Correlation of parents’ longevity with carotid intima–media thickness in patients attending a Lipid Clinic

Damiano Baldassarre, Mauro Amato, Fabrizio Veglia, Linda Pustina, Samuela Castelnuovo, Silvia Sanvito, Lorenzo Gerosa, Cesare R. Sirtori, Elena Tremoli

Abstract

The relationship between carotid intima–media thickness (IMT) and the subject’s parents’ longevity has been investigated. The association between parents’ age at death and IMT was estimated in 593 consecutive patients attending a Lipid Clinic by survival-analysis methods. Average maximum IMT (Avg-IMT), maximum IMT (Max-IMT), clinical and laboratory variables and parental age at death, were assessed. Kaplan–Meier analyses showed significant differences in survival curves, low IMTs being associated with long-lived parents \( p = 0.0003 \) and 0.001 by log-rank test for fathers and mothers, respectively). A Cox proportional hazards regression model showed that higher carotid IMT values were associated with father’s and mother’s deaths at an early age, even after adjusting for conventional cardiovascular risk factors. These data were confirmed after the stratification of patients into younger (<65 y) and older (≥65 y) or into subjects with and without a family history of dyslipidemia or vascular diseases. In addition, by stratifying subjects into those with no, one or two long-lived parents, we observed a significant trend for the combination of father’s and mother’s longevity on their offspring’s IMTs \( p < 0.01 \) and 0.05 for Avg-IMT and Max-IMT, respectively). These data highlight a significant relationship between carotid artery IMT and a familial predisposition to be long-lived that is independent of the individual’s vascular risk profile.

1. Introduction

Subjects with a parental history of coronary heart disease (CHD) are at higher risk of developing atherosclerosis. A higher familial prevalence of established atherosclerosis risk factors (i.e. hypercholesterolemia, hypertension, diabetes, smoking habit and obesity) may partially explain the familial aggregation of CHD [1–4]. Since conventional risk factors do not fully justify the variability in CHD incidence [5–7], a number of authors have suggested that also other unknown determinants may be involved in the atherosclerotic process and probably also in the familial predisposition to this disease [1,2,8–13]. Intimal thickening of the coronary arteries in infancy, determined in autopsy studies, has been shown to be associated with the grandparents’ history of coronary disease [14]. Angiographic [15–17] and ultrasonic [18–20] studies of atherosclerosis show that patients with a familial aggregation of CHD have more advanced atherosclerosis than appropriate controls. Although a family history of CHD has long been recognized as a major risk factor for atherosclerosis, the possible protective effect of genetic factors or specific family behaviours in a family with long-lived members has not been investigated before.

Longevity is the result of health-promoting behaviours plus genetic factors that promote disease resistance and...
long-term survival. If environmental factors did not change from one generation to the next, parents' and children's longevity would be expected to be similar. Studies do, in fact, show similarities in the age of death in parents and offspring [21–23], while other studies confirm that parental survival is an independent predictor of offspring's longevity [24].

In this study, we have investigated whether familial predisposition to longevity is a determinant of intima-media thickness (IMT) in patients attending a Lipid Clinic, by assessing the relationship between their parents' longevity and the IMT of extracranial carotid arteries, a widely accepted non-invasive surrogate index of CHD [25].

2. Methods

2.1. Subjects

Five hundred and ninety-three consecutive patients (299 men and 294 women) attending the Ultrasound Laboratory of the E. Grossi Paoletti Centre (Niguarda Hospital, Milan, Italy) were analysed by carotid B-mode ultrasound imaging. The ultrasonic procedure is routinely performed in each patient attending for the first time at our Lipid Clinic.

Patients attend our Lipid Clinic either spontaneously or when referred by basic practitioners and as such they can have lipid or lipoprotein abnormalities (plasma LDL cholesterol >4.14 mmol/L, triglycerides >2.28 mmol/L, HDL cholesterol ≤1.04 mmol/L), borderline hyperlipidemias (plasma LDL cholesterol 3.37–4.12 mmol/L, triglycerides 1.71–2.27 mmol/L) and even a normal lipoprotein pattern (plasma LDL cholesterol <3.34 mmol/L, triglycerides <1.70 mmol/L, HDL-cholesterol >1.04 mmol/L).

In the group studied, 480 patients (80.9%) were hyperlipidemic, 86 (14.5%) were borderline hyperlipidemic, and 27 (4.6%) had a normal lipoprotein pattern. Two hundred and fourteen patients (36.0%) were hypertensive (systolic or diastolic blood pressure ≥140 mmHg and ≥90 mmHg, respectively, or under treatment with hypotensive drugs). Thirteen patients (2.2%) were diabetic or were taking oral hypoglycemic drugs. Seventy-seven patients (13.0%) had a previous history of coronary heart disease (CHD), 29 (4.95%) of cerebrovascular disease (CVD) and 43 (7.3%) of peripheral arterial disease (PAD). The patients (46.7%) had a self-reported family history of CHD, 28.8% of CVD and 4.2% of PAD. About 56% of the patients reported a family history of hyperlipidemia, hypertension, diabetes, obesity, CHD (fatal and nonfatal acute myocardial infarction, unstable angina, and coronary revascularization procedures), CVD (fatal and nonfatal stroke, transitory ischemic attack, and carotid surgery) or PAD (critical limb ischemia and revascularization procedures of the lower limbs) were also recorded. Apart from certification of family history of hyperlipidemias (required by Italian health system to allow patients to obtain lipid-lowering drugs free of charge), no further medical records were obtained to validate the self-reported information.

For the deceased parents, fathers’ and mothers’ median ages of death were 69 and 73 years, respectively. Parents dead or still alive after these cut-offs were defined as “Long Lived” and those dead before, as “Short Lived”. Parents still alive but younger than these cut-off ages (42 fathers and 113 mothers) were excluded from some analyses because of the impossibility to be correctly classified.

To define the parental history of longevity, subjects were asked by means of a standardized questionnaire whether their parents were still alive and how old they were. If a parent was deceased, the age and the reason of death were recorded. In the same questionnaire, first-degree family history of hyperlipidemia, hypertension, diabetes, obesity, CHD (fatal and nonfatal acute myocardial infarction, unstable angina, and coronary revascularization procedures), CVD (fatal and nonfatal stroke, transitory ischemic attack, and carotid surgery) or PAD (critical limb ischemia and revascularization procedures of the lower limbs) were recorded. Apart from certification of family history of hyperlipidemias (required by Italian health system to allow patients to obtain lipid-lowering drugs free of charge), no further medical records were obtained to validate the self-reported information.

To investigate if a familial predisposition to be long lived inherited from both parents yields a more favourable IMT profile than having just one or no ‘long-lived’ parent, the association between carotid IMT and the number of long-lived parents was also investigated. The analysis was performed after data adjustment for relevant covariates (see Section 2.5). In these analyses, patients with parents younger than 40 years of age (alive or dead) and/or patients with fathers alive but younger than 69 years and/or mothers alive but younger than 73 years were considered as confounding because of the impossibility to be defined with sureness as long lived (μ=95) and as such, excluded.

2.2. Lipids

Blood samples were collected from the antecubital vein after overnight fasting. Total and HDL cholesterol and triglyceride levels were determined in fresh serum by enzymatic methods [28–29]; HDL cholesterol levels were obtained by selective precipitation with dextran–MgCl2 [30]. Serum LDL cholesterol levels were calculated by the Friedewald’s formula [31].

2.3. Parental history of longevity

To define the parental history of longevity, subjects were asked by means of a standardized questionnaire whether their parents were still alive and how old they were. If a parent was deceased, the age and the reason of death were recorded. In the same questionnaire, first-degree family history of hyperlipidemia, hypertension, diabetes, obesity, CHD (fatal and nonfatal acute myocardial infarction, unstable angina, and coronary revascularization procedures), CVD (fatal and nonfatal stroke, transitory ischemic attack, and carotid surgery) or PAD (critical limb ischemia and revascularization procedures of the lower limbs) were recorded. Apart from certification of family history of hyperlipidemias (required by Italian health system to allow patients to obtain lipid-lowering drugs free of charge), no further medical records were obtained to validate the self-reported information.

For the deceased parents, fathers’ and mothers’ median ages of death were 69 and 73 years, respectively. Parents dead or still alive after these cut-offs were defined as “Long Lived” and those dead before, as “Short Lived”. Parents still alive but younger than these cut-off ages (42 fathers and 113 mothers) were excluded from some analyses because of the impossibility to be correctly classified.

To investigate if a familial predisposition to be long lived inherited from both parents yields a more favourable IMT profile than having just one or no ‘long-lived’ parent, the association between carotid IMT and the number of long-lived parents was also investigated. The analysis was performed after data adjustment for relevant covariates (see Section 2.5). In these analyses, patients with parents younger than 40 years of age (alive or dead) and/or patients with fathers alive but younger than 69 years and/or mothers alive but younger than 73 years were considered as confounding because of the impossibility to be defined with sureness as long lived (μ=95) and as such, excluded.

2.4. Ultrasonography

Ultrasound scanning of the carotid arteries was performed by a single expert sonographer (DB) with a 8-MHz transducer.
ences were examined with the use of contingency tables and triglycerides. For categorical variables, group differences were first evaluated by Kaplan–Meier survival analysis (Fig. 1). By considering total mortality, a significant difference in survival curves of the parents of patients with high or low carotid Max-IMTs was observed (p = 0.02 and 0.006 by log-rank test for fathers and mothers, respectively), low IMTs being associated with long-lived parents. Similar results were observed if Avg-IMT was used instead of Max-IMT (data not shown).

A Cox proportional hazards regression model was used to calculate the adjusted hazard ratio (HR) for parent’s death (Table 2). Both Avg-IMT and Max-IMT were explored as predictors. In the whole group of patients, Avg-IMT (HR = 1.68, 95% CI 1.17, 2.42; p = 0.005) and Max-IMT (HR = 1.15, 95% CI 1.03, 1.26; p = 0.035) were significantly associated with earlier father’s death after adjustment for covariates listed in the legend of the table. Similarly, Avg-IMT (HR = 1.53, 95% CI 1.03, 2.26; p = 0.035) and Max-IMT (HR = 1.17, 95% CI 1.04, 1.32; p = 0.01) were significantly associated with earlier mother’s death.

3. Results

Patients’ characteristics are shown in Table 1. The group was balanced by gender. Ages ranged from 14 to 79 years, mean ± S.D. 55 ± 11.6 years. About one-third of the patients were ex-smokers and one-fifth current smokers. As expected, most patients were dyslipidemic. At the time of the study, 19.6% of the fathers and 43.2% of the mothers were still alive. The median age was 70 and 73 years for fathers and mothers, respectively. About 54.5% of the fathers and 51.7% of the mothers had lived longer than 69 and 73 years, respectively. Carotid IMT values were widely distributed from normal to overtly atherosclerotic, with an Avg-IMT ranging from 0.4 to 2.1 mm and Max-IMT ranging from 0.4 to 5.9 mm.

The association between parents’ ages and IMT variables was first evaluated by Kaplan–Meier survival analysis (Fig. 1). By considering total mortality, a significant difference in survival curves of the parents of patients with high or low carotid Max-IMTs was observed (p = 0.02 and 0.006 by log-rank test for fathers and mothers, respectively), low IMTs being associated with long-lived parents. Similar results were observed if Avg-IMT was used instead of Max-IMT (data not shown).

A Cox proportional hazards regression model was used to calculate the adjusted hazard ratio (HR) for parent’s death (Table 2). Both Avg-IMT and Max-IMT were explored as predictors. In the whole group of patients, Avg-IMT (HR = 1.68, 95% CI 1.17, 2.42; p = 0.005) and Max-IMT (HR = 1.15, 95% CI 1.03, 1.26; p = 0.035) were significantly associated with earlier father’s death after adjustment for covariates listed in the legend of the table. Similarly, Avg-IMT (HR = 1.53, 95% CI 1.03, 2.26; p = 0.035) and Max-IMT (HR = 1.17, 95% CI 1.04, 1.32; p = 0.01) were significantly associated with earlier mother’s death.

3. Results

Patients’ characteristics are shown in Table 1. The group was balanced by gender. Ages ranged from 14 to 79 years, mean ± S.D. 55 ± 11.6 years. About one-third of the patients were ex-smokers and one-fifth current smokers. As expected, most patients were dyslipidemic.

At the time of the study, 19.6% of the fathers and 43.2% of the mothers were still alive. The median age was 70 and 73 years for fathers and mothers, respectively. About 54.5% of the fathers and 51.7% of the mothers had lived longer than 69 and 73 years, respectively. Carotid IMT values were widely distributed from normal to overtly atherosclerotic, with an Avg-IMT ranging from 0.4 to 2.1 mm and Max-IMT ranging from 0.4 to 5.9 mm.

The association between parents’ ages and IMT variables was first evaluated by Kaplan–Meier survival analysis (Fig. 1). By considering total mortality, a significant difference in survival curves of the parents of patients with high or low carotid Max-IMTs was observed (p = 0.02 and 0.006 by log-rank test for fathers and mothers, respectively), low IMTs being associated with long-lived parents. Similar results were observed if Avg-IMT was used instead of Max-IMT (data not shown).

A Cox proportional hazards regression model was used to calculate the adjusted hazard ratio (HR) for parent’s death (Table 2). Both Avg-IMT and Max-IMT were explored as predictors. In the whole group of patients, Avg-IMT (HR = 1.68, 95% CI 1.17, 2.42; p = 0.005) and Max-IMT (HR = 1.15, 95% CI 1.03, 1.26; p = 0.035) were significantly associated with earlier father’s death after adjustment for covariates listed in the legend of the table. Similarly, Avg-IMT (HR = 1.53, 95% CI 1.03, 2.26; p = 0.035) and Max-IMT (HR = 1.17, 95% CI 1.04, 1.32; p = 0.01) were significantly associated with earlier mother’s death.

3. Results

Patients’ characteristics are shown in Table 1. The group was balanced by gender. Ages ranged from 14 to 79 years, mean ± S.D. 55 ± 11.6 years. About one-third of the patients were ex-smokers and one-fifth current smokers. As expected, most patients were dyslipidemic.

At the time of the study, 19.6% of the fathers and 43.2% of the mothers were still alive. The median age was 70 and 73 years for fathers and mothers, respectively. About 54.5% of the fathers and 51.7% of the mothers had lived longer than 69 and 73 years, respectively. Carotid IMT values were widely distributed from normal to overtly atherosclerotic, with an Avg-IMT ranging from 0.4 to 2.1 mm and Max-IMT ranging from 0.4 to 5.9 mm.

The association between parents’ ages and IMT variables was first evaluated by Kaplan–Meier survival analysis (Fig. 1). By considering total mortality, a significant difference in survival curves of the parents of patients with high or low carotid Max-IMTs was observed (p = 0.02 and 0.006 by log-rank test for fathers and mothers, respectively), low IMTs being associated with long-lived parents. Similar results were observed if Avg-IMT was used instead of Max-IMT (data not shown).

A Cox proportional hazards regression model was used to calculate the adjusted hazard ratio (HR) for parent’s death (Table 2). Both Avg-IMT and Max-IMT were explored as predictors. In the whole group of patients, Avg-IMT (HR = 1.68, 95% CI 1.17, 2.42; p = 0.005) and Max-IMT (HR = 1.15, 95% CI 1.03, 1.26; p = 0.035) were significantly associated with earlier father’s death after adjustment for covariates listed in the legend of the table. Similarly, Avg-IMT (HR = 1.53, 95% CI 1.03, 2.26; p = 0.035) and Max-IMT (HR = 1.17, 95% CI 1.04, 1.32; p = 0.01) were significantly associated with earlier mother’s death.

3. Results

Patients’ characteristics are shown in Table 1. The group was balanced by gender. Ages ranged from 14 to 79 years, mean ± S.D. 55 ± 11.6 years. About one-third of the patients were ex-smokers and one-fifth current smokers. As expected, most patients were dyslipidemic.
Fig. 1. Fathers’ (top panel) and mothers’ (bottom panel) survival-distribution curves estimated by Kaplan–Meier analysis of subjects having high (upper tertile: —) or low (lower two tertiles: ——) age-adjusted carotid Max-IMTs.

Since a potential bias might arise from parents’ differences in social, nutritional and medical status between old and young subjects (Cohort effect), the analyses were repeated after dividing the patient population into young (<65 years) and old (≥65 years) subjects. Even after this stratification, the differences in father’s and mother’s Kaplan–Meier survival curves associated with high or low Max-IMT were still significant in both groups (data not shown). The HRs obtained by applying the Cox model to the two groups are shown in Table 2. The differences in HRs between the two strata were tested by computing the interaction terms between IMT size and age group. In no case, was the interaction significant, either for Avg- or Max-IMT, which suggests that any Cohort effect is not strong. Lastly, when a stratified Cox analysis was performed, considering age classes in 10-year spans, the association between both Max-IMT and Avg-IMT with parent’s longevity was still significant (data not shown). No gain in precision was obtained when total mortality was replaced with offspring reported putative cardiovascular mortality. In this analysis, indeed, after adjustment for the same covariates listed in Table 2, Avg-IMT (HR = 1.74, 95% CI 1.10, 2.73; p = 0.017) but not Max-IMT (HR = 1.12, 95% CI 0.97, 1.29; p = 0.115) were significantly associated with earlier father’s death; and both Avg-IMT (HR = 1.46, 95% CI 0.91, 2.36; p = 0.035) and Max-IMT (HR = 1.18, 95% CI 1.03, 1.36; p = 0.02) were significantly associated with earlier mother’s death. Kaplan–Meier and Cox analyses were also repeated after dividing the patient population into those reporting a family history of vascular disease (n = 373) or not (n = 220). The differences in the parents’ survival curves of patients with high or low Max-IMT were still present (data not shown); no significant interaction between IMT size and reported family history was observed. Significances were not modified even after dividing the patient population into those reporting a family history of hyperlipidemias (n = 259) or not (n = 334) (data not shown).

3.1. Combined effect of father’s and mother’s longevity on offspring’s IMT

After stratification into patients having no (n = 69), one (n = 212) or two long-lived parents (n = 217), the three groups did not differ in terms of anamnestic clinical or biochemical variables, with the exception of the slightly higher age of patients with no long-lived parents (60.9 ± 8.1; 58.1 ± 8.6; 57.9 ± 7.7 y for “none”, “only one” and “both parents” long lived, respectively; p = 0.05) and a marginally higher total cholesterol in those with both long-lived parents (6.78 ± 1.12; 6.73 ± 1.19; 6.31 ± 1.20 for “none”, “only one” and “both parents” respectively; p = 0.06). These differences were not modified after dividing the patient population into those reporting a family history of vascular disease (n = 373) or not (n = 220). The differences in the parents’ survival curves of patients with high or low Max-IMT were still present (data not shown); no significant interaction between IMT size and reported family history was observed.
6.67 ± 1.08; 7.09 ± 1.57 mmol/L for “none”, “only one” and “both parents” long lived, respectively; \( p = 0.002 \). A significant trend for both Avg-IMT and Max-IMT was observed across the groups even after adjustment for relevant covariates (Fig. 2).

4. Discussion

This study, performed in a fairly large group of subjects attending a Lipid Clinic, suggests that parents’ longevity is associated with lower IMT values of extracranial carotid arteries even when potentially confounding variables are taken into account. Thus, parents’ longevity may affect IMT, independent of the individual vascular risk profile. Inheritance of a predisposition to longevity from both parents results in the most favourable IMT profile. This protects against atherosclerosis is evident at the highest cholesterol levels of subjects with both long-lived parents, which suggests that heritable protective factors, not yet identified, influence the development of carotid atherosclerosis and act synergistically when inherited from both parents. Our data, based on an early surrogate index of atherosclerosis, agree with those reported by Rosengren et al., who showed [33] that the risk of fatal and non-fatal cardiovascular events decreases continuously with increasing parental age, this association being, like that observed in our study, independent of the major cardiovascular risk factors.

A number of epidemiological studies have shown an association between family history of cardiovascular diseases and the incidence of clinical events [2,10,34], but only a few have examined the role of a family history of cardiovascular events as a predictor of early carotid artery atherosclerosis. In the Cardiovascular Health Study (CHS), a positive association between family history of myocardial infarction and carotid IMT was found [18]. Similarly, Zureik et al. reported an association between parental history of premature death for CHD and the presence of carotid plaques [19]. In contrast, in a Finnish study [35], the severity of carotid atherosclerosis was not associated with a family history of ischemic heart disease. All these studies, however, have focused on the familial pattern of risk factors. This traditional approach, especially when performed in elderly populations, has been recently criticized [19] because of potential survival and self-selection biases. For instance, the survivors might present a low prevalence of carotid plaques merely because subjects with a positive family history of CHD may have died at an earlier age, thus not contributing to the statistical analysis. Our study, instead of evaluating the familial pattern of risk factors or the parents’ history of premature death, has focused on parents’ longevity and strongly suggests that a family history of long-living parents determines carotid IMT in a positive way.

It might be postulated that this relationship arises from a Cohort effect because mothers or fathers of young patients had lifestyles different from those of older ones (e.g. exposure to war or other). This hypothesis was ruled out by the same results being obtained after stratification of the patients into young and old or into 10-year-age classes.

The possibility that the effect observed in the whole group was attributable to a higher prevalence of subjects with a family history of vascular diseases in the subjects included in the highest IMT tertile group was also excluded.

All cause mortality rather than cardiovascular mortality was used in the present study because of the impossibility to obtain in each patient the medical records necessary to validate the putative cardiovascular mortality reported by offspring. Despite this, all the analyses were also repeated by using this information and the associations between parents’ longevity and ultrasonic variables remained significant but did not improve. This lack of improvement suggests that the offspring reported parents’ cardiovascular mortality is not sufficiently trustworthy to be used in this kind of analyses.

The study examined subjects with dyslipidemias in a large majority. This choice could have introduced a bias selection, which could render the reported conclusions not applicable to the general population. Familial hypercholesterolemia, indeed, is associated with premature cardiovascular disease [36,37] and decreased life expectancy [38–40].
Since many of the patients recruited in a Lipid Clinic may have familial hypercholesterolemia or familial combined hyperlipidemia, which means that also many of their parents may have suffered from dyslipidemia as well, the observed parents longevity protective effects might be “lipid-specific” and do not by definition, confer “general genetic protection” against atherosclerosis. This possibility, however, was ruled out by the same results being obtained also after stratification of the patients into those reporting a family history of hyperlipidemia or not.

To the best of our knowledge, this is the first study showing that longevity may be considered as a heritable protective factor for carotid atherosclerosis. Longevity is affected by a health-promoting environment interacting with genes coding for disease resistance and long survival [33]. If environmental factors remained unchanged from one generation to another, a similarity between parents and offspring with respect to longevity would be expected. Similarities in age at death in parents and offspring were already shown in the first part of the last century [21–23], and later studies confirmed that parental survival is an independent predictor of longevity [24,41]. The results reported here provide for the first time a potential explanation for this association by showing that independent of the presence of conventional vascular risk factors, individuals with long-lived fathers or mothers may inherit a familial resistance to atherosclerosis. Obviously, before parents’ longevity can be effectively included as a protective factor in models for the prediction of atherosclerotic disease, further studies in larger and prospectively characterized groups of patients are needed to confirm the association between this parameter and (a) coronary atherosclerosis, (b) occurrence of cardiovascular events, and even (c) offspring’s longevity. In addition, since the mechanism by which parental longevity and offspring’s atherosclerosis are related is not known, and since it is not known to what extent genetic and/or environmental variables affect this relationship, appropriate studies need to be carried out in order to identify the factor(s) involved. If such factors could be identified, it would be possible by acting on them, to improve clinical results, till now obtained only by prevention and treatment of vascular risk factors.

Finally, if the protective nature of a long-lived family history is confirmed, the addition of this variable to algorithms for the cardiovascular global risk calculation [42–44] might improve their predictive power. Asymptomatic atherosclerotic patients who may need preventive treatment may thus be identified, as well as patients lucky enough to have long-lived parents and low carotid IMTs, who may not need preventive drug treatment despite an unfavourable vascular risk profile.

References