Can Resveratrol Supplementation Mitigate Hormonal Migraine?

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(Human Physiology)

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Statement of Originality

I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision. The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

Jemima S.A. Dzator

Acknowledgement of Authorship

I hereby certify that the work embodied in this thesis contains published papers of which I am a joint author. I have included as part of the thesis a written declaration endorsed in writing by my supervisor, attesting to my contribution to the joint publications.

By signing below, I confirm that Jemima Selorm Akosua Dzator contributed significantly towards the study design, data collation, analysis and interpretation, and drafting of the manuscript for the publication entitled 'Profiling cerebrovascular function in migraine: A systematic review and meta-analysis'; contributed significantly towards the data collection, analysis and interpretation, and the drafting of the manuscript for the publication entitled 'Cerebrovascular function in hormonal migraine: An exploratory study'; and contributed significantly towards the study design, data collection, analysis and interpretation, and drafting of the manuscript for the publication entitled 'A randomised, double-blind, placebo-controlled crossover trial of resveratrol supplementation for prophylaxis of hormonal migraine'.

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Jemima S.A. Dzator

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2. Dzator, J.S.A.; Howe, P.R.C.; Griffiths, L.R.; Coupland, K.G.; Wong, R.H.X. Cerebrovascular Function in Hormonal Migraine: An Exploratory Study. Front Neurol 2021, 12, 694980, doi:10.3389/fneur.2021.694980.
3. Dzator, J.S.A.; Howe, P.R.C.; Coupland, K.G.; Wong, R.H.X. A Randomised, Double-Blind, Placebo-Controlled Crossover Trial of Resveratrol Supplementation for Prophylaxis of Hormonal Migraine. Nutrients 2022, 14, 1763.

Conference Presentations

1. Centre for Brain and Mental Health Research 10th Annual Conference: Interrelationships between brain, bone health and blood vessel function
2. Cardiovascular Research Network New South Wales 3-Minute Research Competition (PhD Student Heat): Can resveratrol supplementation mitigate menstrual migraine?
3. Cerebrovascular Biology Australasia Symposium: Associations between cerebrovascular function and migraine-related disability in menstrual migraineurs – preliminary findings
4. Brain and Brain PET Conference 2022: Can resveratrol supplementation increase neurovascular coupling capacity in menstrual migraineurs? A pilot study

Awards

1. International Society of Cerebral Blood Flow and Metabolism Travel Award

Media Engagements

Radio

1. Triple J Radio Interview: Hope could be on the horizon for period-related migraines
2. 2NUR-FM Radio Interview**:** Resveratrol for Menstrual Migraine Clinical Trial Radio Interview

Newspaper

1. Triple J News Article: Do you suffer from period-related migraines? Researchers think they may have found a treatment
2. Newcastle Herald Article: University of Newcastle research looks at natural substance resveratrol to see whether it alleviates symptoms and frequency of menstrual migraines
3. Newcastle Herald Article: Migraine study: Newcastle University researchers predict women who suffer hormonal migraines may have poorer blood vessel function in the brain

Other

1. Migraine Australia YouTube Interview: Jemima Dzator - Research into menstrual migraine and hormones

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List of Abbreviations

ACA	Anterior cerebral artery
ANZCTR	Australian New Zealand Clinical Trials Registry
BFV	Blood flow velocity
BHT	Breath hold task
BMI	Body mass index
BP	Blood pressure
CBF	Cerebral blood flow
CGRP	Calcitonin gene-related peptide
CONSORT	Consolidated standards of reporting trials
CRI	Cerebrovascular reactivity index
CVR	Cerebrovascular responsiveness
DBP	Diastolic blood pressure
fMRI	Functional magnetic resonance imaging
HIT-6™	Headache impact test-6™
HMBI	Hormonal migraine burden index
HR	Heart rate
LAEI	Large artery elasticity index
LS	Left-side
MBFV	Mean blood flow velocity
MCA	Middle cerebral artery
MD	Missing data
MIDAS	Migraine disability assessment
MSQoL	Migraine-specific quality of life

NIRS	Near infrared spectrometry
NKA	Neurokinin A
NOS	Newcastle-Ottawa scale
PACAP	Pituitary adenylate-cyclase activating peptide
PCA	Posterior cerebral artery
PI	Pulsatility index
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RI	Resistive index
RS	Right-side
SAEI	Small artery elasticity index
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Standard error of the mean
SPECT	Single photo emission computed tomography
TCD	Transcranial Doppler
VA	Vertebral artery

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Thesis Abstract

Migraine is a neurovascular disorder that is estimated to affect 10% of the global population. Approximately half of female migraineurs suffer from hormonal migraine, which is characterised by a painful migraine that occurs within a few days of the onset of menstruation. These migraines are more painful, recurrent and resistant to current treatment options than regular migraines and are triggered by the rapid decrease of estrogen that precedes menstruation. Estrogen is particularly important for maintaining proper cerebrovascular function and interestingly, migraine is associated with an increased risk of cerebrovascular disease. However, it is unclear if migraine or more specifically, hormonal migraine, is associated with cerebrovascular dysfunction. In light of this, it is unclear if improvements of cerebrovascular function in hormonal migraineurs can prevent hormonal migraine. This thesis is comprised of three studies across four chapters to address these gaps in the literature.

The first study (Chapter 2) in this thesis is a systematic review and meta-analysis that investigated whether migraine is associated with poor cerebrovascular function. Findings from this review showed that migraineurs have poorer cerebrovascular function than controls as represented by higher intracranial stiffness and lower cerebrovascular responsiveness to hypercapnia in the posterior circulation. Interestingly, migraineurs also had higher resting cerebral blood flow velocity than controls in the anterior and posterior circulations.

The second study (Chapter 4) in this thesis is a cross-sectional comparative study conducted in 50 hormonal migraineurs and 29 controls. Participants visited the Clinical

Nutrition Research Centre at the University of Newcastle, Australia, on one occasion for measurements of cerebrovascular function using transcranial Doppler ultrasound. The hormonal migraineurs included in this cross-sectional study had poorer cerebrovascular function than controls as represented by lower resting cerebral blood flow velocity and lower neurovascular coupling capacity in the anterior circulation during a cognitive task.

The third study (Chapters 5 and 6) is a randomised, double-blind, placebo-controlled, crossover intervention trial conducted in 62 hormonal migraineurs who consumed both 75 mg trans-resveratrol twice daily for three months and a placebo supplement for 3 months. Resveratrol is a phytoestrogen with demonstrated beneficial effects on cerebrovascular function in older adults. I hypothesised that resveratrol supplementation would improve the deficiencies of cerebrovascular function that were observed in Chapter 4 and prevent hormonal migraine, reduce migraine-related disability and improve migraine-related quality of life. However, no differences in the average number of hormonal migraine days per month or migraine-related disability and quality of life were found between the resveratrol and placebo treatments (Chapter 5). Additionally, ten participants underwent further testing at baseline and after each of the 3-month intervention periods to investigate effects of resveratrol supplementation on cerebrovascular function (Chapter 6). This pilot study detected minimal change in cerebrovascular function; resting cerebral blood flow velocity in the posterior circulation was higher following resveratrol supplementation when compared to placebo.

This thesis makes several contributions to knowledge: firstly, both migraineurs and hormonal migraineurs have poorer cerebrovascular function than controls; secondly, taking a low dose of resveratrol twice daily does not alter migraine frequency, reduce migraine-related disability or improve migraine-related quality of life in hormonal migraineurs; thirdly, pilot data indicates that resveratrol supplementation for three months has a minor effect on cerebrovascular function in hormonal migraineurs. A larger, longitudinal study is needed to fully ascertain and confirm the effects of resveratrol supplementation on the cerebrovascular function of hormonal migraineurs.

Thesis Structure and Layout

This thesis comprises the following seven chapters:

- Chapter 1 provides an overview of migraine and hormonal migraine and briefly describes associations between migraine, hormonal migraine and cerebrovascular function. Resveratrol is identified as a potential prophylactic therapy for hormonal migraine based on the available literature. This chapter contains the thesis aims and hypotheses.
- Chapter 2 compares the cerebrovascular function of migraineurs and non-migraineurs in a systematic review of 70 studies, 40 of which met the criteria for quantitative analysis. The systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. This chapter has been published in a peer-reviewed journal. Dzator, J. S., Howe, P. R., & Wong, R. H. (2021). Profiling cerebrovascular function in migraine: A systematic review and meta-analysis. Journal of Cerebral Blood Flow and Metabolism, 41(5), 919–944. Impact Factor: 6.2.
- Chapter 3 details the approach and methodology for the two clinical trials that are included in this thesis: a cross-sectional trial (Chapter 4) and a randomised, controlled intervention trial (Chapter 5 and Chapter 6).
- Chapter 4 describes the cross-sectional trial that investigated whether hormonal migraineurs and non-migraineurs differ in cerebrovascular function, which was assessed on a single occasion using transcranial Doppler ultrasound. This chapter has been published in a peer-reviewed journal. Dzator, J., Howe, P., Griffiths, L. R., Coupland, K. G., & Wong, R. (2021). Cerebrovascular Function

in Hormonal Migraine: An Exploratory Study. Frontiers in neurology, 12, 694980. Impact Factor: 3.552.

- Chapter 5 describes a double-blind, placebo-controlled, crossover intervention trial to evaluate whether resveratrol supplementation can prevent hormonal migraine. Conducted in 62 hormonal migraineurs, the trial assessed by questionnaire the average number of hormonal migraine days per month, average hormonal migraine severity, migraine-related quality of life, and migraine-related disability following 3 months of resveratrol versus 3 months of placebo. This chapter has also been published in an international peer-reviewed journal. Dzator, J.S.A.; Howe, P.R.C.; Coupland, K.G.; Wong, R.H.X. A Randomised, Double-Blind, Placebo-Controlled Crossover Trial of Resveratrol Supplementation for Prophylaxis of Hormonal Migraine. Nutrients 2022, 14, 1763. Impact Factor: 5.719.
- Chapter 6 describes outcomes from a subset of 10 participants in the intervention trial who were able to visit the research centre on three occasions for testing of cerebrovascular function.
- Chapter 7 provides a summary of the thesis findings, outlines the overall strengths and limitations of the thesis and provides recommendations for future research.