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Original Article

Fibroblast growth factor-23 in patients with homozygous familial hypercholesterolemia

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BACKGROUND: Patients with homozygous familial hypercholesterolemia (HoFH) develop significant vascular calcification early in life, the cause of which is not yet fully understood. Patients with chronic kidney disease have similar vascular calcification, with fibroblast growth factor-23 (FGF23) implicated in these patients.

OBJECTIVE: To determine whether there was a difference in FGF23 between patients with HoFH and age- and gender-matched controls and whether there is a correlation between FGF23 and serum low-density lipoprotein, total cholesterol, and carotid intima-media thickness in patients with HoFH.

METHODS: The study was a cross-sectional review involving 30 patients with HoFH attending the Charlotte Maxeke Johannesburg Academic Hospital Lipid Clinic in Parktown, South Africa, as well as 30 age- and gender-matched healthy controls. FGF23, fasting lipid profiles, calcium, and phosphate were measured. B-mode ultrasonography of the carotid arteries was done to assess the extent and severity of arterial calcification.

RESULTS: There was no difference in mean FGF23 between the patient and control groups (62.07 ± 26.42 pg/mL vs 63.69 ± 19.84 pg/mL; $P = .4621$) nor was there any correlation between FGF23 and low-density lipoprotein cholesterol ($P = .9483$ and .8474) or total cholesterol ($P = .9261$ and .859). In the HoFH patients, FGF23 did not correlate significantly with any cardiovascular disease.

CONCLUSIONS: Serum FGF23 is not elevated in patients with HoFH when compared to non–familial hypercholesterolemia age- and gender-matched controls, and there is no correlation between serum FGF23 and cardiovascular disease in patients with HoFH. FGF23 does not appear to be a major factor for arterial calcification in HoFH.

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disorder resulting from mutations that affect the function of the low-density lipoprotein (LDL) receptor. It remains an important condition in South Africa, given the greater prevalence, due to a founder effect, when compared to that reported globally.[1–3] FH can be divided into 2 broad categories: the more common (1 in 200–500) heterozygous

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FH, where patients tend to have an elevation of their low-density lipoprotein cholesterol (LDL-C) to approximately double the normal level and the much less common (1 in 300,000–1,000,000), but more severe, homozygous FH (HoFH).[4,5] HoFH patients effectively express few, if any, LDL receptors on their cell surfaces and thus have extremely elevated LDL-C levels (often 4 to 6 times normal). These patients develop premature accelerated atherosclerotic cardiovascular disease that, if untreated, can lead to fatal myocardial infarction, often in the second or third decade of life.[5]

The quadrupled level of plasma LDL-C at birth in patients with HoFH leads to atherosclerosis in all arterial beds from early on in life.[6] This "accelerated atherosclerosis"[7] is not limited to the coronary vasculature—carotid arteries, renal arteries, aortic valve cusps, aortic root, and descending aorta are all frequently affected.[6,7] Inflammation within the atherosclerotic plaque produces inflammatory mediators that are thought to interact with vascular cells capable of osteogenic differentiation, in turn leading to the vascular calcification seen in these patients.[8] Importantly, the distribution of vascular calcification tends to be localized to the intima of blood vessels as opposed to the medial calcification (Monckeberg's sclerosis) seen in subjects with end-stage renal disease, the elderly, and in those with diabetes mellitus.[9] Nevertheless, both types of calcification are associated with increased cardiovascular morbidity and mortality.[8]

Coronary artery calcification, which can be detected and scored by computed tomography scanning, is an early marker of coronary artery atherosclerosis and together with carotid intima-media thickness (CIMT) can be used as surrogate markers for atherosclerosis in other vessels. Wiegman et al. report that 25% of 11- to 23-year-old patients with heterozygous FH have coronary calcification, whereas it is barely, if ever, detected in the same age group in the general population.[10]

The extensive vascular calcification seen particularly in HoFH leads to surgical challenges at the time of aortic valve and coronary surgery. In a cohort of 25 HoFH patients, followed up for a mean of 18 years, 45% required coronary artery bypass graft surgery and over 50% had evidence of either aortic stenosis or aortic root calcification of which half required aortic valve replacement. All but the 2 youngest patients in this cohort had calcification of the aorta.[5] Similarly, aortic root calcification was found in all patients of a smaller cohort of 7 HoFH patients from the United Kingdom.[11] This is significant considering the incidence of aortic calcification in the general population in the Western world is only 3% in adults older than 75 years.[8]

Fibroblast growth factor-23 (FGF23) is a hormone that acts with its cofactor (α-klotho) via FGF receptors to decrease circulating levels of 1,25-dihydroxycholecalciferol (vitamin D_3) and increase renal excretion of phosphate by inhibiting renal tubular reabsorption of phosphate. Raised FGF23 is an early finding in patients with chronic kidney disease, and elevated FGF23 is an independent marker for cardiovascular events and mortality in these patients. A positive correlation has been noted between elevated levels of FGF23 and coronary artery stenosis as well as between FGF23 and "total body atherosclerosis" (defined as the sum of vascular calcification at vasculature in the neck, aorta, kidney, upper leg, and lower leg).[12]

In their 2015 study, Turan et al. demonstrated a 17% increase in risk for severe coronary artery calcification, as determined by computed tomography scan, for every 50 pg/mL increase in serum FGF23. Of significance is that this independent correlation continued to exist in patients with a glomerular filtration rate > 60 mL/min/1.73 m^2.[13] A further independent correlation between FGF23 and aortic calcification was noted by Nasrallah et al.,[14] Desjardins et al.,[15] and Schoppet et al.[16]

A statistically significant positive association between FGF23 and coronary artery calcification was revealed in a study of 545 African-American patients with type 2 diabetes mellitus implying a race-independent correlation between FGF23 and vascular calcification. However, there was no correlation between carotid and aortic calcification and FGF23.[17]

In patients with FH, vascular calcification continues to progress despite statin therapy and reduction in LDL-C, suggesting that "the calcification process may proceed independently of cholesterol levels, once subendothelial damage has occurred".[5,8] A two-hit hypothesis in the development of vascular calcification in patients with FH has therefore been proposed.[8,9]

Given that FGF23 is an independent risk factor for vascular calcification, we hypothesized that FGF23 could be one of the additional factors responsible for the vascular calcification seen in patients with FH.

Methods

This was a cross-sectional study undertaken at the Carbohydrate and Lipid Metabolism Research Unit at the Charlotte Maxeke Johannesburg Academic Hospital in Parktown, South Africa. Permission to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (medical), reference number M160537.

The main objective of the study was to compare serum FGF23 levels between patients with HoFH and age- and gender-matched healthy controls without hypercholesterolemia to determine whether FGF23 could be implicated in the pathogenesis of the severe vascular calcification seen in patients with HoFH. The secondary objective was to assess whether any correlation exists between FGF23 levels and total and LDL-C as well as CIMT in patients with HoFH.

Thirty HoFH patients who follow up at the Charlotte Maxeke Johannesburg Academic Hospital Lipid Clinic and 30 age- and gender-matched control patients were studied. Patients with a creatinine clearance of less than 60 mL/min/1.73 m^2 were excluded from the study.