Chapter

Effects of Metabolic Syndrome on Parkinson's Disease and Nutraceutical Intervention Strategies

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Abstract

Hyperglycemia, insulin resistance disturbances, and other common metabolic syndrome signs are currently related to a poor outcome of Parkinson disease. There were no widely accepted nutritional intervention protocols approved for Parkinson's disease. That author exposes a brief revision of the role of insulin resistance and glycemic metabolism dysfunction in Parkinson's patients with diabetes. In an ongoing study, with a complete record of dietary habits and diet components, it was demonstrated no significant differences between diabetics (n = 19) and nondiabetics (N = 53). But body composition shows some particularities. A result that attracts attention is total fat analysis and percentage of fat of PD patients showing that diabetics are somewhat fattier. The self-reported presence of obesity does not differ from recorded data of weight and BMI, with no significant differences between the two groups. Taking into consideration that both groups have comparable degrees of disease progression, as measured by the UPDRS, it could be possible to infer that the maintenance of a relative overweight was a protective factor in this group of diabetic evaluated patients. Considerations are made about hasty intervention of nutritional approach for PD patients with diabetes, including body fat reduction, prescription of statins and therapeutic options for diabetes control.

Keywords: Parkinson's disease, metabolic syndrome, diabetes

1. Introduction

The concurrent involvement by diabetes, a common metabolic disease, is frequent in Parkinson's disease (PD). In addition, there is strong evidence of pathological interlinking between the two entities [1, 2], and there are reports that a pre-existing diabetes could be a risk factor for more severe PD symptoms [3]. In such a relationship the mechanisms involved in the process are not fully understood [4, 5]. The same

could be applied to the therapeutic and nutritional support to PD patients [6]. Just in 1992, Dirrieu et al. [7], published a study about nutritional evaluation and PD, comparing with a control group [7]. There is no unquestionably response about the influence of diabetes treatment over PD outcome. The possibility that usual therapeutic measures, per si, could be a risk factor for aggravation of that disease was discussed [8]. Only recently there have been reports of the role of diabetes medications and risk of Parkinson's disease. The effect could be so intense that the authors stated that "The incidence of Parkinson's disease in patients diagnosed with diabetes varies substantially depending on the treatment for diabetes received. The use of DPP4 inhibitors and/or GLP-1 mimetics is associated with a lower rate of Parkinson's disease compared to the use of other oral antidiabetic drugs" [9, 10]. Glucose reduction induced by hypoglycemiants could lead to less disponibility of cerebral glucose, disturbing the GLti expression in astrocyte cells. The result is a deficit in lactate and pyruvate synthesis, bearing in mind that glial astrocytes seem to play a role in the basal cell functions maintenance, especially during the events of enhanced metabolic demand or hypoglycemia [11].

Abnormalities of glucose tolerance curves associated with PD have been published over 30 years ago [12]. Many studies [1, 13, 14] had failed to demonstrate changes in glucose levels. Nevertheless, there are studies demonstrating some correlation between diabetes, metabolic syndrome and DP and their complications [1, 15–19]. Results from a survey conducted in our service showed reduced insulin resistance and low levels of plasmatic cholesterol in parkinson's patients with dementia (PPD) associated with PD, without evidence of ponderal gain compared with control patients [14]. On the other hand, hyperinsulinemia can provoke cerebral glycogen depletion, with reduction of ATP and cell death [20]. In the same way there are reports of functional dysfunctions of mitochondria related to insulin resistance and fat deposition [21].

There are few reports about the influence of severe hypoglycemia on the outcome of PD. It was found that low and high HbA1c but not diabetes was associated with faster motor symptom progression in no diabetic patients [22]. In a relatively recent study measuring glycemic levels of 11 patients, three of them with PD, only one had severe hypoglycemia (54 mg/dL; 7.5% -72 hours, closer to the critical level established by the American Society of Endocrinology (11.7% in 72 hours). The analyzed patients do not have diabetes diagnosis [23]. In a description of an isolated case, it was determined to be a severe hypoglycaemia in a diabetic patient with parkinsonian symptoms for a few months. The neuroimage evaluation shows a vasogenic lesion in basal ganglia. With antidiabetic drugs adjustment occurred glycemia normalization and clinical improvement [24]. A confounder factor could be the occurrence of hypoglycemia provoked by statins prescription to control dyslipidemia [25].

There is some evidence that the so-called Mediterranean diet is a protective factor for development of PD [26–28].

In an ongoing study, with a complete record of dietary habits and diet components, including body mass determination, it was demonstrated no significant differences between diabetics (n = 19) and non diabetics (N = 53). But body composition shows some particularities. Our goal will be a revision of literature, comments on our results and discussion about the non-individualized, standardized nutritional orientations commonly adopted to treat glycemia fluctuations in diabetic PD patients. The usual prescription of a fractionated diet with a supplement in some periods seems to be not enough and adequate to control glycemia fluctuations and other associated factors related to cholesterol metabolism. Some alimentary components and other measures will be appointed.

2. Metabolic syndrome, reverse epidemiology and Parkinson's disease

The influence of the so-called metabolic syndrome over PD was analyzed with the same conclusion in a couple of studies, that no direct correlations could be determined even with and without subgroups stratification [29, 30]. Similar results were obtained among patients with associated dementia [13, 31]. Others still question the association because it is a premorbid situation, multifactorial, and dependent on individual factors, like weight, genetic predisposition among others [32]. Even so, there are reports showing a close relationship between the modified metabolic syndrome criteria, with a poorer prognosis of motor symptoms in PD [18, 19]. A few years ago there was a publication calling attention to the so-called reverse epidemiology and the occurrence of some "abnormalities" like weight gain, among others, not as a risk factor but as a protective factor against degenerative diseases consequences [33]. On the basis of these considerations there is a place of considerations about the role of some corporal changes including weight, insulin resistance and cholesterol disturbances, either as a result of degenerative diseases like PD, or as factors related to poorer outcome of these groups of diseases [34]. The applicability of concepts of reverse epidemiology in PD was not fully discussed in current literature. In this connection, it is important to put some considerations on the role of the isolated component of metabolic syndrome on PD outcome.

2.1 Cholesterol abnormalities in PD

Some studies do not demonstrate a low if any significant association between dyslipidemia with PD [13, 33, 35]. Even so, it was possible to demonstrate that plasmatic cholesterol was lower in older patients with amnestic dementia, compared with those without cognitive dysfunctions [14]. Relevant to remember that the analyzed sample in that study was older, compared with PD patients without cognitive impairment. Others, still, point to an apparent protective effect of hypercholesterolemia in PD [36, 37]. One aspect that drew attention was that findings, cholesterol level related, was restricted to younger females and the follow-up time was twice as long as that of manns and younger. Corroborating the studies showing the apparent protector effect of cholesterol, there is a report demonstrating that increased seric cholesterol levels are associated with low levels of iron in substantia nigra and pallidus in PD patients [38]. The use of total cholesterol as a biomarker for malnourishment is also well demonstrated [39]. The question about maintenance of body mass in PD patients is still an open issue. The role of adequate nutritional advice is not questionable. Although some studies limit the importance of eggs and meat as nutritional source of cholesterol, pointing out saturated fatty acids as the highest source of cholesterol [40], it is possible to assume that that the aim is not only increase body mass, but also maintain a minimum supply of diet cholesterol, preserving striatal tissue in PD patients. A question that needs to be answered is if the "cholesterol paradox", as part of reverse epidemiology in the geriatric population, is a cause or consequence of changes observed among PD or PDD.

Abnormalities in both synthesis and absorption of cholesterol has an influence on the plasmatic cholesterol levels [41, 42]. It is also important to note that weight reduction is related with reduction in plasma cholesterol levels [43] and as it can also be artificially enhanced by increased insulin resistance observed in diabetes mellitus treated with insulin [44]. The concurrent action of cholesterol metabolic disturbances, glycemic fluctuations [45], especially hypoglycemia and concomitant insulin resistance activity must be considered as risk factors to poor outcome of PD. Is not

well understood all possible interlinking between the distinct components of isolated metabolic disturbances. It seems plausible to suppose that the PD brain is sensitive to abrupt hypoglycemic variations, added to disturbances in cholesterol metabolism and the concurrent action or lack of response of insulin resistance. The presence of malnourishment or visceral fat deposition, could be considered as adjuvant risk factors in the same way as type II diabetes. The recent demonstration that cholesterol metabolic disruptions are associated with an inherited form of PD [46] open new avenues to the understanding of the apparent unsolved question of the relationship of cholesterol metabolism dysfunctions and PD.

2.2 Glycemia, insulin resistance and Parkinson's disease

The potential implications and correlation between glucose metabolism and insulin resistance, were demonstrated both in evaluation of dopamine response [47] with evidence that insulin resistance is even lower in older demented patients [14, 48]. On this topic there was demonstrated insulin immunoreactivity disturbances in PD patients compared to controls [49]. The evidence that insulin low levels lead to a reduction in lipogenesis more than food digestion and absorption [50], reinforce the relationship of loss of fat mass, insulin resistance and DP [14, 51, 52].

There is some evidence showing that higher glycaemic load and index [53] as well as total fat intake [27, 31] are not associated with PD. Increased food intake, including glycaemic load and índex, was found to be strongly correlated with aging and decreased tendency to lose weight [54]. Prospective studies were not able to confirm the association of high caloric intake and increased risk of PD [55], as well as between high caloric values or lower caloric intake and increased risk of PD [56, 57]. But a newly released study demonstrated that both low HbA1c (HR 2.7; 95% CI 1.3–6; P = 0.01) as well as high HbA1c (HR 3.6; 95% CI 1.5–8.9; P = 0.005) were independent predictors of unfavorable motor outcome in PD. In this regard euglycemia seems to be associated with a better prognosis in PD [22]. The relationship between energy and caloric consumption could explain some of the body composition changes observed in PD outcome. The fact that carbohydrates are easily chewed and digested may represent a facilitator aspect for the preference. Some epidemiological data reinforces the association between enhanced ingestion of carbohydrates and increased risk of PD, which is correlated to consumption level [15, 58].

A confounding factor could be the possible intercurrence of hypoglycemia triggered by the prescription of statins to control dyslipidemia, so common in diabetes mellitus. Despite the beneficial reduction in low-density cholesterol as well as apolipoprotein B, atorvastatin treatment results in a significant increase in baseline, fasting insulin and glycated hemoglobin levels [59]. This is consistent with insulin resistance and elevated blood glucose in hypercholesterolaemic patients.

However, the use of statins in patients with low serum albumin is associated with risk for hyperglycaemic events, independent of diabetes [60]. On the other hand the prescription of atorvastatin may inhibit glucose utilization by muscle [61], with inhibition of translocation of the transporter, GLUT4, cholesterol-dependent glucose, which may lead to the inference that such effect may also occur in the striatum. Even considering that the use and availability of glucose in the brain, mediated by GLUT 1, 2 and 3 [62] and is not directly insulin-dependent, but may be affected by elevation of insulin in the periphery, it is possible to assume that the impairment of peripheral glucose metabolism also produces effects in a striatum already compromised by PD.

Regarding this aspect, as early as 1996, when attempts to implant striatal tissue fetal cells in Parkinson's disease patients were still being made, there was a demonstration of the presence of GLUT 1 in the striatum [63]. It was demonstrated that paraquat, a recognised toxic agent for brain tissue, promotes an increase in glucose transport to the cell, displacing GLUT 4 and Na+-dependent glucose transporters (SGLT), to the cell membrane, in patients with Parkinson's disease [64], thus contributing to the death of dopaminergic cells. In any case the effect of hypoglycemia on striatal glucose transporters in the presence of hypoglycaemia has not yet been demonstrated.

It is possible to assume that both hyperglycemia, induced by toxic agents (paraquat) or even antidyslipidemic drugs (atorvastatin), and hypoglycaemia, caused by hypoglycemic drugs (insulin, oral hypoglycemic agents), have a deleterious effect on brain tissue. Evidence from studies point to a less relevant role of hyperglycaemia. Yet, even accepting the premise that we should control glycemic levels more carefully in Parkinson's patients, we have no definition or even indications of the spectrum to be achieved. As an example, the levels proposed for stroke 80–130 mg/dL may not be the most recommendable for diabetics with Parkinson's disease.

On the other hand, glucose reduction, also induced by hypoglycemic drugs, may reduce cerebral glucose availability, downregulating GLTi expression in astrocytes. The result is a deficit in lactate and pyruvate synthesis. Glial astrocytes lactate appear to play a crucial role in maintaining cellular function, especially during periods of elevated metabolic demand or hypoglycaemia [11]. In this regard, there are studies, correlating functional impairment of mitochondria with insulin resistance and abdominal fat accumulation in obese subjects [21].

The demonstration that convencional hypoglycemiant drugs are associated with increase in the incidence of PD [9, 10] is also a point of interest. An apparent inverse association of insulin use and Parkinson's incidence was found in one study. But the small sample of insulin users limits the analysis [4, 9]. The demonstration that exenatide may improve motor symptoms in PD [65], confirm the importance of adequate blood glucose control in patients with PD and prone to developing the disease, offering promising data to control the deleterious effects of commonly used oral hypoglycemic drugs. Again, the interest of cholesterol and insulin resistance gain importance in dietary intervention.

3. Nutritional habits and Parkinson's disease incidence and severity

The studies on the impact of dietary habit, Dietary Components and Supplementation effects on PD incidence and outcome are fairly recent and point to the same conclusions. Among the quoted articles, all, without exception, show a correlation between malnourishment and poor PD prognosis [66], both in relation to cognitive dysfunction [67] as to motor impairment, fatigue, anxiety and depression [68]. However, others do not find any association between motor symptoms and dietary habits [69]. Likewise, the weight gain and increased central obesity observed in newly Parkinson's diagnosed patients were not associated with cognitive impairment [70].

Still in reference to dietary components and supplementation, there are some authors showing the influence of housing and untreated waters with PD features [71]. Several mechanisms may contribute to a possible association between nutritional

habits and PD, with or without metabolic impairment. The so-called brain-intestinal axis can be pointed out as one of the related factors [72]. Some medications, like pramipexole, used in the treatment of PD as a dopamine agonist, can cause hyperphagia, but they are not considered as a major factor for weight gain. [73].

The supremacy of some bacteria in the bowel, with consequent gut dysbiosis, was found to be more prevalent in patients with PD. This condition promotes a pro-inflammatory bowel offering a competitive advantage for some bacterial strains over others [74]. There is evidence that enteric α-synuclein and phosphorylated α-synuclein (αSyn) abnormalities are more common among patients with PD, and could affect both the extra-nigral structures and vagus dorsal motor region [75].

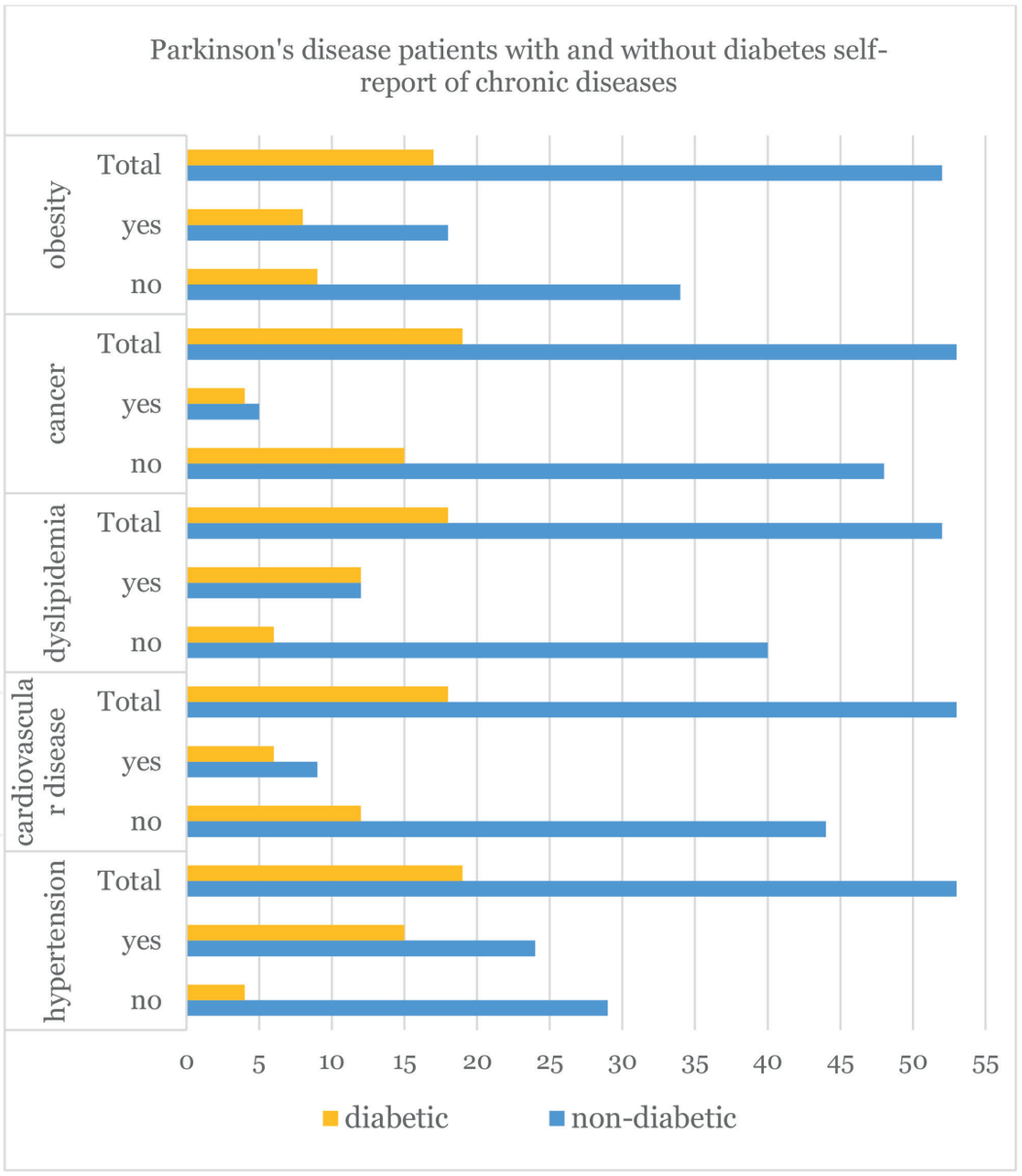

Figure 1.
Parkinson's disease patients with diabetes reported more dyslipidemia and obesity than patients without diabetes.

The bowel permeability dysfunction facilitates the entry of lipopolysaccharides into the body circulation, increasing systemic and brain inflammation [74, 76]. The findings, observed in older patients, could be associated with a greater preference for processed foods, in line with the energetic demands. The data correlate also with poor ingestion of fat, fiber-rich food, antioxidants contents and others.

Maintenance and delay of muscle mass loss may also be associated with low calorie diets, preventing sarcopenia. On the other hand, we observed in the dietary survey of our patients (unpublished results), a preference for diets rich in carbohydrates, which may lead to worsening of the sarcopenic pattern. Thus, the increase in body mass, associated with physical exercise, fatty or hypocaloric diet and even increased amino-acid supplementation, could be recommended for patients with Parkinson's disease.

In a complete record of dietary habits and diet components, including body mass determination, it was demonstrated no significant differences between diabetics (n = 19) and non diabetics (N = 53). Some data call attention, that is, a self-reporting for the presence of dyslipidemia points to dyslipidemia among diabetic patients (**Figure 1**), but the data from the medical records does not confirm it (**Figure 2**). It is still under analysis, but one hypothesis is the use of statins. Another result that draws attention is total fat analysis and percentage of fat of diabetic PD patients showing that diabetes are something fattest (**Figure 3**). The self-reported presence of obesity does not differ from recorded data of weight and BMI, with no significant differences between the two groups. Noting that both groups have comparable degrees of disease progression, as measured by the UPDRS. It could be possible to infer that the maintenance of a relative overweight was a protective factor in this group of evaluated patients.

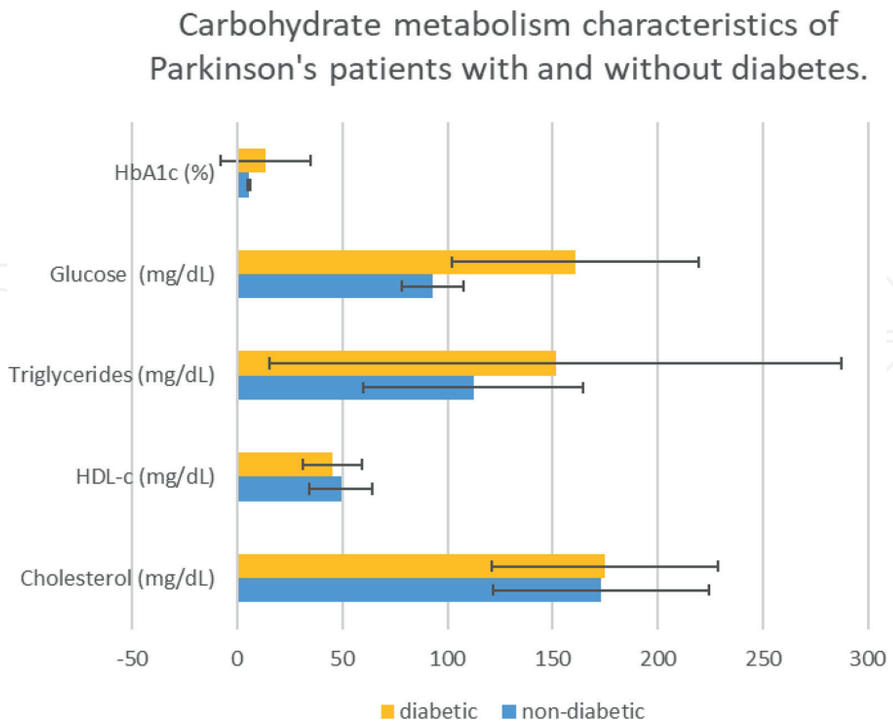

Figure 2.
Similar cholesterol laboratory tests in Parkinson's disease patients with and without diabetes but slightly lower HDL-c in patients with diabetes.

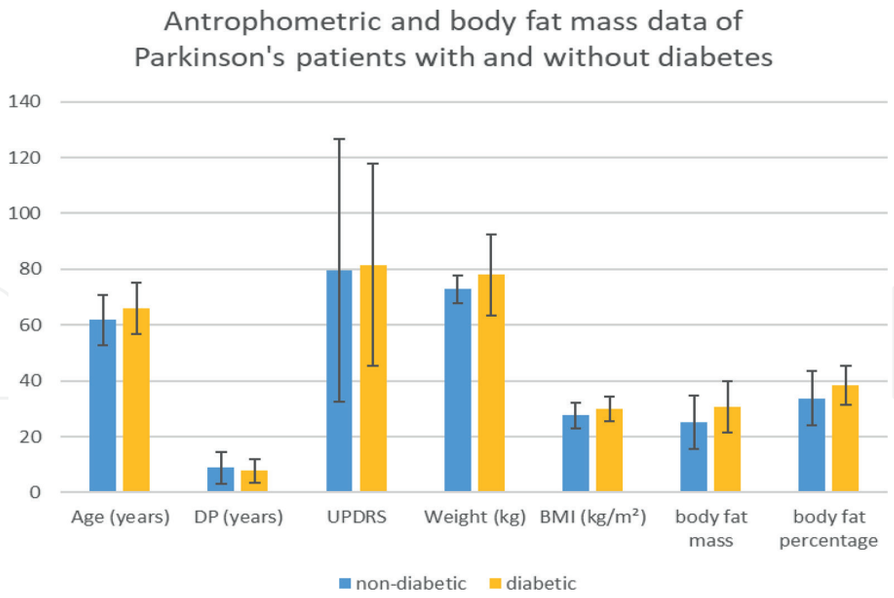

Figure 3.
Higher percentage of body fat in Parkinson's patients with diabetes did not provide an increase in disease severity.

4. Considerations about nutraceutical intervention in Parkinson's disease

The much evidence in the literature of the associations of malnutrition and low weight with poor prognosis of PD, together with the evidence that high cholesterol levels are unrelated to PD, and that low cholesterol and lack of resistance to insulin in older patients are correlated with dementia and poor outcome, enable the assistants to propose some nutritional intervention, especially in those affected by diabetes. A negative correlation between fat android mass composition and severity of parkinsonism has been evidenced [77], but the demonstration of this association is not yet well established in diabetics with Parkinson's disease, especially regarding lipid metabolism and its interactions with glucose. Again, we must keep in mind that the malnutrition observed in many PD patients may be the consequence not only of dysphagia, loss of appetite, bradykinesia and hyperkinesia, but also of abnormalities in lipid and glucose metabolism. This situation in the presence of diabetes can be an aggravating factor. As many as 90% of individuals with type 2 diabetes are overweight or obese [78], which was demonstrated, with some accumulation of fatty tissue, in our population of diabetics with PD. Although there are indications of potential therapeutic effect of ketogenic diets with different degrees of carbohydrate restriction to PD patients [79], this alternative is not viable for application in patients with PD, since it would interfere directly in the control of glycaemic levels in patients with PD and diabetes. The initial purpose should be to avoid malnourishment and, if necessary, to achieve a moderate and stable overweight status. The prescription of statins should be judicious. There is insufficient data to assume that high cholesterol levels would be worse for Parkinson's patients. In this case a mild obesity could be accepted on PD, mainly at the cost of fat accumulation. The possibility of lack of adequate insulin response in PD can also be discussed. Amid so many open questions it is feasible to affirm that obesity can be seen not as a disease but as a physiological adaptive factor to face PD, especially when associated with diabetes. The role of obesity as a functional adaptation and not as an aggravating factor in certain circumstances has been well discussed by Robert Eckel in his book [80], and should be considered. That author

draws attention and exposes a revision of the role of secreted fatty tissue proteins in insulin resistance and inflammation regulation in humans. A final consideration is that the nutritional approach for PD patients with diabetes should include concern of more aggressive intervention on body fat reduction, parsimony in statin indication and therapeutic options for diabetes control. Alternative measures to control dyslipidemia in the face of cardiovascular disease should include regular physical activity.

Abbreviation

PD Parkinson's disease
PPD Parkinson's disease patients with dementia

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