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# Low dose resveratrol improves cerebrovascular function in type 2 diabetes mellitus

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**Abstract** *Background and aims:* Progressive microvascular dysfunction in type 2 diabetes mellitus (T2DM) may impair the ability of cerebral vessels to supply blood to brain regions during local metabolic demand, thereby increasing risks of dementia. Having previously demonstrated that resveratrol can enhance vasodilator function in the systemic circulation, we hypothesised that resveratrol could similarly benefit the cerebral circulation. We aimed to determine the most efficacious dose of resveratrol to improve cerebral vasodilator responsiveness (CVR) in T2DM.
*Methods and results:* In a double-blind, placebo-controlled, balanced crossover intervention, 36 dementia-free, non-insulin dependent T2DM older adults (49–78 years old) consumed single doses of synthetic trans-resveratrol (0, 75, 150, and 300 mg) at weekly intervals. Transcranial Doppler ultrasound was used to assess CVR to a hypercapnic stimulus, both before and 45 min after treatment. CVR, measured bilaterally in the middle cerebral arteries (MCA) and posterior cerebral arteries (PCA), was expressed as the percentage change in mean blood flow velocity from baseline to the peak velocity attained during hypercapnia. Resveratrol consumption increased CVR in the MCA; mean within-individual changes for each dose from placebo were 13.8 ± 3.5% for 75 mg ($P = 0.001$), 8.9 ± 3.5% for 150 mg ($P = 0.016$), and 13.7 ± 3.3% for 300 mg ($P < 0.001$); only the 75 mg dose was efficacious in the PCA (13.2 ± 4.5%, $P = 0.016$).
*Conclusions:* Our results provide the first clinical evidence of an acute enhancement of vasodilator responsiveness in cerebral vessels following consumption of resveratrol in this population who are known to have endothelial dysfunction and sub-clinical cognitive impairment. Importantly, maximum improvement was observed with the lowest dose used.
*Clinical trial registration:* ACTRN12614000891628 (www.anzctr.org.au).


## Introduction

Much attention has been focused on the systemic complications of type 2 diabetes mellitus (T2DM), whilst the impact of microvascular dysfunction in the brain and the associative prevalence of cognitive impairment in this population have been less widely recognised. One postulated underlying mechanism for T2DM-related cognitive

*Abbreviations:* BFV, blood flow velocities; BP, blood pressure; CNRC, Clinical Nutrition Research Centre; CVR, cerebrovascular responsiveness; FMD, flow-mediated dilatation; MCA, middle cerebral artery; PCA, posterior cerebral artery; PI, pulsatility index; T2DM, type 2 diabetes mellitus; TCD, transcranial Doppler.

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impairment is chronic hypoperfusion in the brain, attributable to the hastening of hyperglycemia-induced endothelial dysfunction in the cerebral microvasculature beyond that of normal ageing [1,2].

Cerebrovascular responsiveness (CVR) of the middle cerebral arteries (MCA) to a hypercapnic challenge is often used to assess the health of the cerebrovasculature, as the MCA perfuse two thirds of the brain [1]. The ineffective dilatation of cerebral vessels in response to this physiological challenge is partly due to the arterial stiffening associated with the disease [2]. This is evidenced by a higher cerebral pulsatility index (PI) in the conduit vessels that supply blood to the anterior and posterior brain regions [3]. Indeed, impaired CVR is implicated in Alzheimer's disease as it correlates with decline in cognition [4] and is a predictor of future ischaemic stroke or transient ischaemic attack [5]. Metformin treatment can improve flow-mediated dilatation of the brachial artery (FMD), which is a surrogate measure of vasodilator health in the systemic circulation [6]; however, evidence indicates that this benefit may not extend to the cerebral vessels [7,8]. Moreover, there is no evidence that hypoglycemic therapy can restore cerebrovascular function or attenuate the cognitive impairment in this population.

Present in the skins of grapes, resveratrol offers multiple benefits for vascular, metabolic and neurological systems [9,10]. Resveratrol has also been shown to improve metabolic control in T2DM [9]. We have pioneered the clinical evaluation of vasodilator benefits of resveratrol [11,12] and have shown that acute resveratrol consumption can improve FMD in a dose-dependent manner at oral doses an order of magnitude lower than those of other bioactive nutrients such as green tea polyphenols, grape polyphenol extracts or cocoa flavanols [12]. However, as previously noted, improvements in FMD cannot necessarily be extrapolated to cerebral vessels. A recent 6-month supplementation trial indicates that resveratrol 200 mg/d can enhance basal cerebral blood flow and this is associated with improved learning performance in healthy older adults [13]. Moreover, in young adults, acute consumption of 200 mg and 500 mg of resveratrol has been shown to increase basal perfusion and neurovascular coupling capacity [14]. No studies have yet estimated the optimal dose for enhancing CVR in a population with known microvascular dysfunction. Therefore, the aim of this study is to determine the most efficacious dose of resveratrol to improve CVR to hypercapnia in adults with T2DM.

## Methods

### *Study design and participants*

An acute randomised, double-blind, placebo-controlled dietary intervention was undertaken at the University of Newcastle's Clinical Nutrition Research Centre (CNRC). The study was conducted according to the International Conference on Harmonisation guidelines for Good Clinical Practices and approved by the University of Newcastle Human Research Ethics Committee. This study is registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12614000891628). Adults aged 40–80 years with a diagnosis of T2DM were recruited from the Hunter region in Australia via radio and newspaper announcements. All participants provided written, informed consent prior to participation.

Volunteers underwent a series of assessments to determine their eligibility to participate in the trial at the screening visit. They were excluded if they met any of the following conditions: were taking insulin or warfarin therapy; had a history of serious head injury; were diagnosed and/or treated for severe depression, stroke or neurological conditions; had renal or liver disease; smoked or used nicotine therapy; were likely to change pre-existing medication/supplements during the intervention. Additional exclusion criteria determined at screening included suspected dementia (score $<$78/100 on the Australian version of the Mini Modified Mental State Examination) (3MS) (http://www.dementia-assessment.com.au/cognitive/); clinic blood pressure (BP) $>$ 160/100 mmHg, body mass index (BMI) $>$ 40 mg/m$^2$ or inability to obtain satisfactory images of the MCA bilaterally by transcranial Doppler (TCD) ultrasound.

### *Randomisation and masking*

The doses of synthetic *trans*-resveratrol (resVida™, DSM Nutritional Products Ltd, Switzerland) selected for this study were 0, 75, 150 and 300 mg, which is similar to our previous study of acute resveratrol and FMD in hypertensive adults and was shown to be safe and well tolerated [12]. Placebo (inert excipients) and active treatments were encapsulated in an opaque film and supplied by DSM Nutritional Products Ltd (Kaiseraugst, Switzerland). The doses were packaged by a research assistant not involved in data collection and labelled as A, B, C or D; they were provided to the participants in an order determined by Latin Square design. Participants and investigators were masked to the doses corresponding to these letters. The code was held by an investigator who was not involved in data collection or analysis and was revealed after the data had been analysed.

### *Procedures*

Volunteers arrived at the CNRC following a 2 h fast (no food/beverage, medication or supplement, except water) for further study eligibility screening. Height, weight and waist circumference were measured and blood pressure (BP) readings were taken in accordance with published procedures [15] using an automated oscillometric monitor (HDI 2000 Cardiovascular Profiler CR 2000). After 10 min of seated rest, four consecutive readings of BP were taken at 5 min intervals by a single observer. The first reading was discarded and an average of the remaining measurements was recorded. Participants who met the inclusion criteria for BMI and clinic BP undertook the 3MS. Those scoring below 78/100 were excluded. Volunteers were then fitted with a headpiece