

Vascular endothelial and smooth muscle function
in children at risk of cardiovascular disease and
the effect of folic acid supplementation

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ABSTRACT

Cardiovascular disease secondary to atherosclerosis is the most common cause of human morbidity and mortality. An early and fundamental event in the development of atherosclerosis is abnormal vascular endothelial and smooth muscle function. This can be measured by flow mediated dilatation and glyceryl trinitrate mediated dilatation in children at risk of atherosclerosis. Folic acid improves endothelial function (flow mediated dilatation) in adults with coronary artery disease. No studies have previously investigated the effects of folic acid on vascular function in at risk children with diabetes or obesity.

In a cross sectional study an evaluation of vascular endothelial and smooth muscle function and their determinants was performed in 159 children with type 1 diabetes, 58 children with obesity, and 53 healthy children. Children with type 1 diabetes and children with mild to moderate obesity had comparable and severe vascular dysfunction but different determinants. Vascular function in healthy and obese children related to both body mass index and weight (adjusted for age and sex), and blood glucose. Children with obesity had lower folate levels and higher homocysteine levels than children with type 1 diabetes, an abnormal lipid profile and raised inflammatory markers.

A randomised double blind placebo controlled cross over trial of 8 weeks of folic acid supplementation was performed in 38 children with type 1 diabetes. In these children, folic acid improved endothelial function with a sustained increase in folate levels but independent of homocysteine levels. Folic acid did not improve smooth muscle function.

A randomised double blind placebo controlled parallel trial of 8 weeks folic acid supplementation was performed including 53 obese children. Folic acid did not improve

vascular function in obese children in spite of sustained increase in folate levels, and a decrease in homocysteine levels.

It was concluded that children with type 1 diabetes and obesity have comparable and severe endothelial and smooth muscle function. Determinants of vascular function in children, including weight and glucose, represent a continuum effect. Folic acid supplementation improved endothelial function in children with type 1 diabetes but not in children with obesity, whose metabolic changes causing endothelial dysfunction differ from children with diabetes.

DECLARATION

This work contains no material which has been accepted 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 in the text.

I give consent to a copy of this thesis, when deposited in the University Library being available for loan and photocopying.

.....

Alexia Sophie Peña Vargas

September 28th 2007

Date

DEDICATION

To Mellick

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LIST OF SPECIAL ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
APEG	Australian Paediatric Endocrine Group
ATL	Advanced Technology Laboratories
BMI	Body Mass Index
CI	Confidence Interval
CRP	C-reactive protein
CV	Coefficient of variation
DEXA	Dual Energy X-ray Absorptiometry
eNOS	endothelial Nitric Oxide Synthase
ECG	Electrocardiogram
ET-1	Endothelin-1
FMD	Flow Mediated Dilatation
FABF	Forearm Arterial Blood Flow
GTN	Glyceryl Trinitrate Mediated Dilatation
HbA1c	Haemoglobin A1c, glycosylated haemoglobin
HDL	High Density Lipoprotein
HsCRP	High Sensitive C reactive protein
LDL	Low Density Lipoprotein
MTHFR	Methylenetetrahydrofolate reductase
NO	Nitric Oxide
PAI-1	Plasminogen Activator Inhibitor-1
RCF	Red Cell Folate

SD	Standard Deviation
SE	Standard Error of Mean
tHcy	Total Plasma homocyst(e)ine
TNF- α	Tumour Necrosis Factor α
tPA	Tissue Plasminogen Activator
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
VD	Vessel Diameter
vWF	von Willebrand Factor

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