diabetic patients who develop a painful swollen muscle.

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Potentially Important Contribution of Dextrose Used as Diluent to Hyperglycemia in Hospitalized Patients

Several recent studies have shown increased morbidity and mortality associated with hyperglycemia in patients hospitalized for cardiovascular illnesses and acute illness requiring intensive care (1). While many of these studies have utilized intensive insulin therapy (IIT) as a means of controlling hyperglycemia, to our knowledge the possible iatrogenic contribution of intravenous medications has been overlooked.

A 78-year-old man with type 2 diabetes was hospitalized for respiratory failure. Glycemic control was suboptimal despite continuous insulin infusion. The diabetes service observed infusion of Vancomycin mixed in 250 ml of 5% dextrose (D5W) while examining the patient. Medication review revealed four different intravenous medications in D5W amounting to >1 l daily. This prompted review of medication profiles for all patients followed by the diabetes service. Of 10 patients, 7 were receiving intravenous medications mixed in D5W (median 1 [range 1–4]). All of these patients required insulin therapy, and three (43%) required an insulin drip to achieve mean glucose values ranging from 129 to 223 mg/dl. Several of the intravenous medications could be given in normal saline rather than D5W (2) (Table 1). Five of these patients were hospitalized long enough for an intervention. After removing dextrose diluent from their intravenous medications, four of the five patients showed improved glycemic control with mean glucose values decreasing by 17–51 mg/dl (mean 39 mg/dl). We attempted to reduce subsequent iatrogenic hyperglycemia by communicating with the pharmacist to "provide all intravenous medications mixed in normal saline" for each diabetic patient we managed.

Hyperglycemia is common in hospitalized patients and has been shown to be an important marker of increased mortality and poor clinical outcome (1). A recent

Table 1—*Drugs compatible in normal saline automatically made in D5W

Acetazolamide	Cimetidine	Doxycycline	Norepinephrine
Alprostadil	Ciprofloxacin†	Esmolol†	Octreotide
Aminophylline†	Clindamycin†	Heparin†	Penicillins*†
Argatroban	Cyclosporine	Ibutilide	Steroids‡
Azithromycin	Dobutamine†	Lidocaine†	Valproate sodium
Cephalosporins†§	Dopamine†	Nesiritide	Vancomycin

*Includes nafcillin, penicillin G potassium, and piperacillin/tazobactam. †Manufacturer premade item(s). ‡Includes dexamethasone, hydrocortisone, and methylprednisolone. §Includes cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, and cefuroxime.

study found that a modest increase in mean glucose from 80–99 to 100–119 mg/dl in an intensive care unit (ICU) setting led to a 27% relative increase in mortality (3). A prospective, randomized, controlled trial found that the use of IIT to maintain blood glucose ≤110 mg/dl led to relative risk reduction of death in the ICU by 42% (4). The American Association of Clinical Endocrinologists (AACE) has recently published guidelines on the management of inpatient hyperglycemia (1). Protocols to prevent iatrogenic hyperglycemia induced by use of dextrose as a diluent would also decrease resource utilization by decreasing the frequency of blood glucose measurement and insulin administration.

Our preliminary observations suggest that inpatients with diabetes frequently receive intravenous medications mixed in dextrose. Review of medications used in intravenous lines while examining the patient and careful review of medications and diluents can improve glycemic status and clinical outcomes. Creating a system to correct and prevent this occurrence can improve patient care and decrease resource utilization. Future guidelines for inpatient diabetes management would be improved by including this recommendation.

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Use of Insulin Glargine During the First Weeks of Pregnancy in Five Type 1 Diabetic Women

The long-acting analog glargine is a new insulin with 24-h persistence. This peculiar peakless action profile accounts for significant risk reduction for nocturnal hypoglycemia and a more stable daily plasma glucose profile (1,2). Only a few reports have described the use of insulin glargine during human pregnancy, so its use is not recommended at present. Animal studies have addressed the safety and efficacy of glargine during pregnancy, showing no direct effect on reproduction and embryo-fetal development (3). Recently, Devlin et al. (4) and Holstein et al. (5) reported the use of insulin glargine in two type 1 diabetic women; both cases were free of any pregnancy complications and with no direct effect on embryogenesis.

We report on five case subjects who used glargine during unplanned pregnancy (Table 1). All five diabetic women attended their first diabetes evaluation at our Outpatient Clinic between November 2002 and February 2004. None had evidence of retinopathy or autonomic neuropathy and they had normal urinary albumin excretion. They initiated glargine 5–12 months before conception because of frequent nocturnal hypoglycemia and suboptimal glycemic control. Insulin glargine was started as part of a basal-bolus regimen with an average dose of 25 ± 17 IU/day (range 14–56) given as a single predinner subcutaneous injection. The first diabetes assessment after commencement of pregnancy occurred at the 6th gestational week in three cases, while the remaining women were seen at the 8th and 12th week of gestation, respectively. Their HbA_{1c} at that time was 7.3 ± 0.8%. Due to the lack of controlled data on the safety and efficacy of glargine in pregnant women, all patients were switched to NPH in the morning and bedtime, along with the usual premeal insulin therapy. After 2 weeks of the new insulin regimen, three women were started on continuous subcutaneous insulin infusion because optimal control could not be attained. In all five patients, strict glycemic control was achieved, with an average HbA_{1c} of 6.0 ± 0.2% at the end of pregnancy. Pre-eclampsia developed in one patient at the 32nd week of gestation, and neither progression in retinopathy nor other microangiopatic complications were detected. Previous observations have reported that the use of glargine is associated with worsening eye disease in type 2 diabetic women (2). Babies (two males and three females) were delivered at a mean gestational age of 36.6 ± 1.1 weeks by cesarean section in all but one woman. Mean birth weight was 3,066 ± 898 g, with one baby >4 kg, whereas the other four babies' weights were adequate for gestational age. There was neither major nor minor congenital malformation, and none of the babies had any complications during the postpartum period.

Our experience is limited to a few subjects; nevertheless, all the observed women used insulin glargine from the preconception period to 6–12 weeks'

Table 1—*Clinical characteristics of five type 1 diabetic pregnancies*

Patient	Age (years)/ white class*	HbA_{1c} preconception/ end of pregnancy (%)	Use of glargine in pregnancy (weeks)	Glargine dose in pregnancy (IU/day)	Time of delivery (weeks)	Newborn weight (g)	Perinatal mortality and/or congenital malformation
1	32/B	7.0/6.7	6	18	35	2,220	No
2	26/C	6.4/6.4	12	56	37	3,500	No
3	41/C	7.0/6.2	8	18	38	4,400	No
4	32/D	7.6/5.8	6	14	37	2,850	No
5	27/B	8.7/5.8	6	20	36	2,360	No

*White Classification of Diabetes in Pregnancy (7). Class A: Diet alone, any duration or onset age. Class B: Onset at age ≥20 years, duration <10 years. Class C: Onset between the ages of 10 and 19 years, duration 10–19 years. Class D: Onset before the age of 10 years, duration <20 years, background retinopathy or hypertension (not pre-eclampsia). Class R: Proliferative retinopathy or vitreous hemorrhage. Class F: Nephropathy with >500 mg/day proteinuria. Class RF: Criteria for both classes R and F coexist. Class H: Arteriosclerotic hearth disease clinically evident. Class T: Prior renal transplantation. All classes below A require insulin therapy.

postconception. Hyperglycemia during the first 8 weeks of gestation, as clearly reported by Mills et al. (6), increases the risk of congenital anomalies. In our report, insulin glargine does not seem to affect embryo-fetal development in this critical period of embryogenesis. However, the small number of women and the early discontinuation of therapy with insulin glargine do not allow us to draw any final conclusion. Nevertheless, this observation, as well as other anecdotic observations, emphasizes the need for properly planned investigations.

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Successful Treatment of Insulin Allergy in a 1-Year-Old Infant With Neonatal Diabetes by Lispro and Glargine Insulin

Systemic insulin allergy is a rare condition and has usually been reported in adults. Human insulin analogs have been proposed for the treatment of insulin allergy (1,2). Here we report a 1-year-old infant with generalized allergy to insulin who has been successfully treated with the insulin analogs lispro and glargine. To our knowledge, this case subject is the youngest child reported with systemic insulin allergy and the only patient who was treated without any adverse event by glargine insulin in infancy.

A neonate girl, the first child of consanguineous parents, was born at full term after uneventful pregnancy. She was small for gestational age with a birth weight of 1,430 g. Although the infant had been fed properly from birth, she was presented with complaint of poor weight gain at 2 months of age. On admission, she weighted 1,700 g (below the third percentile) and appeared malnourished and dehydrated. The blood glucose concentration was 33.2 mmol, and there was no acidosis or ketonuria. HbA_{1c} and C-peptide levels were 9.7% and <0.5 ng/ml, respectively. Anti-GAD and anti–islet cell antibodies were negative. The diagnosis of neonatal diabetes was established. The treatment with human NPH insulin (Humulin N; Lilly) was initiated. During subsequent 10-month follow-up, the patient demonstrated normal growth and development and HbA_{1c} level decreased to 5.7%.

At 1 year of age, immediately after each insulin injection, she developed allergic reactions, including macular skin rush, pruritus, and dermographism, on her trunk and all injection sites. Although she had been treated with antiallergic drugs along with NPH insulin, the allergic reactions continued. Eosinophilia on peripheral blood smear was not detected, and the serum level of total IgE was 18 IU/ml (normal range <150 IU/ml). Unfortunately, tests for insulin-specific IgE and IgG were not performed. However, the patient demonstrated allergic reactions to different kinds of human insulin, including human regular insulin (Humulin R; Actrapid) and NPH insulin (Humulin N; Insulatard), not only following subcutaneous injection but also after intradermal test. Intradermal tests confirmed the insulin allergy.

Gradual insulin desensitization with low doses of regular insulin was not successful. We considered treating the patient with rapid-acting insulin analogs and examined skin reactions to lispro (Humalog; Lilly) and aspart (Novorapid; Novo Nordisk). Intradermal tests were negative for both. Lispro treatment was initiated, and no allergic reaction was observed. However, prolonged treatment of a 1-year-old infant with repeated injections of lispro four to five times a day was

very difficult. We therefore decided to test the long-acting analog insulin glargine that would meet daily requirement of basal insulin. Skin tests were also negative with glargine insulin. Thus, the treatment with glargine insulin (Lantus; Aventis) was commenced with the permission of parents. The patient received bedtime glargine insulin (0.7 units · kg^{-1} · day^{-1}) and, as needed, mealtime lispro insulin (0.1 units · kg^{-1} · day^{-1}). This insulin regimen provided less hypoglycemic episodes than NPH insulin twice daily and achieved HbA_{1c} values <7%. During the 6-month follow-up, we did not observe any allergic reaction or adverse event due to insulin glargine.

Insulin glargine has been used in the treatment of toddlers and children with type 1 diabetes (3). Because the systemic insulin allergy did not respond to the antihistaminic drug and desensitization therapies, we have inevitably used insulin glargine to treat the 1-year-old infant with neonatal diabetes. Once-daily dose of insulin glargine provided effective glycemic control and less hypoglycemic event and was well tolerated in our infant patient. This case indicates that the insulin analog glargine can be considered as a safe alternative treatment in very young children with allergic reactions to human recombinant insulin.

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Charcot Neuroarthropathy of the Wrist in Type 1 Diabetes

Charcot neuroarthropathy typically affects the joints of the foot and ankle in diabetes (1); neuroarthropathy of the wrist is extremely rare (2,3).

A 53-year-old right-handed white Caucasian woman, who was a rose grower, presented to rheumatology with an uncomfortable, swollen right wrist. She had type 1 diabetes of 23 years' duration and had undergone right ulnar nerve decompression at the elbow for focal entrapment neuropathy 3 years previously. She had residual wasting of the small muscles of the right hand with mild weakness of the abductor digiti minimi and sensory signs consistent with bilateral ulnar neuropathy (more marked on the right). At the right wrist, there was loss of 50° of both dorsiflexion and palmar flexion.

Plain X-ray showed cystic changes in the distal radius and carpus with joint space narrowing, which had not been present 3 years earlier at the time of ulnar nerve decompression. Laboratory investigation revealed a markedly elevated alkaline phosphatase (250 units/l [normal range 25–110]) and a normal C-reactive protein (<2 mg/l [normal range 0–10]). No sedimentation rate was recorded. Radioisotope bone scan demonstrated increased uptake in the right radiocarpal joint. A diagnosis of osteoarthritis was made, and she was treated with a splint and nonsteroidal anti-inflammatory drugs with some initial symptomatic benefit. However, she experienced continual wrist swelling, and repeat plain X-ray 2 years later showed further loss of joint space and more subchondral sclerosis but no periarticular osteoporosis (Fig. 1*A*). This was accompanied by progressive deformity of the right wrist, eventually leading to marked limitation of movement and loss of function. At referral to our clinic, the clinical appearances (Fig. 1*B*) and sequence of events suggested a probable diagnosis of wrist neuroarthropathy. In addition, there were also signs of a marked peripheral sensorimotor neuropathy affecting the lower limbs and a typical Charcot pattern of deformity affecting the left foot (although it had not previously been recognized as such). This had started with a spiral fracture of the left fibula following minor trauma, with later development of spontaneous fractures of the proximal phalanx of the second toe and the base of the fifth metatarsal, eventually leading to typical clinical and radiological appearances of midfoot neuroarthropathy.

Charcot neuroarthropathy rarely affects joints other than the foot and ankle in diabetes (1). Joint involvement in the upper limb is extremely unusual; only two reports of neuroarthropathy affecting the wrist have been described before (2,3). The likely explanation for the rarity of wrist neuroarthropathy probably reflects the lesser degrees of peripheral sensorimotor and autonomic neuropathy affecting the upper compared with the lower limbs and the fact that the latter possess major weight-bearing joints (especially foot and ankle), which are subjected to continual trauma. Neuroarthropathy likely results from the combination of loss of protective sensation, a direct result of sensorimotor neuropathy, and hemodynamic changes (hyperemia) due to autonomic neuropathy, which eventually lead to osteolysis and demineralization of bone (4), in the presence of recurrent minor joint trauma (5). We believe that within a susceptible milieu (later development of foot neuroarthropathy), the impact of ulnar entrapment neuropathy (6) and the patient's vocation (rose pruning, which generated recurrent wrist trauma) contributed to the development of wrist neuroarthropathy in this particular case. When neuroarthropathy affects the lower limb, treatment is focused on weight-sparing maneuvers and off-loading of the joint (5). However, this case suggests that the benefits of using casts in neuroarthropathy may not lie solely in weight redistribution/off-loading, but also in reducing the attendant hyperemia by enforced underuse of the limb.

Charcot neuroarthropathy can, albeit rarely, affect joints other than those of the foot (2,3,7). Early recognition is crucially

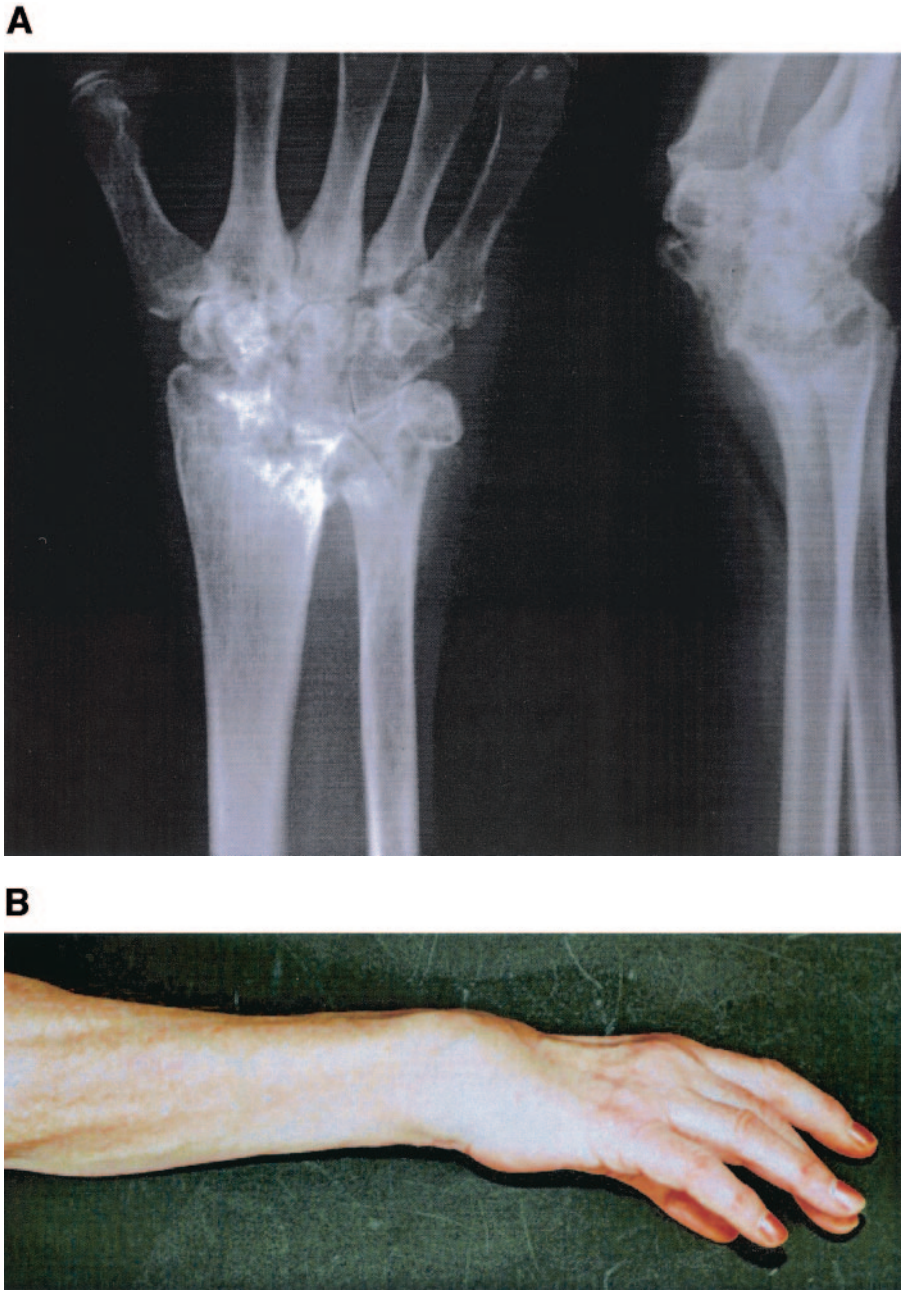

Figure 1—A: *Plain X-ray of the right wrist showing loss of joint space with increasing subchondral sclerosis.* B: *Right wrist deformity.*

important because joint immobilization combined with the use of bisphosphonates may halt the process of joint disintegration and prevent ensuing joint deformity and loss of function (5,8).

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COMMENTS AND RESPONSES

Lipids and Glucose in Type 2 Diabetes: What About the β-Cell and the Mitochondria?

Response to Boden and Laakso

In the September issue of *Diabetes Care*, Boden and Laakso (1) review various methods by which fatty acids and fat tissue promote the pathogenic process deteriorating to type 2 diabetes. They emphasize the effect of peripheral fat storage in muscle and liver on the development of insulin resistance and diabetes but neglect, however, to discuss the effect of fat deposition in and around the β-cell on β-cell function and apoptosis as a pathophysiologic event in the development of the disease.

In their review, Boden and Laakso mention only the increase in insulin se-

cretion and glucose-stimulated insulin secretion (GSIS) in response to exposure to free fatty acids (FFAs). This response is said to be attenuated in diabetic patients and their relatives, thus demonstrating a tendency toward β-cell failure during the disease. This effect is a short-term effect. When obese individuals were exposed to high levels of FFAs for prolonged periods of time, a decline in GSIS was observed (2). The effect of chronically elevated FFAs highlights a major contribution of β-cell lipotoxicity to the pathogenic process deteriorating to type 2 diabetes . This β-cell lipotoxicity has been studied thoroughly. It has been shown that high levels of FFAs have a detrimental effect on β-cell survival and insulin secretion (3). In ZDF rats, these effects were related to enhanced accumulation of triglycerides in the islets and β-cells (4). A high FFA and triglyceride load in human islets induced caspase-mediated apoptosis, probably through the ceramide pathway (5). Furthermore, thiazoldinediones, which are known to improve insulin resistance through a reduction in fat content of muscle and liver, cause a dramatic improvement in insulin secretion in diabetic patients (6). Based on these effects, it would seem nearsighted to emphasize the role of FFAs in diabetes as mainly a peripheral one on muscle and liver tissue. Although type 2 diabetes is characterized by peripheral insulin resistance that might be related to deranged fat metabolism, it is becoming clear that it is not solely a disease of glucose-utilizing tissue but might also be a result of a lipotoxic effect on the β-cell.

Other areas that should be highlighted include the role of lipotoxic mitochondrial damage as a core process in the pathogenesis of type 2 diabetes and the role of mitochondrial uncoupling proteins (UCPs) as culprit proteins and a possible defense mechanism in diabetes. Mitochondrial dysfunction has been noted in diabetes and may result from an enhanced effect of lipid peroxides formed in the mitochondria as a result of FFA excess. This damage can then lead to further FFA accumulation through diminished oxidative capacity (7). The mitochondrial UCPs seem to play a role in the protection of the mitochondria from these harmful effects by preventing the formation of lipid peroxides (7). They were implied as culprit proteins in diabetes when a 50% reduction in UCP3 levels was found in diabetic patients (8), thus rendering them more susceptible to FFA-induced mitochondrial damage and the slippery slope that follows. Another uncoupling protein, UCP2, is suspected of playing a role in glucose sensitivity and insulin secretion in β-cells and is upregulated by chronically elevated FFAs (9). Genetic polymorphism in this protein was found to be associated with insulin resistance and increased risk of type 2 diabetes (10).

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Lipids and Glucose in Type 2 Diabetes: What About the β-Cell and the Mitochondria?

Response to Eldor and Raz

Drs. Eldor and Raz (1) assert that "high levels of FFAs [free fatty acids] have a detrimental effect on β-cell survival and insulin secretion." We agree, but only in relation to patients who have dysfunctional β-cells, i.e., patients with pre-diabetes, impaired glucose tolerance, or type 2 diabetes (2–5). On the other hand, in people with normally functioning β-cells, there is much evidence that FFAs, rather than impairing, actually augment insulin secretion. For instance, several groups have recently shown that in healthy individuals, elevation of plasma FFAs, for as long as 96 h, potentiated glucose-stimulated insulin secretion (2,6–8). Moreover, lowering plasma FFA levels, rather than improving insulin secretion, has been shown to actually decrease insulin secretion (9,10). Thus, there is currently little evidence to support the concept of FFA-induced β-cell lipotoxicity in normal human subjects. Moreover, the concept of β-cell lipotoxicity would be difficult to reconcile with the observation that >50% of obese people with chronically elevated FFA levels never develop type 2 diabetes during their

lifetime, despite the fact that most of them are insulin resistant.

Drs. Eldor and Raz also state that lipotoxicity-induced mitochondrial damage is a "core process in the pathogenesis of type 2 diabetes." We agree that there is mitochondrial dysfunction in patients with pre-diabetes as well as in patients with diabetes. It is not known, however, whether this is a primary or secondary defect. Moreover, whereas it is possible, perhaps even likely, that high fatty acid levels contribute to mitochondrial dysfunction, to our knowledge, there are presently no human data to support this assertion.

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