Clinical Neurology and Neurosurgery 158 (2017) 60–66

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Review

Neurological outcomes of antidiabetic therapy: What the neurologist should know☆

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ARTICLE INFO

Keywords:
Stroke
Dementia
Polyneuropathy
Diabetes mellitus
Disease prevention

ABSTRACT

Considering the causative or contributory effects of diabetes mellitus on common neurological diseases such as polyneuropathy, stroke and dementia, modern antidiabetic drugs may be expected to reduce incidence or progression of these conditions. Nevertheless, most observed benefits have been small, except in the context of therapy for diabetes mellitus type I and new-onset polyneuropathy. Recently, semaglutide, a GLP-1 analog, has been shown to significantly reduce stroke incidence in a randomized controlled trial. Beneficial effects of antidiabetic drugs on stroke severity or outcome have been controversial, though. The level of risk conferred by diabetes mellitus, the complex pathophysiology of neurological diseases, issues of trial design, side-effects of antidiabetic drugs as well as co-medication might be interacting factors that determine the performance of antidiabetic therapy with respect to neurological outcomes. It might be speculated that early treatment of prediabetes might prevent cerebral arteriosclerosis, cognitive decline or polyneuropathy more effectively, but this remains to be demonstrated.

1. Introduction

The prevalence of diabetes mellitus still seems to be on the rise in many industrialized countries, and negative impacts on the prevalence of diabetes complications might be anticipated. Therefore, the potential preventive effect of antidiabetic drugs to reduce diabetes complications has met increasing interest, particularly as the number of available diabetes drugs has increased considerably in recent years.

In stroke, diabetes mellitus is an established risk factor, and diabetes mellitus seems to increase the risk for both vascular and Alzheimer dementia. Furthermore, diabetic neuropathy is one of the leading but still essentially untreatable etiologies of polyneuropathy. For the neurologist, effective strategies to reduce diabetic polyneuropathy would, therefore, be as welcome as drugs to effectively prevent incident stroke or dementia. As neurological outcomes have been addressed in many recent diabetes trials, we review the evidence for neurological risk reduction conferred by antidiabetic drugs in published clinical trials.

2. Diabetes mellitus and stroke risk

The risk for ischemic stroke risk is already elevated at the prediabetic stage, i.e. by 20–25% with impaired glucose tolerance or when fasting glucose levels surpass 6 mmol/l [1]. Stroke risk seems to be correlated with the duration of diabetes mellitus, though [2].

It has been suggested that 12–20% of the risk for stroke can be attributed to diabetes mellitus, which has been particularly evident in individuals below 80 years [3]. While a hazard ratio for stroke of 1.62 has been observed in the pivotal SPARCL trial with manifest diabetes mellitus, a recent metaanalysis has indicated an even higher stroke risk in diabetic women (women RR 2.3, men RR 1.8) [4]. This translates into an annual stroke incidence of 0.7% in diabetics aged between 50 and 75 years [5]. In recently diagnosed diabetes mellitus, even larger stroke rates (9.1% over 5 years) have been reported [6]. Not unexpectedly, atrial fibrillation adds significantly to the risk for stroke in diabetes mellitus. In the majority of studies, diabetes mellitus was also associated with a larger risk for post-stroke dementia.

☆ This article has not been published elsewhere, is not under consideration of publications elsewhere, has not been submitted to another journal and is fully approved by both authors. If accepted, it will not be published elsewhere. Both authors have made substantial contributions to the article. No financial support was accepted by the authors in the course of preparation of this article.

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http://dx.doi.org/10.1016/j.clineuro.2017.04.014
Received 13 November 2016; Received in revised form 5 March 2017; Accepted 15 April 2017
Available online 24 April 2017

2.1. Antidiabetic therapy and stroke risk

While one study suggested that medication or other strategies to lower glucose levels in prediabetes might lower stroke risks to some extent (RR 0.76) [7], a Cochrane analysis (HR 0.96) and two other metaanalyses (RR 1.02 and RR 0.94, respectively) have not shown an effect of strict glucose control on stroke incidence in established diabetes mellitus [8,9].

The evidence for efficacy of individual diabetes drugs in stroke prevention is mixed at best. While a subgroup analysis of the PROactive trial had suggested a preventive effect of pioglitazone on recurrent stroke, this effect has not been observed in a small trial of prediabetic patients or regarding the incidence of first-ever stroke in another trial [10–13]. Recently, the results of the IRIS trial, investigating pioglitazone in secondary stroke prevention in patients with diabetes mellitus and prior stroke or transient ischemic attack, have been published [14]. There was a non-significant trend toward a lower stroke risk (as a secondary outcome) in the pioglitazone group after a follow-up of 4.8 years (pioglitazone 6.5%, controls 8.0%; HR 0.82, 0.61–1.10). Divergent incidence curves, at least for the combined primary outcome including myocardial infarction, might suggest that beneficial effects of the compound may become identifiable with longer periods of follow-up. Weight gain, edema and bone fractures were reported as prominent side-effects. Besides, a positive impact of pioglitazone on post-stroke depression has been suggested.

There are some reports on beneficial effects of gliptins (dipeptidyl peptidase 4 inhibitors) in animal models of stroke, as they have been hypothesized to exert neuroprotective effects via the GLP-1 receptor. On the other hand, sitagliptin seems to have no effect on recurrent stroke risk [15]. The combination of linagliptin to metformin seemed advantageous in terms of stroke reduction in a randomized study, but a recent metaanalysis failed to show any effects of DPP4 inhibitors or sodium-glucose linked cotransporter-2 (SGLT2) inhibitors on stroke risk [16,18]. Another recent metaanalysis found a significant risk reduction for stroke due to DPP4 inhibitors only for patients without cardiovascular disease compared to the active control, but not compared to placebo [17]. The effect of sulfonylurea treatment on stroke incidence can be said to be neutral at best.

While metformin was associated with a lower stroke rate in a Taiwanese study (adjHR 0.47) [19], it is still questionable to what extent these findings can be translated to non-Asian populations.

Recently, the EMPA REG Outcome trial demonstrated no benefit of empagliflozine treatment on stroke as non-primary outcome (HR 1.18) [20]. Similarly, liraglutide, a glucagon-like peptide 1 analog, failed to show a significant reduction of stroke incidence (HR 0.86; 0.71–1.06) in patients with type 2 diabetes and high cardiovascular risk after 3.8 years [21].

At this point, semaglutide, another GLP 1 analog, remains the only antidiabetic drug that has shown a significant effect on stroke incidence in a randomized controlled trial that has been published recently [22]. In this study, non-fatal strokes occurred at a rate of 1.6% in the semaglutide group after two years of follow-up, and at 2.7% in the placebo group (HR 0.61; 0.38–0.99). About 15% of the participants had experienced a stroke prior to study entry. Blood pressure and body weight also dropped more efficiently in the verum group and no increase in hypoglycemic episodes was observed, both of which might have contributed to the positive treatment effect [22].

Other multidisciplinary interventions seem to show further promise for stroke prevention in diabetes. Every lowering of blood pressure by 5% has been calculated to reduce stroke risk by about 13% [23]. Broader life-style changes in diabetics including weight loss, exercise, improved diet, less smoking und less alcohol consumption might cut stroke risk by 35–40% according to two Asian studies [24]. The I-D-HEALTH study pursuing a similar approach at lifestyle intervention in ongoing.

Interestingly, brain swelling after stroke might be responsive to continuous intravenous glibenclamide (glyburide) according to a recent randomized phase II trial, but glucose management might be challenging in this setting [25].

2.2. The impact of antidiabetic therapy on stroke severity and clinical outcome after ischemic stroke

Several studies have shown that diabetes mellitus leads to worse outcomes after ischemic stroke [26,27], in the minor stroke subgroup [28], after intravenous thrombolysis [29] and after carotid endarterectomy [30], but without impact on potential recovery after rehabilitation [31,32].

On the other hand, there is sparse evidence of a positive impact of antidiabetic drugs on stroke severity or clinical outcome after ischemic stroke [33]. Although sulfonylureas, metformin and insulin seemed to alleviate stroke severity at admission, functional outcome was not improved after 90 days in a prospective study [34]. A study that claimed that metformin might ameliorate stroke severity suffered from monocentric design and lack of exclusion of possible confounding factors [35]. Similarly, only one small retrospective case–control study has suggested that thiazolidinediones improve stroke recovery [36]. Functional stroke outcome was improved by DPP4 inhibitors in a monocentric study [37], but not by metformin [35]. Sulfonylureas seemed to positively influence National Institutes of Health Stroke Scale scores in a small study, but this was not corroborated in an earlier study [38,39]. Antidiabetic pharmacotherapy lowered stroke mortality only non-significantly in a Danish population based study [40].

Taken together, the evidence for a positive role of antidiabetic drug therapy on stroke severity or stroke outcome is conflicting, and any positive effects are probably not sufficient to counter the detrimental prognostic consequences of diabetes mellitus.

3. Diabetes mellitus type II and the risk of dementia

Insulin receptor-mediated signaling seems to be involved in regulating synaptic activity in the brain, but the significance of cerebral insulin resistance in the development of dementia remains unclear. It is known, though, that cerebral insulin signaling declines in Alzheimer dementia, due to a loss of insulin receptors, insulin receptor substrates and IGF-1 receptors.

Some studies have suggested that up to 80% of Alzheimer patients may show impaired peripheral glucose tolerance, on the other hand. There seems to be molecular crosstalk between insulin, Aβ (secretion, deposition) and tau (hyperphosphorylation), respectively.

Cognitive functions already start to decline during prediabetes, particularly in the elderly [41]. Cognitive decline seems to be accentuated in manifest diabetes mellitus compared to controls, although this has been controversial (e.g. [42,43]). Large fluctuations in glucose levels may have a negative impact on cognition, as HbA1c levels alone can explain only 10% of the variance in cognitive performance [44]. In particular, recurrent severe hypoglycemia may accelerate cognitive decline in the elderly.

The risk for conversion of minimal cognitive impairment to dementia rises 1,5-3-fold in manifest diabetes mellitus [45–47]. In the end, dementia affects 6–39% of type II diabetics, depending on diagnostic criteria, age and comorbidities. The percentage of dementia attributable to diabetes mellitus has been estimated at 6–7% (i.e. 1 in 15 cases). Although the relative risk for developing vascular dementia is higher (RR 2.2–2.5) than for Alzheimer disease, the latter outnumbers vascular dementia due to its higher prevalence [48,49].

Typically, cortical und subcortical atrophy including hippocampal atrophy [50], and, at least in some studies, increases in subcortical vascular lesions and white matter lesions have been reported to correlate with dementia in diabetes mellitus [51–53]. While an Alzheimer-like FDG-PET pattern of hypometabolism may be found in demented diabetics, amyloid imaging or post mortem examination of