

Type 2 diabetes and Parkinson's disease

Ken Shaw

By definition, common conditions commonly occur, and so the occurrence together of two relatively prevalent conditions, type 2 diabetes (T2DM) and Parkinson's disease (PD), might be considered simply by chance. Although the prevalence of T2DM (5% of UK population) is greater than that of PD (0.2% overall), both conditions increase with age, particularly PD (1% over 60 years; 5% over 85 years). Moreover, each shares some similarity in generally being as of later, slow onset and progressive in nature. As to causation, these two conditions, again, share similar concepts of genetic predisposition interacting with environmental factors in line with current understanding. So, by the laws of probability, it would be expected that these two conditions are likely to arise together in a proportion of either diabetes or Parkinson's disease clinics. But, when the two occur together, is it indeed a chance observation or is there a more significant association? With this in mind, it should be remembered that an association does not necessarily indicate a causal link in either direction, but it does raise interesting issues to consider in terms of respective relationships between the two conditions.

Diabetes in Parkinson's disease

Firstly, is there evidence that patients with PD have an increased risk of developing diabetes? Remarkably, in 1974 it was reported¹ that a large percentage of patients with PD had impaired glucose tolerance, and that 52.4% actually fulfilled criteria for the diagnosis of diabetes. However, a number of subsequent published studies, relatively few and small scale, proved inconclusive with no clear confirmation that diabetes occurred more frequently with PD. A US prospective study² of 1565 'older adults' (mean age 62 years!) with known PD identified diabetes in 12% of self-reported responders, but with a greater proportion of those with PD and diabetes duration over 10 years to indicate the complexity of the relationship.

To date, the largest observational study³ derived from the UK General Practice Research Database (1994–2005) has found the prevalence of diabetes (all T2DM) to be similar for those with newly-diagnosed PD (8%; 90% aged over 60 years) compared to matched control patients without PD (8.5%). In a second part to the study, the risk of developing incident diabetes during follow-up was found to be lower with PD (relative risk [RR] 0.55). Although the time-scale for diagnosing diabetes following diagnosis of PD is not provided, the reduced risk appeared restricted to those using levodopa, the main treatment for PD. In our own prospective study⁴ (1969–1979) of a cohort of 178 patients with idiopathic PD, we observed that life expectancy over a period of six years was normal in those able to tolerate sustained levodopa therapy. We observed a number of comorbidities, but did not identify diabetes as then of particular note. The evidence that diabetes occurs more frequently in people with PD remains inconclusive.

Parkinson's disease in diabetes

However, from the reverse perspective, does diabetes itself associate with a greater risk of developing PD? Again, the published evidence has been mostly equivocal, some studies showing possible increased risk of PD with preceding diabetes; others the opposite. A relatively large-scale, prospective Finnish study⁵ of 51,552 adults without a history of PD at baseline reported that, over a mean follow-up period of 18 years, those with known T2DM at baseline (2% of participants; mean age 53 years) had a significantly increased risk of developing incident PD (RR 1.85) compared to those without diabetes. In a critical appraisal of relevant publications, a systematic review and meta-analysis⁶ of nine prospective (cohort) and case-controlled studies concluded that, although the evidence was still limited, the onset of diabetes before the onset of PD was suggestive of diabetes being a risk factor for future PD (overall RR 1.37). The data analysis could not clearly distinguish relative risk between type 1 and type 2 diabetes, but commented that in numerical terms the latter would predominate.

The largest study to date⁷ – from combined researchers at University College London, University of Oxford and Queen Mary University of London – would appear to have established a definitive link between T2DM and PD. Based on a retrospective cohort study, derived from English National Hospital Episode statistics and mortality data (1999–2011), the authors reported a significant increased association of developing future PD with preceding T2DM. The association was greatest with younger-onset T2DM (RR 3.81) and those with known diabetes-related complications (RR 1.49). Those with potential 'vascular' or drug-induced parkinsonism, and other movement disorders, were excluded from analysis, but other possible confounding factors such as diabetes medication (see below) or cigarette smoking (the one risk factor associated with reduced risk of PD) could not be excluded.

Shared pathogenic processes

Having identified a specific association between T2DM and subsequent development of PD, the authors⁷ speculate with interest on possible underlying mechanisms. With the greater risk in individuals of younger-onset T2DM, it is suggested that genetic factors may be important, with comment that over 400 genes have been identified closely linked to both conditions. In contrast, the increased association in older patients, particularly in those of longer diabetes duration, and with diabetes-related complications, could indicate a shared link to abnormal pathogenic processes and metabolic dysfunction. A recent editorial,⁸ reflecting on the similarities between T2DM and PD, commented that in both cases there was a progressive reduction of specialised tissue cells (pancreatic beta cells in T2DM; substantia nigral neurons in PD) with loss of the respective 'biological product' (insulin and dopamine). Each condition is treated by either agonists or replacement of the appropriate agent. A *Practical Diabetes* editorial leader⁹ has reviewed the emerging

evidence of central metabolic dysfunction in T2DM, noting potentially pathogenic processes of chronic neuroinflammation, increased oxidative stress, and accumulation of toxic amyloid beta protein aggregates, seemingly associated with an underlying brain insulin-resistant state. In comparison, PD is a neurodegenerative disorder, also associated with similar central pathogenic metabolic dysfunction, leading to loss of dopaminergic neurons in the substantia nigra. Further linking the two conditions together, T2DM without PD has been reported¹⁰ as exhibiting lower striatal dopamine transporter binding and abnormal cerebrospinal fluid protein (alpha-synuclein) levels, suggestive of Parkinson-like pathology and potential predisposition to PD. More specifically, insulin resistance and hyperglycaemia have been cited⁸ as factors suppressing dopaminergic neuronal activity and decreasing dopamine turnover, thus contributing to the possible progression and onset of PD. Furthermore, a high prevalence (58.4%) of undiagnosed insulin resistance has been reported¹¹ in non-diabetic subjects with PD, partly related to body weight, but still present in a substantial percentage (41%) of lean PD patients.

Is Parkinson's disease a further complication of type 2 diabetes?

That there is an identified association between T2DM and PD would now no longer seem to be in doubt. But the nature of the relationship is still tantalisingly difficult to unravel. Patients with PD have been reported as having significant underlying subclinical insulin resistance, but less evidently diabetes itself.

Indeed, the UK General Practice Research Database study³ found PD patients treated with levodopa, the most commonly prescribed treatment for PD, had a significantly lower risk of developing diabetes (odds ratio [OR] 0.22) than those not using levodopa (OR 1.11). From the converse perspective, both the earlier Finnish⁵ and the recent UK⁷ studies have reported a positive association between T2DM and future incident PD, particularly linked to longer duration of diabetes and the presence of diabetes-related complications. The finding of similar shared pathogenic features of central metabolic dysfunction asks the question as to whether either condition directly predisposes to the other, or whether the association is independent in terms of susceptibility. The myriad metabolic consequences of T2DM include increasing focus on disturbed brain metabolism and, in this context, specifically adverse effects on striatal dopaminergic tissue, to suggest that such could predispose to development of PD, and thereby add yet a further diabetes-related complication to the ever-enlarging list.

Therapeutic implications

By its very nature diabetes overlaps with almost every other medical specialty, providing mutual interest in clinical management. Neurologist colleagues have taken note that T2DM may link to the development of PD, and have begun to investigate drugs used for T2DM as of potential benefit in the treatment of PD. Metformin has been shown to have inherent neuroprotective properties and of therapeutic potential for a number of neurodegenerative diseases including PD.¹² A retrospective cohort study¹³ from the UK Clinical Practice Research Datalink

found patients with T2DM treated with glitazones had a reduced risk (RR 0.75) of developing PD, suggesting that PPAR gamma pathways may be a useful drug target in PD. But, knowledge that GLP-1 receptors have been identified throughout the brain, including dopaminergic neurons in the substantia nigra, has stimulated particular interest in the use of GLP-receptor agonists as a treatment of PD. The exenatide-PD trial¹⁴ reported significant improvement of motor symptoms in PD after 48 weeks of treatment with once-weekly subcutaneous injections of exenatide. Neurologists would therefore seem to have innovative therapeutic opportunities using drugs which are familiar to those managing diabetes. But, conversely, is there counter potential for those with T2DM to prevent them from developing PD? At the moment, the essential sound principles of managing T2DM – lifestyle measures, weight loss where appropriate, risk factor reduction and good glycaemic control – still offer the best prospect of minimising risk of PD. Despite associating with an apparent lower incidence of diabetes in patients with PD, levodopa is not presently considered a drug with preventative potential, and is unlikely in itself to have a disease-modifying effect.¹⁵

To conclude this current understanding of an association between T2DM and PD, it is fascinating to note that both conditions would seem closely connected to alterations of the gut microbiome (dysbiosis) directly linked to disturbed brain function. Even more thought provoking, appendectomy in young adults is reported¹⁶ with a 20% risk reduction of developing future PD, which confusingly contrasts to the latest study¹⁷ showing the reverse, with a threefold increase in PD following earlier appendectomy. Has anyone looked into whether appendectomy influences subsequent risk of T2DM?!

Professor Ken Shaw, MA, MD, FRCP, Emeritus
Professor of Medicine, University of Portsmouth, UK

Postscript. Having kept true to the original references, it will be noted that both relative risk (RR) and odds ratio (OR) have been quoted in seemingly comparable circumstances. Both are measures of association: either a ratio of two odds (OR) or a ratio of probabilities (RR). The differences are statistically subtle and do not significantly alter the overall outcome of association. Again, an association between two conditions does not necessarily indicate a causal relationship in either direction.

Acknowledgements

Acknowledgement is made with much appreciation to the late Gerald Stern (obituary *BMJ* 12 January 2019) who masterfully mentored my MD thesis in Parkinson's disease over 50 years ago, and to my old research colleague Andrew Lees, with whom I have again shared common interest between our respective specialties.

Declaration of interests

There are no conflicts of interest declared.

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References are available in *Practical Diabetes* online at www.practicaldiabetes.com.

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