

Detection of subclinical atherosclerosis by electron beam tomography in females with heterozygous familial hypercholesterolaemia

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Familial hypercholesterolaemia (FH) is a common genetic disorder that affects around 1 in 500 people in its heterozygous form (HeFH). HeFH is associated with an early onset of coronary heart disease (CHD), especially in men.¹ In women the risk of first CHD event is much less than in men, generally < 1% by 40 years of age, 12% by 50 years, 58% by 60 years, and 74% by 70 years of age. In spite of increased cholesterol values, the clinical expression of CHD in HeFH is variable and is also dependent on other risk factors. Currently there is consensus that males with HeFH should be treated early and aggressively with lipid lowering drugs. However, there is some controversy over when females with HeFH should be treated with statins since CHD generally manifests itself 10 years later than in men¹ and there are restrictions to the use of statins in women during their reproductive years. Most importantly, cost effectiveness data on this issue are not available. Current CHD prevention guidelines recommend the use of clinical scores such as the Framingham risk charts in order to predict CHD risk and to guide pharmacological treatment.² However, these scores were not developed for HeFH patients, therefore clinicians should rely empirically on plasma lipid concentrations, early CHD family history, and on the presence or absence of other CHD risk factors to institute treatment.

The detection of subclinical atherosclerosis could be helpful in determining selected subjects at high risk and therefore candidates for more aggressive and early lipid lowering.^{3,4} Coronary artery calcification (CAC), as determined by electron beam tomography, is a marker of coronary artery plaque burden. Severe CAC—that is, above the 75th centile for the population distribution for age and sex—is associated with a high risk of CHD.³ A few studies have evaluated the presence of subclinical atherosclerosis by electron beam tomography in FH patients.^{5,6} In these studies the cholesterol–age product, a marker of exposure to the cholesterol burden during lifetime, was associated with the presence of CAC.^{5–7}

The objective of our study was to evaluate CAC in asymptomatic female HeFH patients and compare it to normal women. We also evaluated whether the cholesterol–age product correlates with the intensity of CAC in females with and without HeFH.

PARTICIPANTS AND METHODS

HeFH was diagnosed using the US MED PED criteria that rely on low density lipoprotein (LDL) cholesterol values and on a previous diagnosis of FH in first and second degree relatives.⁸ At the time of evaluation no patient was using lipid lowering drugs. CAC was determined by electron beam tomography with an Imatron C-150 scanner (Imatron Corporation, San Francisco, California, USA) in 27 consecutive HeFH females (10–74 years old, mean 40 years, median 39 years) from the

Lipid Outpatient Clinic of the Heart Institute (InCor) and in 71 asymptomatic normolipidaemic females from the Preventive Medicine Centre of the Albert Einstein Hospital (34–68 years old, mean 47 years, median 46 years).

The tomography scanning protocol comprised 40 axial cross sections of the heart with 3 mm slice thickness obtained after a 100 ms exposure time acquired during inspiratory breath hold. Two contiguous pixels with attenuation coefficient > 130 Hounsfield units were required to qualify as calcium deposit. CAC (calcium scores) was determined by the Agatston's method⁹ and its distribution in age strata was compared with previously determined calcium scores of 471 normal consecutive asymptomatic Brazilian women (24–87 years old) referred for a routine medical evaluation at the Preventive Medicine Centre (table 1). In this study the cholesterol–age product was defined as: LDL cholesterol concentrations in mmol/l × age in years.

Data normality was tested by the Kolmogorov-Smirnov procedure; parametric and non-parametric data were compared, respectively, by Student's *t* test and Mann-Whitney test. CAC is expressed as mean (95% confidence intervals (CI)). Categorical data were analysed by χ^2 or Fisher's exact test when necessary. The correlation of cholesterol–age product with CAC in both groups was performed by the Spearman test.

The study complied with the declaration of Helsinki and was approved by the Heart Institute ethics committee.

RESULTS

Table 2 shows that HeFH patients were younger and had a lower prevalence of smokers and former smokers than normal women. Total cholesterol, LDL cholesterol, and plasma triglycerides were higher in HeFH women compared to normal women. Figure 1 shows the distribution of calcium scores in HeFH and in normal women. There was a greater prevalence of CAC in the HeFH group than in the normal women (51.8% (n = 14) and 16.9% (n = 12), p = 0.0009, respectively), corresponding to a relative risk of 3.07 (95% CI 1.63 to 5.77). The values of calcium scores were higher in HeFH than normals: 66.0 (95% CI 18.0 to 113.0) v 11.0 (95% CI 1.5 to 20.0), p = 0.004. Also, the prevalence of severe CAC was greater in HeFH than in normals (100% (n = 14) and 66.6% (n = 8), p = 0.03) corresponding to a relative risk of 2.3 (95% CI 1.42 to 3.82). Of those HeFH females with severe

Abbreviations: CAC, coronary artery calcification; CI, confidence interval; CHD, coronary heart disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia

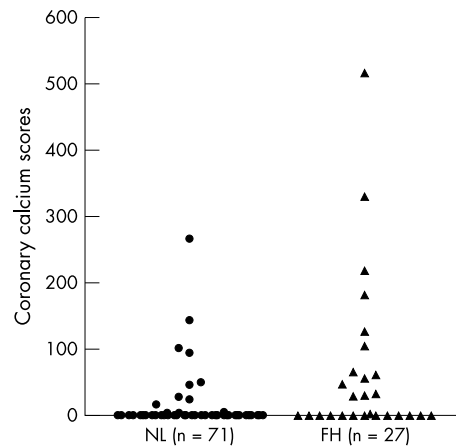
Table 1 Age distribution of coronary artery calcification in 471 women asymptomatic for coronary heart disease

	Age (years)				
	<40	40–49	50–59	60–69	≥70
n	54	135	155	85	42
25%	0	0	0	0	1
50%	0	0	0	5	76
75%	0	0	31	58	379
90%	0	24	168	237	517

CAC, 5 (57.1%) were at reproductive age (< 45 years old). The cholesterol–age product (mmol–year/l) was greater in HeFH than in normal women (277.4 (176.0) and 146.0 (52.0), respectively, $p < 0.0001$) and it was correlated with CAC in HeFH but not in normal women (respectively $r^2 = 0.46$, $p = 0.0002$, and $r^2 = 0.0081$, $p = 0.21$).

DISCUSSION

In this study females with HeFH had a greater prevalence and severity of subclinical atherosclerosis as determined by electron beam tomography than normal women. Electron beam tomography could be useful to stratify the risk of CHD in these patients since CAC correlates with atherosclerotic plaque burden and with the risk of clinical events.³ The detection of severe subclinical atherosclerosis would warrant initiation of aggressive statin treatment in these women, mainly in those with disease diagnosed at an early age. Studies performed in non-FH patients showed that subjects with severe subclinical atherosclerosis³ have a risk of CHD events greater than the 2% annual threshold chosen to start statin treatment by the joint task force of European and other societies on coronary prevention.² In non-FH subjects the absence of CAC indicates a very low risk of clinical CHD events in the short and medium term, even in the presence of CHD risk factors.³ This could be used as a reason for postponing pharmacological treatment, especially in younger women, and for emphasising a healthy lifestyle and non-pharmacological treatment when risk factors other than increased LDL cholesterol values are detected. However, this hypothesis should be tested in HeFH in a prospective study. In spite of that, the detection of subclinical atherosclerosis indicates the presence of the disease and could help, as suggested previously,⁴ in deciding whether or not to start statin treatment in selected populations such as women with HeFH.

**Figure 1** Coronary calcium scores in normal women (NL) and women with familial hypercholesterolaemia (FH).

Another potential use of electron beam tomography in HeFH patients would be for following up disease progression—that is, calcification—and for evaluating the effectiveness of lipid lowering treatment in modifying the course of the disease.

In non-FH subjects the intensity of CAC is greater in men than women, and age is the most important determinant of CAC presence and severity.^{3–10} However, other risk factors such as smoking, hypercholesterolaemia, and hypertension have also been associated with the intensity of CAC. Despite being younger and having a lower prevalence of smokers and former smokers, HeFH women had a greater prevalence and severity of CAC than normal women. The exposure to high cholesterol concentrations during their lifetime, as shown by the increased cholesterol–age product and its correlation with CAC, in HeFH patients but not in normal women is certainly associated with this finding. Our results are in accord with previous studies performed in children and young adults as well as in homozygous FH patients who showed a correlation of cholesterol–age product and intensity of CAC.^{5–6} The greater prevalence of severe CAC in HeFH is in accord with the high and early prevalence of clinical CHD in HeFH.¹

In conclusion, HeFH females had a higher prevalence and greater intensity of CAC than normal women. Electron beam tomography might be helpful in identifying female subjects with early onset and severe subclinical atherosclerosis, and might also help in deciding when to start lipid lowering treatment with statins.

Table 2 Clinical and laboratory characteristics of heterozygous familial hypercholesterolaemia (FH) and normal women

	FH women	Normal women	p Value
n	27	71	–
Age (years)	40 (18)	47 (8)	0.01
High blood pressure (%)	14.8	11.3	ns
Smokers and former smokers (%)	14.8	40.8	0.017
Obesity (%)	14.8	12.7	ns
Diabetes (%)	0	1.4	ns
Total cholesterol (mmol/l)	9.64 (3.91)	4.95 (0.9)	<0.0001
LDL-C (mmol/l)	7.62 (3.82)	2.97 (0.74)	<0.0001
HDL-C (mmol/l)	1.34 (0.25)	1.47 (0.33)	ns
VLDL-C (mmol/l)	0.27 (0.1)	0.22 (0.01)	0.03
Triglycerides (mmol/l)	1.34 (0.53)	1.12 (0.49)	0.03

Data for age and cholesterol concentrations presented as mean (SD).

HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol.

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IMAGES IN CARDIOLOGY

Pulmonary atresia with intact ventricular septum and right coronary artery to right ventricle fistula detected in utero

Pulmonary atresia with intact ventricular septum was diagnosed in a fetus at 29 weeks' gestation. In addition an enlarged right coronary artery with a fistulous connection to the right ventricle (centre panel). Postnatal ultrasonography (right upper panel) and selective coronary angiography (right lower panel) confirmed the diagnosis.

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