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.

........................................... September 28th 2007
Alexia Sophie Peña Vargas Date
DEDICATION

To Mellick
ACKNOWLEDGMENTS

It is impossible to adequately acknowledge the help of the people who have been instrumental in this thesis and to whom I am deeply indebted.

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# LIST OF SPECIAL ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin Converting Enzyme</td>
</tr>
<tr>
<td>APEG</td>
<td>Australian Paediatric Endocrine Group</td>
</tr>
<tr>
<td>ATL</td>
<td>Advanced Technology Laboratories</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual Energy X-ray Absorptiometry</td>
</tr>
<tr>
<td>eNOS</td>
<td>endothelial Nitric Oxide Synthase</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ET-1</td>
<td>Endothelin-1</td>
</tr>
<tr>
<td>FMD</td>
<td>Flow Mediated Dilatation</td>
</tr>
<tr>
<td>FABF</td>
<td>Forearm Arterial Blood Flow</td>
</tr>
<tr>
<td>GTN</td>
<td>Glyceryl Trinitrate Mediated Dilatation</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Haemoglobin A1c, glycosylated haemoglobin</td>
</tr>
<tr>
<td>HDL</td>
<td>High Density Lipoprotein</td>
</tr>
<tr>
<td>HsCRP</td>
<td>High Sensitive C reactive protein</td>
</tr>
<tr>
<td>LDL</td>
<td>Low Density Lipoprotein</td>
</tr>
<tr>
<td>MTHFR</td>
<td>Methylene tetrahydrofolate reductase</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric Oxide</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Plasminogen Activator Inhibitor-1</td>
</tr>
<tr>
<td>RCF</td>
<td>Red Cell Folate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SE</td>
<td>Standard Error of Mean</td>
</tr>
<tr>
<td>tHcy</td>
<td>Total Plasma homocyst(e)ine</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumour Necrosis Factor α</td>
</tr>
<tr>
<td>tPA</td>
<td>Tissue Plasminogen Activator</td>
</tr>
<tr>
<td>T1DM</td>
<td>Type 1 Diabetes Mellitus</td>
</tr>
<tr>
<td>T2DM</td>
<td>Type 2 Diabetes Mellitus</td>
</tr>
<tr>
<td>VD</td>
<td>Vessel Diameter</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand Factor</td>
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