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Dietary Factors in the Management of Parkinson's Disease

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Oral administration of L-dopa is currently the most effective way to treat the cerebral dopamine deficiency which causes Parkinson's disease. Unfortunately, many patients with advanced Parkinson's disease develop an unstable pattern of response to L-dopa because of fluctuating delivery of the drug to the brain. Diet contributes to this problem through its adverse effects on L-dopa pharmacokinetics. This article reviews dietary strategies to improve responsiveness to pharmaceutical L-dopa treatment and the potential use of food as a source of L-dopa. Nutritional factors concerning weight loss and energy balance in Parkinson's disease are also discussed. A set of dietary guidelines is developed to assist clinical nutritionists and neurologists in the practical management of patients with Parkinson's disease.

Introduction

Parkinson's disease is caused by idiopathic progressive degeneration of pigmented neurons in the substantia nigra region of the brainstem. These neurons use the neurotransmitter dopamine and innervate the motor portions of the basal ganglia, in particular the caudate nucleus and putamen. Although the precise role of the substantia nigra in normal motor control is uncertain, the deficiency of dopamine that results from degenerative changes in this region leads to a disturbance of motor function manifested clinically as Parkinsonism.

Following a series of improvements in the understanding of brain catecholamine neurochemistry in the 1950s, levo-dihydroxy-phenylalanine (L-dopa), the amino acid precursor of dopamine, was first used to treat Parkinson's disease. The effectiveness of this drug soon became clear, with dramatic improvement in many previously severely disabled patients.[1] However, further experience exposed certain complications of long-term L-dopa treatment. In some cases, the pattern of response to L-dopa became unstable and was further marred by the development of periodic involuntary movements.[2,3]

L-Dopa medication is now usually initiated in patients with relatively mild Parkinson's disease early in the course of the illness. Modern treatment combines L-dopa with a peripheral decarboxylase enzyme inhibitor (carbidopa or benserazide) to minimize conversion of L-dopa to dopamine outside the nervous system. In most cases, motor symptoms improve and a stable and satisfactory response continues for the next few years. With further disease progression, many patients begin to experience fluctuation of response to L-dopa, and drug-induced dyskinetic involuntary movements may then accompany the beneficial effects of the medication. Significant motor fluctuations develop at a rate of about 10% per treatment year.[4] In their most severe form, motor fluctuations produce the "on–off" syndrome.[5] Patients with this affliction swing between severe Parkinsonian disability ("off" phases) and relative improvement of motor function which restores mobility at the expense of involuntary movements ("on" phases). Capricious and abrupt fluctuation between these states occurs many times each day. The fact that patients cannot predict when sudden loss of independent mobility will occur is in itself a major cause of disability in this syndrome.

The pharmacokinetic properties of L-dopa lead to fluctuating blood levels, generating fluctuation of motor function in susceptible patients.[6] The drug has a relatively short half-life because of enzymic catabolism, and dietary intake is apt to interfere with its absorption and transport within the body. Fluctuating delivery of L-dopa to the brain does not seem to matter early in the disease course. How-

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Table 1. Dietary Factors Which Affect Clinical Response to L-Dopa Medication

1. Timing of L-dopa doses in relation to mealtime.
2. Effects of food on gastric emptying
   Energy content of food
   Meal size
   Food viscosity
3. Competition between dietary neutral amino acids and L-dopa for absorption across the intestinal mucosa.
4. Competition between circulating neutral amino acids and L-dopa for active transport across the blood–brain barrier.

ever, disease progression brings increasing dependence on pharmacological dopamine receptor stimulation. Severe motor fluctuations are generally seen in patients who retain a capacity to respond well to L-dopa but have lost most of their endogenous dopamine production because of nigral cell loss. A precipitous decline in motor function thus occurs each time that the supply of exogenous L-dopa to the brain lapses.

Despite a number of refinements to pharmacological treatment in recent years, L-dopa remains the most physiological and effective method to stimulate the central dopamine receptors and is the mainstay of treatment for most Parkinsonian patients. Some dopamine receptor agonist drugs have a longer and more stable duration of action but cannot match the potent clinical effects of L-dopa. The complication of fluctuating motor response to L-dopa is therefore one of the major problems in the long-term care of patients who have Parkinson's disease. Because food intake contributes to the vagaries of L-dopa pharmacokinetics, diet is an important influence on the effectiveness of pharmacological treatment.

Other nutritional factors such as food toxicants[7] and dietary antioxidants[8] may eventually be shown to play a role in the etiology or progression of Parkinson's disease. However, this review will concentrate on aspects of clinical nutrition that relate to the practical management of Parkinson's disease.

Dietary Influences on L-Dopa Pharmacokinetics

L-Dopa is normally present as an intermediate metabolite in neurons which produce catecholamine neurotransmitters (dopamine, noradrenaline, and adrenaline). It is synthesized by the enzyme tyrosine hydroxylase from the diet-derived aromatic amino acid tyrosine. Brain tyrosine hydroxylase is confined to dopaminergic and noradrenergic neurons, has a high affinity for its substrate tyrosine, and its activity is regulated by the rate of neuronal firing.[9,10] Administration of tyrosine to Parkinsonian patients may increase dopamine synthesis and turnover in the central nervous system,[11] but there is no evidence of any clinical benefit from treatment with tyrosine. Phenylalanine is an indirect amino acid precursor of L-dopa but has no clinical effect on Parkinsonism.[12] A normal diet contains little L-dopa,[13] and the small amount of circulating L-dopa in normal subjects probably emanates from synthetic activity in peripheral sympathetic neurons and the adrenal medulla.[14]

To exert its action in Parkinson's disease, L-dopa must be absorbed from the gastrointestinal tract into the bloodstream, cross the blood–brain barrier, and then be enzymatically converted to dopamine within the brain to interact with striatal dopamine receptors. Intake of food, particularly protein, can interfere with this process at a number of levels. Single oral doses of L-dopa, when administered in the fasting state, produce efficient and reliable absorption of L-dopa, which corresponds to predictable and relatively prolonged motor responses even in patients with the most erratic pattern of response to their usual oral L-dopa medication.[15]

Patients are often advised to take L-dopa doses with meals. By reducing L-dopa absorption, food may reduce side effects such as nausea on first exposure to medication containing L-dopa. However, once motor fluctuations have developed after prolonged treatment, food is usually a hindrance to the bioavailability and clinical effectiveness of L-dopa.

L-Dopa is optimally absorbed from the duodenum and proximal jejunum.[16] The drug is not absorbed across gastric mucosa,[17] but oral doses are dependent on gastric emptying for access to absorption sites. The rate of gastric emptying is chiefly determined by the energy content of food and is inversely proportional to the energy density of a meal.[18] Thus fat will retard gastric emptying to a greater degree than either protein or carbohydrate. Low gastric acidity slows emptying[19] although routine administration of antacids to Parkinsonian patients does not improve L-dopa absorption.[20] Some types of dietary fiber increase food viscosity and slow gastric emptying.[21] The gastric mucosa contains the enzyme dopa decarboxylase,[22] which will catalyze unwanted conversion of L-dopa to dopamine, reducing the amount of L-dopa available for subsequent absorption from doses affected by delayed gastric emptying.

When L-dopa is administered by naso-duodenal tube[23] or to subjects who have previously had a gastrectomy,[19] absorption is very rapid and efficient. Effects on gastric emptying are probably largely responsible for the observation that when L-dopa is given with food, the rise in plasma concentration is

reduced, delayed and unpredictable as compared with fasting.[24,25]

On reaching the proximal small gut, L-dopa crosses the mucosal barrier by a stereospecific, saturable active transport mechanism shared by large neutral amino acids such as phenylalanine, tyrosine, tryptophan, leucine, isoleucine, valine, methionine, and histidine.[26] Dietary protein can thus lead to competition for these active carrier sites. Once L-dopa molecules have reached the bloodstream, access to the brain is dependent on similar active amino acid transport across the blood–brain barrier for which it must compete with other circulating neutral amino acids.[27]

Intravenous infusion of L-dopa at a constant rate can produce stable and sustained motor responses in patients with motor fluctuations. When oral protein or neutral amino acid loads are then administered, a transient loss of response occurs without change in blood L-dopa concentration, indicating a block to L-dopa passage into the brain through competition for transport across the blood–brain barrier.[24] Constant rate intraduodenal infusion also produces efficient L-dopa absorption, stable L-dopa blood level, and sustained clinical responses in fasting patients. With oral administration of protein, the relative importance of competition by dietary neutral amino acids at gut and blood–brain barrier levels can be compared. Oral protein causes a loss of clinical response to L-dopa without affecting blood concentration: this indicates that the major site of interference between L-dopa and amino acid active transport is at the blood–brain barrier.[28] Experimental data regarding the equilibrium constant for active transport of large neutral amino acids also agree with this observation. In gut, as in most tissues, the equilibrium constant is considerably higher than physiological concentrations of neutral amino acids. However, the constant for brain capillary endothelial cells (which form the physiological blood–brain barrier) is about 10 times less than for other tissues and approaches the sum of postprandial plasma concentrations of large neutral amino acids.[29]

Unpredictability is a major feature of severe motor fluctuations. Although patients experience the fluctuations every day, the timing of dramatic changes in motor disability and the amount of "on" and "off" time per day are never the same despite constant pharmacological treatment. Erratic L-dopa absorption due to the influence of food on gastric emptying[30] and the dissociation between L-dopa plasma concentration and clinical effect because of dietary neutral amino acids in the bloodstream[31] appear to be the chief factors generating the unpredictable element of motor fluctuations.

Table 2. Practical Dietary Guidelines for Parkinsonian Patients

Dietary advice relevant to all patients with Parkinson's disease
Take L-dopa doses with food when starting treatment.
Energy intake at upper limit of age-related energy requirement (probably greater than 30 kcal/kg of ideal weight), particularly if patient is below ideal weight or has a history of weight loss.
Calcium intake above recommended dietary allowance of 800 mg/day.
Supplementation with dietary fiber and adequate fluid intake to prevent or reduce constipation.
Patients with fluctuating response to L-dopa
Take oral L-dopa doses at least 30 minutes before meal times to minimize effects of postprandial gastric emptying.
Protein intake not to exceed recommended dietary allowance and evenly distributed throughout the day.
Trial of protein redistribution diet for patients with refractory motor fluctuations.
Careful monitoring of weight and nutrition by a clinical nutritionist or dietitian.
Return to standard diet if significant clinical benefit does not occur within 2 weeks.
Supplement calcium intake if necessary.
Judicious use of broad beans in season or frozen alternative (pods and legumes cooked gently and consumed together) in substitution for protein-rich foods.

Dietary Strategies to Improve the Response to L-Dopa Treatment

Most patients with Parkinsonian motor fluctuations are able to observe effects of food intake on motor function, and many remark spontaneously that meals tend to cause shortening or failure of response to L-dopa tablet doses. Parkinsonian patients are also particularly amenable to dietary modification strategies. In many situations in medical practice, dietary modification is an important aspect of treatment, but from a patient's perspective, changes in life-long dietary habits are required for an abstract goal of improved general health at some future time. For patients suffering from Parkinsonian motor fluctuations, interference between food and response to medication contributes to disability on an hour-to-hour basis, and any response to dietary therapy is likely to be immediate. In practice, Parkinsonian patients will often accept quite drastic dietary changes and some will institute their own empirical modifications of diet.

Manipulation of protein intake has been the most widely studied dietary strategy. Various protein-restriction diets have been evaluated with clinical and pharmacokinetic measurements.[31–36] Most

studies agree that a high protein intake inhibits the effectiveness of L-dopa treatment and that the benefits of reduced protein intake are mediated through reduction in circulating neutral amino acid concentration rather than increased L-dopa absorption.[31,35,36] Carter et al. found that protein restricted to the recommended dietary allowance (RDA) level of 0.8 g/kg/day allowed a better response to L-dopa than a usual protein intake of 1.6 g/kg/day.[35] However, the most effective dietary strategy involves redistribution of protein intake.[31] This requires protein to be virtually excluded in food taken during the day (protein content restricted to 7 g) with daily protein requirement being made up in a high-protein evening meal. Carter et al compared various diets in a group of fluctuating patients on standard oral L-dopa medication. While taking an average American amount of protein in their diet, these patients were "on" for 51% of the waking day. When protein intake was reduced to the RDA level, "on" time increased to 61% and when a protein redistribution diet was taken, patients remained "on" for 71% of the time.[35] The protein redistribution diet requires considerable reorganization of mealtimes, and patients have to accept a period of loss of response to medication following the higher-protein evening meal. Nevertheless, with appropriate dietary guidance and encouragement, the majority of patients are able to comply with the diet. About 60% of patients report improvement in control of motor symptoms and a more stable response to L-dopa, usually within a few days.[34] The diet offers no benefit to patients who do not fluctuate because of poor responsiveness to L-dopa.[34]

Long-term experience with the protein redistribution diet suggests that 70% of patients who gain an initial advantage will use the diet for 12 months or more.[37] A study of the nutritional status in patients restricting daytime protein intake for 2 months showed that significant reduction in the intake of protein, calcium, phosphorus, iron, riboflavin, and niacin occurred.[38] However, only calcium intake fell to below the RDA level, probably because of a restriction on the intake of dairy products. Body weight and serum prealbumin concentration did not change significantly. Although dietary protein redistribution is an effective long-term treatment in some patients, careful monitoring of nutrition is required. This is of particular importance when the usual diet is marginally adequate, and when patients are at risk for osteoporosis.

Manipulation of dietary components other than protein has been studied less extensively. Carbohydrate loads, by stimulating insulin secretion, reduce circulating amino acid levels.[39] This may be the explanation for the observation that the effectiveness of oral L-dopa doses is enhanced by glucose loading.[40] Berry et al administered balanced carbohydrate : protein (ratio = 5) meals to Parkinsonian patients and found that plasma neutral amino acid levels did not change.[41] They suggested that the effect of carbohydrate in lowering amino acid concentration could cancel out the rise following a moderate protein load and that a balanced dietary intake may be as effective as protein restriction/redistribution.

Limiting or redistributing protein intake may minimize competitive inhibition of transmembrane passage of L-dopa into the brain but may not be the best way to influence other forms of dietary interference with the action of L-dopa, particularly the effects of food on gastric emptying. Redistribution of the dietary energy content or adjustment of the fiber-type and viscosity of meals may allow more efficient access of L-dopa medication to absorption sites. These forms of dietary manipulation have not been systematically evaluated in Parkinson's disease. Meal size will also affect the time taken for gastric emptying. Small snacks taken with L-dopa medication do not significantly interfere with the clinical response to the drug.[42] However, dividing daily dietary intake into multiple small feedings rather than three standard meals does not improve the effectiveness of treatment.[33]

Dietary Sources of L-Dopa

Food can also be a source of L-dopa. In 1913, Guggenheim first isolated dihydroxyphenylalanine in its levorotatory form after extracting it from *Vicia faba* beans.[43] He was also first to demonstrate a pharmacological action of L-dopa when he ingested some of his bean extract and became nauseated. He found the bean pods to be a richer source of L-dopa than the beans.

There are anecdotal reports that patients with Parkinson's disease will benefit from meals of broad beans, and that response to *Vicia faba* may even be better than to conventional L-dopa medication in some cases.[44] Recent studies have established the dose–response and L-dopa absorption characteristics of *Vicia faba*.[45,46] There is sufficient L-dopa in broad bean pods to be pharmacologically active in Parkinson's disease. The beans are a natural food which contains L-dopa in a physicochemical form different from that of tablet formulations and may thus have some use in the management of Parkinsonian motor fluctuations.

In our single-dose studies[46], we evaluated patients with pronounced "on–off" motor oscillations. Clear and unequivocal responses to L-dopa doses occur in such cases and their magnitude and time course can be accurately quantified by serial objective motor assessments. Simple meals of broad

bean pod mixture were prepared by microwave cooking and homogenization and were administered with carbidopa. In five of six patients studied, *Vicia faba* meals produced motor improvement accompanied by dyskinetic involuntary movements in the absence of other dopamine receptor–stimulating pharmacological agents. Motor responses following *V. faba* ingestion were generally equivalent to but no better than responses to conventional oral L-dopa doses, suggesting that the motor benefits of *Vicia faba* can be attributed to their L-dopa content alone, rather than to other pharmacologically active naturally occurring substances.

We measured the L-dopa recovery at 0.25% per weight of *Vicia faba* pods. (Guggenheim, who used stoichiometric methods to measure the L-dopa content of a sample of fresh bean pods, obtained an identical result.[41]) Thus a 100-g serving of *Vicia faba* pods contains about 250 mg of L-dopa, equivalent to the L-dopa content of one of the standard pharmaceutical formulations. Our pharmacokinetic measurements were consistent with ingestion of L-dopa doses of that order of magnitude although plasma L-dopa concentration following *V. faba* doses was more variable than for tablet doses after fasting. Prolonged freezing did not lead to clinically significant degradation of the L-dopa content of *Vicia faba*. Figure 1 shows a comparison of motor response and plasma L-dopa concentration following standard L-dopa/carbidopa and broad bean pod doses in a patient with pronounced motor fluctuations. The magnitude of response (difference between "off" and "on" states) is almost identical. The *V. faba* meal produces a longer response which seems to be explained by a larger L-dopa dose and higher plasma concentration. The post-dose rate of rise and decay of plasma L-dopa level in our studies was similar to standard L-dopa preparations; *V. faba* meals did not have the properties of a slow release L-dopa preparation.[47]

Most of the L-dopa contained in *V. faba* exists in a free form in the bean pods although small quantities of a dopa glucoside can be detected in both legumes and pods.[48] L-Dopa also occurs naturally in significant quantities in several other leguminous species. It is present in the Georgia velvet bean (*Stizolobium deeringianum*)[49] and the legumes and seeds of the Indian medicinal plant *Mucuna pruriens*.[50] The L-dopa yield per weight of the latter plant is considerably greater than from *Vicia faba*.

Natural sources of L-dopa cannot compete with tablet formulations for convenience and predictable bioavailability. However, *V. faba* does have some potential advantages in reducing the interaction between oral L-dopa medication and diet. Rather than simply restricting oral protein intake, a diet that substitutes *V. faba* for other foods which contain protein, in conjunction with conventional L-dopa/decarboxylase inhibitor medication, may have a stabilizing effect on motor fluctuations and reduce food-induced "off" phases. *Vicia faba* is a relatively rich protein source (if both legumes and pods are ingested),[51] which has a positive effect on both plasma L-dopa concentration and motor function.

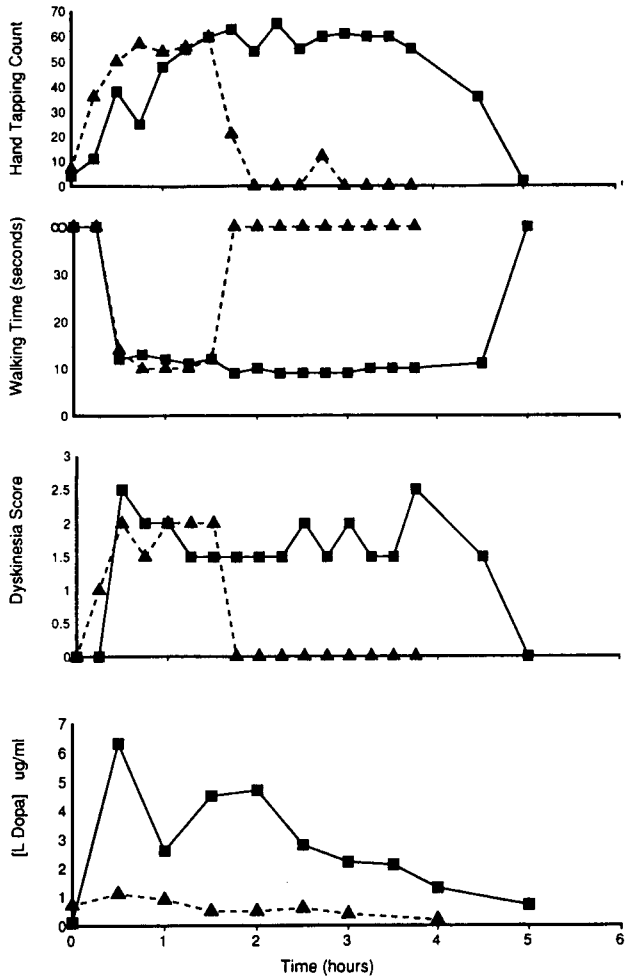

Figure 1. Comparison of motor response to *Vicia faba* with standard oral L-dopa medication. Graph of serial motor assessments (hand tapping count, time to walk a fixed distance, and scoring for severity of L-dopa-induced dyskinesia) and plasma L-dopa levels. *Vicia faba* 200 g (squares) and a standard L-dopa 100-mg/carbidopa 25-mg tablet dose (triangles) administered at time=0. Figure reprinted with permission from Asia Pac J Clin Nutr 1993: 2(2).

Lack of availability of pharmaceutical L-dopa/decarboxylase inhibitor drugs is a major limitation to the management of Parkinson's disease in developing countries. *Vicia faba* is widely grown in some regions of the world and is inexpensive, both as a nutritional substance and as a pharmacological treatment. *Vicia faba* or one of the other L-dopa-containing plant species could be used where standard pharmacological treatment is not available or

is in short supply. Higher doses of L-dopa are required when a decarboxylase enzyme inhibitor is not administered. However, the early phase of L-dopa treatment in the 1960s and 1970s demonstrated that high-dose L-dopa was effective in Parkinson's disease despite some side effects because of excessive peripheral conversion of L-dopa to dopamine.[1]

Weight Loss and Energy Balance

Weight loss is a common symptom in Parkinson's disease. James Parkinson mentioned cachexia as part of the first description of the disorder.[52] Two anthropometric surveys of Parkinsonian patients have shown that mean body mass is significantly lower than for age-matched controls. In one study, females were predominantly affected,[53] while in the other, weight loss affected both sexes with evidence of protein/calorie depletion in men and energy subnutrition in women.[54] Weight loss often occurs in phases during the disease course, followed by periods of stabilization of weight. Sometimes, weight loss can be so rapid and severe that investigation for underlying malignancy is carried out.[55] Many patients with advanced disease and severe motor fluctuations have low body weight and deficient body fat stores. Alterations in both energy input and output occur in Parkinson's disease and may contribute to weight loss.

Energy Input

Reduction in food intake may contribute to negative energy balance. Nausea and anorexia can occur in relation to most anti-Parkinsonian medications including L-dopa and dopamine receptor agonist drugs. Depression and cognitive impairment are both common in Parkinson's disease and may reduce apetite. Olfactory sensation has been shown to be reduced, and this might affect taste and desire for food.[56] The degenerative changes of Parkinson's disease result in a 60% reduction of dopamine content in the hypothalamus,[57] and hypothalamic Lewy bodies (neuronal intracellular inclusion bodies which are the pathological hallmark of Parkinson's disease) may also be found.[58] In theory these changes could impair the central weight and appetite control mechanisms.

Disturbances of motor function affecting mastication and swallowing are common in Parkinson's disease and will impair the ingestion of food if severe. However, a recent study comparing body weight of patients with Parkinson's disease and Steele-Richardson syndrome (a separate extrapyramidal degenerative disease entity) found that body weight was slightly lower in Parkinson's disease.[59] The fact that Steele-Richardson syndrome usually causes greater impairment of bulbar muscle function than Parkinson's disease suggests that bulbar involvement is not the chief cause of weight loss.

Energy Output

The motor disability of Parkinson's disease impairs mobility and may reduce the level of physical activity. Yet in some situations, energy consumption by skeletal muscle may be increased. Involuntary motor activity due to tremor or L-dopa induced dyskinesia are the most obvious examples of this. Extrapyramidal rigidity (increased resting muscle tone) and dystonia (sustained abnormal limb or truncal postures due to abnormal cocontraction of agonist and antagonist muscle groups) may also increase muscle energy use. Resting energy expenditure, as measured by oxygen consumption, is increased in Parkinsonian patients.[60,61] Levis et al. measured energy expenditure before and after L-dopa doses and found that both increased muscle tone in "off" phases and involuntary movements in "on" phases could increase oxygen consumption.[61]

One of the major evolutionary influences on the development of motor control in animals is the requirement that essential motor activity be performed with minimum expenditure of energy. The motor system achieves this goal through appropriate selection of agonist and antagonist muscle groups and by coordinating contraction of these muscles. The basal ganglia play a central role in this process, which occurs "automatically" as part of every voluntary movement and which is disturbed in various basal ganglia disease states. In Parkinson's disease, the basic pattern of muscle selection and activation for movement is preserved, but insufficient muscular activity is recruited for a specific task.[62] For a movement to continue, additional cycles of motor recruitment are required. Control of complex, simultaneous, or sequential movements is impaired to an even greater degree.[63] One consequence of these abnormalities of the organization of movement may be a loss of efficiency of energy consumption. Thus, for a given level of physical activity, a patient with Parkinson's disease may expend more energy than a normal subject.

Conclusion

The 20th century has seen the progressive development of the scientific basis of an expanding discipline of clinical nutrition, scarcely articulated until recently.[64] The progression has been from micronutrients and deficiency disease, to macronutrients and chronic noncommunicable disease, to an interest in nonnutrients in food of biological importance and how they modulate the expression of disease and provide opportunities for management.

The present interest in food as a source of L-dopa stems from embryonic knowledge obtained early this century and now has to be reconciled with other nutritional factors which affect motor function and response to pharmacological therapy in Parkinson's disease.

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