Reduction of Total Homocysteine Levels by Oral Folic Acid Fails to Improve Endothelial Function in Children With Chronic Renal Failure

To the Editor:

We read with great interest the study by Bennett-Richards and colleagues\(^1\) that examined the effect of oral folic acid on total homocysteine concentrations and endothelial function in children with chronic renal failure (CRF). They found that folic acid supplementation for 8 weeks significantly reduced homocysteine concentrations and increased low-density lipoprotein lag times (indicating a reduction in susceptibility of low-density lipoprotein to oxidation). Despite these favorable effects of folic acid on parameters that are detrimental to endothelial function, however, there was no significant improvement in flow-mediated dilatation (FMD) compared with placebo.\(^1\) The authors suggested several explanations, including the inability to normalize homocysteine levels in CRF, abnormal folate metabolism, and inadequate folate supplementation. We would like to propose an additional mechanism that is pivotal in chronic renal failure.

It has been shown that plasma concentration of asymmetrical dimethylarginine (ADMA), an endogenous nitric oxide (NO) synthase inhibitor, accumulates in CRF.\(^2\) High plasma ADMA has also been found in experimentally induced hyperhomocysteinemia in subjects with normal renal function.\(^3\) Hence, it is highly likely that plasma ADMA (not measured in their study) is markedly elevated in children with hyperhomocysteinemia and CRF. Elevated ADMA inhibits NO synthase, resulting in diminished NO synthesis with subsequently impaired FMD. Because ADMA is excreted by the kidneys, normalization of homocysteine alone in CRF is sufficient to cause a significant reduction in plasma ADMA. Therefore, accumulation of ADMA is highly likely to have contributed to the lack of improvement in FMD after folic acid supplementation.

Understanding of the pathophysiological mechanism contributing to endothelial dysfunction in CRF is important because novel therapies targeting these abnormalities may result in improved clinical outcomes in children with CRF. Probucol has been shown to reduce plasma ADMA and to preserve endothelial function.\(^4\) Additionally, dietary L-arginine (substrate for NO synthesis) increases the L-arginine:ADMA ratio, and this therapeutic approach has been shown to improve endothelial function in conditions in which plasma ADMA concentrations are elevated.\(^5\) Whether the use of drugs that can lower ADMA (such as probucol) and/or L-arginine in conjunction with folic acid results in improved endothelial function and clinical outcome in CRF warrants further investigation.

N.N. Chan, MD, MRCP
W.B. Chan, MRCP
J.C.N. Chan, MD, FRCP
Department of Medicine & Therapeutics
Prince of Wales Hospital
The Chinese University of Hong Kong
Hong Kong
nnkachan@aol.com

Response

We note with interest the comments of Chan et al on the mechanism of endothelial dysfunction in children with chronic renal failure (CRF). We did not measure the effect of folic acid on asymmetrical dimethylarginine (ADMA) levels in this study.\(^1\)

In another study now published, we have investigated the mechanism described by Chan et al. ADMA levels were elevated in children with CRF when compared with the only available published control data \((1.19 \pm 0.5 \text{ versus } 0.77 \pm 0.18 \text{ mmol/L, } P=0.05)\).\(^2\) Oral supplementation with L-arginine, however, had no beneficial effect on endothelial function, ADMA levels, or nitric oxide production, despite a significant increase in serum L-arginine.\(^3\)

The levels of ADMA were not as high as those reported in adults with CRF,\(^4\) hypercholesterolemia\(^5\) (in which beneficial effects of L-arginine have been demonstrated), or in experimental acute hyperhomocysteinemia.\(^6\)

This may suggest that in children with CRF, modestly elevated ADMA levels do not primarily account for endothelial dysfunction. Use of an alternative to L-arginine to lower ADMA combined with folic acid certainly warrants consideration.

K.J. Bennett-Richards, MB, BS, MRCP
M. Kattenhorn, BSc, Hons
A. Donald, AVT
G. Oakley, RGN, MSc
L. Rees, MD, FRCP, FRCPCH
J.E. Deanfield, FRCP
Vascular Physiology Unit
Great Ormond St Hospital for Children NHS Trust
London, UK
KatyJBR@aol.com

Z. Varghese, PhD, FRCPath
Royal Free Hospital Renal Research Unit
Royal Free and University College Medical School
London, UK


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