

Clinic at Wake Forest University School of Medicine to determine the need for insulin.

The four women whose treatment we describe here were referred to our clinic and delivered between 1 December 2003 and 31 March 2005. The decision to initiate insulin glargine in these patients was based on postprandial self-monitored blood glucose readings <150 mg/dl. All four maintained blood glucose values that, on average, met the American College of Obstetricians and Gynecologists' criteria for the remainder of their pregnancies using insulin glargine alone. Two of four patients had average fasting blood glucose values \leq 95 mg/dl; the other two maintained average fasting blood glucose values \leq 98 mg/dl. Their starting doses of insulin glargine ranged from 10 to 50 units, with an average of 29 units. Doses at delivery ranged from 18 to 78 units, with an average of 44 units.

For three patients with well-documented blood glucose values before initiating insulin glargine, the average reduction in fasting blood glucose was 15 mg/dl and the average postprandial decrease was 17 mg/dl. One patient experienced an average blood glucose reduction of 30 mg/dl, including reductions from 21 mg/dl after breakfast to 49 mg/dl after dinner.

All four women reported successful pregnancy outcomes. No infants were reported to have hypoglycemia, and one weighed >9 lb. One patient experienced hypoglycemic episodes using insulin glargine, with six episodes of blood glucose <60 mg/dl (53, 57, 54, 54, 59, and 58 mg/dl). She also reported skipping meals, especially breakfast. All six of her hypoglycemic episodes were in the time period labeled "2 h after breakfast."

Starting doses of insulin glargine were implemented using half of the estimated total daily dose needed during that trimester. Total daily dose was calculated as 0.4–0.5 units/kg in the 1st trimester, 0.5–0.6 units/kg in the 2nd trimester, or 0.7–0.8 units/kg in the 3rd trimester. Insulin glargine was injected in the morning before breakfast and increased rapidly until blood glucose was at target. Throughout the rest of the pregnancy, insulin glargine doses were advanced by 3–5 units whenever readings reached the upper limit of the target range.

Morning dosing of insulin glargine contributed to target postprandial readings throughout the day, with no nocturnal hypoglycemia reported and without

altering fasting glucose levels. Though the usual recommended starting dose of insulin glargine is 10 units, we found that higher starting doses were required to achieve blood glucose goals during pregnancy, especially in obese women.

Multiple studies (3–5) over many years have shown that tight glucose control during pregnancy is important to promote normal perinatal outcomes. Insulin glargine offers an alternative in GDM, especially for women with mild glucose intolerance. Additional research is needed to further elucidate the safety and effectiveness of using insulin glargine in women with GDM.

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Bowel Dysfunction in Wolfram Syndrome

Bowel dysfunction is a common problem in patients with metabolic/neurological disorders and ranges from constipation and intestinal pseudo-obstruction to intractable fecal incontinence. However, the mechanism of it remains not entirely clear, although the bowel dysfunction severely affects the quality of life in the patients.

Here, we report on a 32-year-old man with clinically diagnosed Wolfram syndrome (WFS), which is thought to be caused by a *WFS1* gene mutation that encodes *wolframin*, an endoplasmic reticulum calcium channel in neurons and pancreatic β -cells. He also presented with severe bowel (urgent fecal incontinence that started at age 24 years) and bladder dysfunction. His previous illnesses included congenital cataracts, progressive optic atrophy that started at age 3 years, and diabetes that started at age 11 years (under insulin treatment). At that time, he had first begun to have mild urinary urgency/frequency. At age 21 years, he was found to have hearing loss and diabetes insipidus (then, urine output 1,200 ml/day under desmopressin treatment with no upper urinary tract dilatation). A nerve conduction study in the extremities revealed sensory-dominant axonal neuropathy. A brain magnetic resonance imaging scan revealed atrophy in the cerebellum and the brainstem, although he had no cerebellar ataxia. Urodynamic study with pressure-flow analysis showed detrusor filling overactivity/voiding underactivity without detrusor-sphincter dyssynergia. Twenty milligrams a day of propiverine, an anticholinergic agent, once ameliorated his bladder and bowel symptoms. However, he again became fecally incontinent, and after tapering the drug, we performed a bowel function test in the patient. Colonic transit time test using Sitzmarks (1) showed normal colonic transit time (24.0 h, 16.0 < normal < 48.0). However, videomanometry (1) showed loss of spontaneous phasic rectal contractions (SPRCs) that were seen in normal subjects and sphincter weakness. Then he was taught to perform pelvic floor exercise, and his fecal incontinence became slightly ameliorated.

Bladder dysfunctions reported in WFS include hydroureter due to excessive urine output (2), detrusor-sphincter dyssynergia (2), and detrusor overactivity

(2); the latter was the main bladder abnormality in our patient, presumably reflecting the brainstem atrophy. Previously, bowel dysfunction has only rarely been documented in WFS (3,4). In our case, loss of SPRCs and sphincter weakness were the main bowel abnormalities. The SPRCs are likely to reflect the intrinsic neuronal activities of the pacemaker cells in the myenteric plexus, which can be damaged in peripheral neuropathies that involve small fibers. Sphincter tone is maintained by the extrinsic somatic nerve for the external sphincter and sympathetic nerve for the internal sphincter, respectively, which can also be damaged in peripheral neuropathies. These bowel dysfunctions need specific management to maximize the quality of life in patients with WFS.

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Objective Evidence for the Reversibility of Nerve Injury in Diabetic Neuropathic Cachexia

Diabetic neuropathic cachexia is an acute complication of diabetes marked by such extreme pain and weight loss that, although exceptionally rare, it imparts major challenges in management and diagnosis. Little is known of the fundamental pathophysiologic features of the peripheral nervous system in this condition; for example, the symptomatic resolution that is classically observed may arise from either complete destruction of pain-transmitting nerve fibers or from their repair. To reconcile this issue, we report the first case to our knowledge that the nerve dysfunction is reversible. A 36-year-old woman presented with subacute hyperglycemic symptoms. Soon after initiation of insulin therapy and the decline of HbA_{1c} from 14.9 to 5.5%, she developed severe lancinating pain and profound weight loss associated with anorexia, amenorrhea, insomnia, and dehydration. On examination, allodynia was so pronounced that a light touch to her shoulder would cause her to weep. Profound loss of subcutaneous adipose tissue and loss of muscle bulk was evident, such that her weight had decreased from a baseline of 58.3 to 41.8 kg (corresponding to a decrease in BMI from 21 to 15.7 kg/m²). Pain, temperature, and light touch sensation were abnormal in the hands and feet.

Blood count, chemistries, and thyroid and cortisol levels were normal. Further tests for malignancy and malabsorption, including serum immunoelectrophoresis, computed tomography, bone scan, and endoscopy with biopsies, were normal. Titers for antinuclear antibodies and viral etiologies were negative. Nerve conduction studies demonstrated impaired conduction velocity (indicative of impaired myelin sheath function) and impaired amplitude potentials (indicative of impaired nerve axon function) of both sensory and motor nerves.

Hydration, oral nutritional support, and opiate therapy were provided during an 8-week hospitalization. She subsequently received symptomatic therapy with amitriptyline and gabapentin; a year later these analgesic therapies were dis-

continued, and her weight had returned to baseline. The aberrations in nerve function had normalized; most dramatic was the improvement in nerve axon function, represented by a doubling of amplitude potentials. For example, in the sural nerve the conduction velocity improved by 30% (from 36 to 47 m/s) and the sensory amplitude potentials doubled (from 3.4 to 7.5 μV) from baseline. Similar changes were seen in the median and peroneal nerves for these parameters and also for F-wave latencies and vibration perception thresholds.

The profound weight loss, the symmetrical sensorimotor polyneuropathy associated with dramatic painful paresthesias devoid of weakness, the temporal relation with insulin therapy, and the chronic course are in complete accordance with the diagnosis of diabetic neuropathic cachexia (1). This report emphasizes the need for vigilant symptomatic therapy of diabetic neuropathic cachexia while expediting investigations for eliminating alternate causes. Unique to this report, however, is the objective finding of nerve dysfunction that was dramatically reversed after symptomatic recovery; it supports the proposed hypothesis that paradoxical hypoxic injury occurs at the initiation of insulin therapy (2,3). This case fundamentally suggests that the reversal of painful symptoms is associated with repair of functional aberrations in nerve fibers induced by hypoxia rather than their irreversible ischemic destruction.

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