

the metabolic syndrome were entered as categorical variables (instead of the metabolic syndrome as a single entity), only hypertension and dyslipidaemia ($P < 0.001$ for both), along with older age, male sex and smoking history, showed independent associations with incident CVD events (data not shown).

In conclusion, these results indicate that the presence of metabolic syndrome is associated with a moderately increased risk of incident CVD events in Type 2 diabetic individuals, independent of a broad spectrum of potential confounders. Thus, the new IDF definition of the syndrome can perform well as a marker for classifying Type 2 diabetic individuals according to their risk for future CVD. Further prospective studies are needed to validate the prognostic value of the new IDF definition in different populations.

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Hippocampal volume and cognitive performance in long-standing Type 1 diabetic patients without macrovascular complications

In a recent paper, Lobnig *et al.* [1] have examined the prevalence of memory dysfunction and have measured hippocampal volume in a small, case-control study of 13 middle-aged adults with Type 1 diabetes. Poorer performance on tests of selective attention and psychomotor speed, and mild brain atrophy were observed in the group with Type 1 diabetes. These differences were attributed to Type 1 diabetes per se. We have reservations about the design of this study and the failure to consider potential confounding variables that would invalidate this conclusion.

First, the most powerful determinant of memory or cognitive performance is pre-morbid intellectual ability, i.e. intelligent individuals generally perform better than those who are less intelligent. Without a formal evaluation of pre-morbid intellectual ability, the authors cannot conclude that any pathological difference in cognitive ability existed between the group with Type 1 diabetes and the control group. Secondly, the study was not adequately powered to detect performance differences on the battery of memory and cognitive ability tests utilized. Thirdly, any performance difference that was observed could

be attributed to the effects of other pathologies, specifically microangiopathy, visual dysfunction and hypertensive disease. Microangiopathy complicating Type 1 diabetes is known to be associated with poorer performance on tests of cognitive ability, including those domains studied by Lobnig and colleagues [2,3]. The nature and degree of severity of diabetic retinopathy affecting the study participants has not been stated. This is important as laser-treated retinopathy can cause subtle degrees of visual dysfunction, which can confound performance during any cognitive ability or memory tests dependent upon visual function. Furthermore, the participants in the present study had hypertension of long duration, requiring on average three anti-hypertensive medications to control blood pressure. The presence of controlled hypertension, despite effective therapy, is known to be associated with poorer performance on the two tests in which performance differences were observed [4]. Hypertension is associated with the development of cerebral macrovascular disease, manifest as stroke, haemorrhage or vascular dementia. However, hypertension is also associated with the development of more subtle structural changes, including high-intensity white matter lesions and cerebral atrophy [5]. The interpretation of the present study with respect to structural brain measures may therefore be confounded.

Cerebral atrophy has been observed previously in association with Type 1 diabetes, and this is not therefore a novel finding. A study in Edinburgh of normotensive young adults with Type 1 diabetes of long duration has demonstrated the presence of mild central brain atrophy, most notably in those who had developed the disorder in early childhood [6]. The above factors significantly confound the interpretation of the present study. We would submit that the authors' conclusions cannot be justified, and the present paper contains few novel findings.

Competing interests

None declared.

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Reply

The goal of our study was to obtain, for the first time, a quantitative volumetric measure of the hippocampus in adult patients with Type 1 diabetes [1]. Moreover, global cerebral atrophy, together with a selected number of neuropsychological tests complementing the magnetic resonance imaging (MRI) investigation, was assessed. Studies in older subjects with glucose intolerance or with Type 2 diabetes [2,3] have reported hippocampal atrophy which has been linked to an increased dementia risk.

In our sample of long-standing Type 1 diabetic patients, we did not find evidence for hippocampal atrophy or memory dysfunction. Instead, we observed mild global atrophy, which was associated with poorer performance in two tests of attention and psychomotor speed. This demonstrates that our study was sensitive enough for the detection of brain differences between the patients and the controls. We attribute this to our reliable volumetric methods and our carefully selected patient population. Our findings of cerebral atrophy and attention deficits are in line with previous findings in Type 1 diabetes, which most often, however, have relied on clinical MRI ratings instead of quantitative volumetric assessment. This agreement with previous work was clearly stated in our discussion [1].

We focused our study on a population with long-standing Type 1 diabetes without macrovascular disease. This excludes complications usually found in Type 2 diabetic patients. It does, however, include the metabolic characteristics of Type 1 diabetes, such as hyperglycaemia, hypoglycaemia, changes in growth factor and cytokine levels and microvascular complications such as retinopathy and nephropathy. In no part of the paper do we refer to ‘diabetes per se’. This terminology introduced by Ferguson and Frier is a misleading summary of our arguments. Possible alternative explanations like hypertension and microvascular disease have been mentioned in our cautious discussion and are only reiterated by Ferguson and Frier.

We can reject the criticism that retinopathy was able to influence the test results. As statistically expected [4], 11 out of 13 patients had retinopathy, four of these had had laser coagulation in the past. All patients were in a stable state of retinopathy without visual impairment at the time of the study.

With respect to the hypertension issue, we want to provide some additional background about our cohort. Our initial intention was to ascertain a population without hypertension.

However, it was not possible to find such a patient cohort despite more than 10 years of disease duration. From more than 800 patients of our diabetes centre, only 60 patients met the inclusion criteria, of these, 14 agreed to take part in the study. One was excluded after detecting signs of cerebral macrovascular disease in the MRI. Out of the remaining 13 patients, only two were free of any microvascular disease and two were free from hypertension. Arterial hypertension is observed in 43% of patients with Type 1 diabetes in population-based studies [5]. In particular, as soon as patients develop albuminuria, hypertension develops [4]. The manifestation of hypertension is most often coupled to albuminuria as an indicator of incipient nephropathy. The cumulative incidence of incipient nephropathy taken from epidemiologic studies is 25% after the first 10 years of disease duration [6] or 41% after 20 years [7]. We investigated a well-defined cohort with well-controlled hypertension to minimize its influence. All patients had been followed up for a median of 7 years, in most cases from manifestation of hypertension onwards. Visits were 4–7 times per year. Home blood pressure was controlled and documented [8]. Our study population was therefore one with excellently controlled hypertension, which is in contrast to most previous work in this area.

Patients and controls did not differ in formal education or socio-economic status. A reading test for the estimation of pre-morbid intelligence might have been a useful addition, even although the relationship of this measure with specific neuropsychological tests is weak [9]. As the deficits we found were specific for certain cognitive domains, and in line with previous studies, we think that a pre-morbid IQ difference between our two groups is unlikely.

In summary, our paper [1] is the first report of hippocampal measurements in adult patients with long-standing Type 1 diabetes, which, in our view, fulfils the criterion for a novel finding. We did not find evidence for hippocampal atrophy, but did for mild global cerebral atrophy. The latter replicates and extends previous work. Our data suggest that the effects of diabetes on the brain may be different in Type 1 and Type 2 diabetes. We hope that our paper stimulates other researchers to study the CNS effects of diabetes using quantitative MRI measures, and that they are not discouraged by the negative comments from Ferguson and Frier. A better characterization of the effects of diabetes on the human brain will, in the long run, allow the protection of this important organ from diabetes-associated damage, thereby increasing the quality of life of diabetic patients.

Competing interests

None declared.

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Birthweight predicts insulin requirements in children and adolescents with Type 1 diabetes

Numerous studies have reported inverse associations between birthweight and insulin resistance, the metabolic syndrome and cardiovascular disease in adulthood [1]. Type 1 diabetes (T1D) is associated with an excess risk of cardiovascular disease. This risk has been linked to elevated HbA_{1c} and microvascular complications, and to markers of insulin resistance such as elevated triglycerides and central obesity [2,3]. The association between birthweight and insulin resistance has not yet been studied in subjects with T1D. Although the determination of the glucose infusion rate from a euglycaemic-hyperinsulinaemic clamp is the gold standard for insulin resistance assessment in subjects with T1D, it is not readily performed in clinical practice [2]. In this work, we used daily insulin requirements (UI/kg/day) as a surrogate for insulin resistance as they have been found to be related to the glucose infusion rate from clamp studies [2].

Insulin requirements in relation to birthweight were measured in 90 Caucasian children (< 18 years) with immune-mediated diabetes selected from an initial cohort of 200 subjects according to the following criteria: (i) HbA_{1c} stably < 8% for the past 12 months, indicating appropriate compliance with insulin treatment and modest glucose control [4]; (ii) diabetes duration of more than 3 years, which is likely to indicate minimal residual insulin secretion [5]; (iii) variation in insulin requirements of no more than 10% during the past year, indicating stability in diabetes management; and (iv) treatment by multiple insulin injections. Subjects born prematurely (< 37 weeks gestational age, as determined by early ultrasound scan) were excluded. The study was approved by the ethics committee of the University of Angers. Written informed consent was obtained from all children and parents.

Birthweight, gestational age, and familial history of cardiovascular disease and risk factors were documented from the individual medical records. Weight, height, and pubertal stage were determined at each visit, every 3 months, by two senior paediatric endocrinologists (RC and SB) [6]. Insulin injections (number per day) and physical exercise (number of hours of school sport and extra-curricular competitive activities per week) were recorded. Mean daily insulin dose was calculated over the previous 3 months. Compliance with diet was assessed by dieticians using a standardized questionnaire: the caloric intake complied with the recommended caloric intake in diabetic children [7] and consisted of 50–55% carbohydrates. HbA_{1c} was measured using a Bayer DCA 2000+ at each visit (Bayer, Tarrytown, NY, USA; non-diabetic range of 4.3–6.3%). Birthweight was expressed as SD score (SDS) for gestational age and gender [8]. Data were expressed as means ± SD and compared using variance analyses followed by least significant difference tests and the χ^2 test. Multiple regression analyses were performed with insulin requirements as the dependent variable. $P < 0.05$ was considered significant (SPSS 12.0; SAS Institute, Chicago, IL, USA).

Insulin requirements varied significantly by birthweight SDS tertile: 1.15 ± 0.26 , 1.02 ± 0.22 and 0.95 ± 0.30 UI/kg/day (1st, 2nd, and 3rd tertiles; $P < 0.05$), whereas other variables potentially influencing insulin requirement were comparable between groups (Table 1).

In multiple regression analyses, insulin requirement was significantly and independently predicted by the birthweight SDS tertile ($\beta = -0.09$, $P < 0.05$), diabetes duration ($\beta = 0.04$, $P < 0.01$), puberty ($\beta = 0.20$, $P < 0.05$; no = 0, yes = 1), and fasting triglycerides ($\beta = 0.0018$, $P < 0.05$), whereas other variables [age, body mass index (BMI), gender, sport per week, familial cardiovascular history or risk factors, HbA_{1c}, number of daily insulin injections, gestational age, total cholesterol, and high-density lipoprotein (HDL) cholesterol] were unrelated to insulin requirement (multiple $R = 0.64$, $P < 0.0001$).

This study showed that birthweight was a negative predictor of insulin requirement in children and adolescents with T1D. Birthweight could thus be a determinant of insulin resistance in these subjects. Further studies are needed to investigate