Treatment of Parkinson disease with diet-induced hyperketonemia: A feasibility study

Abstract—Ketones may bypass the defect in complex I activity implicated in Parkinson disease (PD). Five of seven volunteers with PD were able to prepare a "hyperketogenic" diet at home and adhere to it for 28 days. Substituting unsaturated for saturated fats appeared to prevent cholesterol increases in four volunteers. Unified Parkinson's Disease Rating Scale scores improved in all five during hyperketonemia, but a placebo effect was not ruled out.

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Patients with idiopathic Parkinson disease (PD) may suffer from impairment of complex I activity involving—but not limited to—dopaminergic neurons of the substantia nigra pars compacta (SNpc).[1] The resulting mitochondrial dysfunction could help explain some of the clinical manifestations of the illness. A recent study of isolated mouse brain mitochondria exposed to the complex I inhibitor, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), found that mitochondrial oxygen consumption and adenosine triphosphate (ATP) production were significantly increased when D-β-hydroxybutyrate (DβHB) was added to the preparation, apparently by a complex II-dependent mechanism.[2]

These findings in mice suggested that diet-induced elevation of blood ketones (DβHB and acetoacetate [AcAc]) to concentrations sufficient to replace a substantial proportion of glucose as the brain's fuel might bring about symptomatic improvement in patients with PD by bypassing the presumed complex I defect and boosting mitochondrial function and ATP production. In addition, in vitro and in vivo evidence that DβHB protects against MPTP-induced neurotoxicity[2,3] suggests that sufficiently prolonged nutritional hyperketonemia might also help delay the progression of idiopathic PD.

To increase blood ketones to concentrations within the "therapeutic" range (2 to 7 mmol/L), patients are usually maintained on a "4:1 hyperketogenic diet" (HKD), consisting (by weight) of 4 parts fat and 1 part of a carbohydrate-protein mixture).[4] Although this kind of diet has been used successfully for decades for treatment of children and adults with medication-resistant seizure disorders,[5] it is difficult to follow; moreover, after prolonged use, significant elevations may occur in serum low-density lipoprotein (LDL) cholesterol and other potentially atherogenic serum lipids.[6]

Given evidence that ketones crossing the blood-brain barrier may bypass or compensate for the defect in complex I activity implicated in PD, it seemed desirable to test whether a HKD can benefit patients with PD. However, before attempting an extensive outpatient study, we deemed it essential to determine in a small series whether: 1) ambulatory patients with PD would be able to prepare a HKD in their own homes and remain on it for at least 4 weeks; 2) substitution of mono- and polyunsaturated fats for saturated fats, wherever possible, would mitigate the increases in the serum total cholesterol concentration expected from a very high fat diet; 3) evidence could be obtained to support the clinical safety of the HKD approach in the patients with PD.

Methods. Seven patients with PD volunteered to remain on a HKD for 28 days in an open trial conducted at the Movement Disorders Clinic of the Beth Israel Medical Center. Two dropped out in the first week; one because of a family health emergency and one because of inability to prepare the diet. Table 1 provides information about the five participants who completed the study. Nonfasting concentrations in serum of ketones, total cholesterol, glucose, insulin, and uric acid were measured at baseline, periodically during diet adherence, and once after diet termination. As a safety measure, Unified Parkinson's Disease Rating Scale (UPDRS) scores were determined at baseline and at weekly intervals during HKD adherence by an expert movement disorder practitioner (K.B.) under the supervision of the attending neurologist (A.DiR.). The regimen used in this investigation is called *hyper*ketogenic to distinguish it from the far less restrictive low-carbohydrate "ketogenic" diets currently in use for weight control.[7,8] In the present HKD, the distribution of calorigenic sources (as percentages of total energy intake) was carbohydrate 2; protein 8; and fat 90.

Adherence to the diet was assessed by the dietitian, who maintained ongoing food records for every patient, kept in almost daily telephone communication with them, and met with each frequently during the study.

In an attempt to restrict the rise in serum lipids anticipated from the extremely high content of saturated fats in the HKD, we substituted, wherever feasible, fats rich in mono- and polyunsaturated fatty acids. The approximate distribution (%) of fatty acids in the modified HKD (mean and range) was saturated 31.3 (23 to 38); monounsaturated 49.8 (35 to 65); and polyunsaturated 8.3 (5 to 13).

Results. With two exceptions (Patients 2 and 5), the participants who completed the 28-day study adhered faithfully to the prescribed menus. However, for unknown reasons (perhaps because of the diet's inherent unpalat-

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Table 1 *Information about patients with Parkinson disease (PD) who completed the hyperketogenic diet study*

Patient no./ age, y/sex	PD duration, y	Initial body-mass index, kg/m^2	Principal complaints at baseline	Hoehn and Yahr stage	Antiparkinson medications at baseline
1/69/F	½	28.4	Tremor of right hand, anxiety, depression	I	None
2/74/M	3	30.3	Fatigue, left hand tremor	III	Carbidopa/levodopa
3/57/F	12	35.9	Impaired gait and balance, left hand tremor	III	Carbidopa/levodopa, pramipexole, selegiline, entecapone
4/46/F	11	28.6	Impaired gait, motor fluctuation depression	III	Carbidopa/levodopa, amantadine, entecapone
5/58/F	5	31.3	Impaired gait, foot drag, festination while walking, loss of right hand flexibility	III	Pramipexole, carbidopa/ levodopa, amitriptylene, selegiline

ability), all lost varying quantities of body weight during the study period (mean 6.1 kg [range 4.1 to 9.5]).

Patient 5 had occasional lapses during the last 10 days of the diet, reflected by rises in serum insulin and glucose concentrations and concurrent reductions in ketone and uric acid concentrations. Although Patient 2 did not adhere as rigorously as the other participants, he achieved serum ketone concentrations ranging from 1.13 to 1.56 mmol/L, and improved his UPDRS scores.

The dietitian's estimation of patient adherence was corroborated by the serum ketone concentrations. In the three most compliant subjects, mean serum ketone concentration during diet adherence was 6.6 mmol/L (range 4.8 to 8.9). Urinary ketones, measured daily, were always strongly positive.

Serum total cholesterol concentrations on day 28 of the diet were not significantly different from baseline values in four of the patients. In Patient 5, who was moderately hypercholesterolemic at baseline, serum total cholesterol increased 30% (from 6.5 to 8.4 mmol/L) after 4 weeks on the HKD.

Table 2 shows the changes in the UPDRS scores that occurred in the five patients during the HKD. The mean total decrease in UPDRS scores for all five subjects was 43.4% (range 21 to 81). Among symptoms that improved were resting tremor, freezing, balance, gait, mood, and energy level.

Discussion. Although the HKD is known to be difficult to prepare and follow,[5] most of the volunteers were able to understand the underlying principles of the diet and adhere to it faithfully for 4 weeks. This degree of patient cooperation was achieved because a knowledgeable dietitian carefully explained the diet to each potential participant, gave detailed instruction in its preparation and use, and provided ongoing supervision and encouragement.

Substitution of unsaturated for saturated fats in the HKD was probably responsible for the lack of increase in serum total cholesterol in four of the patients with PD after 28 days on the diet. It has been reported that, in contrast to 10 healthy adults whose total and LDL cholesterol concentrations rose significantly after 5 days on a HKD high in saturated fats, these lipid fractions did not increase in an equal number of comparable subjects who followed a polyunsaturated fat-enriched HKD for the same period of time.[9]

Because of the small series and lack of suitable

Table 2 *Unified Parkinson's Disease Rating Scale (UPDRS) scores in five patients with Parkinson disease (PD) at baseline and after 28 days* of adherence (final) to a hyperketogenic diet (total changes and changes by category)*

Patient no.	Mentation and mood	ADL	Motor function	Treatment complications	Totals	Decreases in total score, %
1	3.0/2.0	2.5/3.0	5.5/3.75	0/0	11.0/8.75	21
2	3.0/0.0	9.0/4.0	18.5/12.5	0/0	30.5/16.5	46
3	2.0/1.0	13.0/6.5	15.0/7.25	1.0/2.0†	31.0/16.75	46
4	3.0/3.25	4.0/3.0	6.25/5.0	6.5/4.0	19.75/15.25	23
5	3.0/0.5	7.0/0.75	9.75/1.00	3.0/2.0	22.75/4.25	81

Scores by category (baseline/final values). All patients were evaluated in their best "on" state.

* After 21 days in patient 4.

† Patient 3 reported feeling overmedicated with increased dyskinesia after 3 weeks on the hyperketogenic diet. Thus, at the end of her 4th week on the diet, her carbidopa/levodopa dose was reduced from 1,100 to 1,000 mg/day.

ADL = activities of daily living.

controls, it is impossible to interpret the improved UPDRS scores in the five patients during the HKD. At best, the improved scores support the safety of the HKD approach. A placebo effect on UPDRS scores has been documented in numerous pharmacologic trials in PD[10] and could have occurred in our patients.

The studies of isolated mouse brain mitochondria exposed to MPTP, referred to earlier,[2] found that ketone supplementation increases the generation of reactive oxygen species, thought by many to be a key mediator of nigral neuron degeneration. This observation is a cause for concern; however, the same investigation also showed DβHB to be neuroprotective in the presence of MPTP. Moreover, despite extensive experience with HKDs for treatment of drug-resistant epilepsy, there have been no reports of neurodegeneration attributable to diet-induced hyperketonemia sustained for many years.[5]

From experience with this small series, we conclude that it is feasible and desirable to conduct additional, carefully controlled trials of the HKD in larger numbers of patients with PD maintained on the diet for prolonged periods. Such trials should make it possible to determine reliably whether therapeutic hyperketonemia can give rise to symptomatic improvement in the short term and, over time, delay progression of the disease.

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