

Ear lobe crease: a marker of coronary artery disease?

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Abstract

The ear lobe crease (ELC) has been defined as a deep wrinkle that extends backwards from the tragus to the auricle. It has been proposed that ELC is a predictor of coronary artery disease (CAD). In this review, we consider the possible association between ELC and CAD. Our aim is to systematically address all the relevant evidence in this field. There are many studies that support an association between ELC and CAD. However, other studies did not find such an association. A recent meta-analysis supports the hypothesis that ELC could be a marker of CAD. However, several limitations raise doubts as to whether we should accept this link.

Key words: ear lobe crease, coronary artery disease, Frank's sign.

Introduction

Coronary artery disease (CAD) is a leading cause of death [1]. It is estimated that by 2030, 40.5% of the US population will have some form of cardiovascular disease (CVD) and the real indirect medical cost relevant to CVD is expected to increase by 61% [1].

Several algorithms have been used to predict CAD or cardiovascular events without the use of invasive methods. These include the Framingham [2], PROCAM (Prospective Cardiovascular Münster) [3] and SCORE (Systematic COronary Risk Evaluation) [4] engines that predict risk in populations without CVD as well as the Diamond Forrester algorithm which predicts the probability of having significant CAD in symptomatic patients [5]. In a recent study, the Framingham risk score seems to outmatch the other three risk scores in 1,296 stable chest pain patients, who underwent cardiac computed tomographic angiography (CCTA) to assess CAD (≥ 1 lesion with luminal stenosis of $\geq 50\%$) [6]. However, the algorithms often overestimate the prevalence of CAD [7].

Coronary angiography and CCTA are used to diagnose or rule out CAD [8]. However, these invasive techniques have limitations since they involve exposure to radiation and the administration of contrast agents [9, 10]. Contrast-induced nephropathy is associated with prolonged hospitalization as well as increased cardiovascular morbidity, renal morbidity and all-cause mortality [10].

There is a need for additional markers which might identify individuals at high risk of CAD. The ear lobe crease (ELC), a simple clinical sign first described by Frank in 1973 [11], could be a potential predictor of CAD. Since then, numerous studies have evaluated the potential link between ELC and risk of CAD [12–15].

In this review, we describe the possible association between ELC and CAD. Our aim is to systematically address all the relevant evidence in this field.

Search criteria

We searched PubMed up to 1st of November 2014 using combinations of the following keywords: earlobe crease, ear lobe crease, ear-lobe crease, ear crease, ear creases, coronary artery disease and Frank's sign. Randomized controlled trials, original papers, review articles and case reports are included in the present review. References of these articles were scrutinised for relevant articles.

Pathogenesis

The ELC is a deep wrinkle, either unilaterally or bilaterally, that extends approximately 45° backwards from the tragus to the auricle. Several mechanisms have been proposed to link ELC with CAD.

It seems that the prevalence of ELC increases with advancing age [16–20]; the same is true for CAD [21, 22]. The ELC is absent at birth and usually appears later in life [23, 24]. Recently, a study involving Japanese male patients with an ELC and metabolic syndrome (a risk factor of CAD) demonstrated the presence of shortened telomeres (extreme ends of chromosomal DNA; the shortening of telomeres implies ageing) in peripheral white blood cells [25, 26].

In a case report, Sapira suggested a link between macrophage activity (which is involved in atherosclerosis), aging and maintaining ear lobe collagen [27].

The ELC and CAD are apparently related to the loss of elastin and elastic fibre [28]. In a subgroup analysis of 421 patients with myocardial infarction (MI) and 421 controls, biopsies of the ear lobes ($n = 12$) revealed tears of the elastic fibres in all subjects with ELC, but not in the 2 subjects with neither MI nor ELC [28].

The ELC may be a consequence of the sleeping position and in its early stages may 'resolve' during the day [23, 27, 29].

The link between ELC and CAD across different ethnic populations supports the possibility that there is a common genetic factor involved [19, 30, 31]. However, we need to consider that this link may be less evident in some ethnicities.

Epidemiology

Studies showing a positive association between ELC and CAD

The possible association between ELC and CAD was first described by Frank in 1973, when he observed that 19 out of 20 patients with an ELC had at least one of the known risk factors for CAD [11]. Small studies with < 10 subjects suggested an association between ELC and CAD [32–38].

The first controlled study that examined the relationship between ELC and CAD was carried out in a USA coronary-care unit [39]. Lichstein *et al.* found that 47% of 531 patients from New York who had acute MI had ELC (unilateral or bilateral), which was significantly greater than the 30% observed among 305 age-matched control subjects with no clinical evidence of CAD ($p < 0.001$) [39].

Others (publishing in the form of letters to editors) have also supported the possible association between ELC and CAD [40, 41]. Christiansen *et al.* examined the prevalence of diagonal ELC among 523 Danes (320 men) admitted to a medical-surgical unit [40]. The prevalence of ELC in patients with an acute MI aged from 50 to 59 (46.8%) was significantly greater than in an age-matched control group (31.6%) [40]. Similar results were obtained in a group aged 60 to 69 years but not in those aged 70–79 years and > 80 years. The investigators concluded that a significant correlation was found between ELC and both CAD ($p < 0.02$) and increasing age of the patients ($p < 0.0001$). Of note, a stronger correlation was found between CAD and ELC than between CAD and other risk factors such as hypertension, smoking and diabetes [40].

In an autopsy study, Lichtstein *et al.* found a positive correlation between diagonal ELC and severe CAD. Subjects with bilateral ELC had more severe CAD than those without ELC ($p < 0.01$) and with unilateral ELC [41].

In 1978, Kaukola reported that 69% of the men and 69% of the women among 219 patients from Finland (165 men, age range: 32–65 years) who sustained an MI had a diagonal ELC. The prevalence of ELC was significantly greater when compared with the prevalence of 24% in a group of 290 healthy, similarly aged subjects (236 men) [42].

In another Finnish study by Kaukola *et al.* [30], from 286 patients (age range: 26–66) who underwent coronary angiography because of typical symptoms or signs of CAD or atypical chest pain, 200 (174 men; mean age: 48) had $\geq 50\%$ stenosis (CAD) in ≥ 1 coronary artery and 86 individuals (35 men; mean age: 50 years) were without any significant stenosis ($\leq 50\%$). The prevalence of ELC in the group with CAD was 72%, whereas in the group without CAD it was only 21% ($p < 0.001$). The authors [30] concluded that the prevalence of

diagonal ELC increases with age and severity of CAD but showed no correlation between ELC and other coronary risk factors such as high cholesterol, high triglycerides, low high-density lipoprotein cholesterol, hypertension, smoking, diabetes and obesity [30].

In 1982, the same author [43] examined the possibility that ELC is inherited. He evaluated 41 male patients (mean age: 44 years) with previous MI and their 134 first-degree relatives, in order to document the prevalence of ELC [43]. The ELC was present in 59% of the patients with MI. From the 74 relatives of this group, those with CAD, approximately 50% of the parents, approximately 25% of healthy brothers and 31% of healthy sisters also had ELC. None of the children had ELC. Kaukola concluded that those results do support an association between ELC and CAD but do not indicate that ELC is an inheritable sign [43].

Sprague examined 222 patients in the USA, who were scheduled for elective surgery [17]. He found that ELC increased with age as only 3 patients out of 120 < 40 years old had the sign whereas the sign was visible in 61 out of the remaining 102 patients who were older than 40 years ($p < 0.0001$, by our calculation, Fisher's test). Among those 102 patients, 50 had CAD. The prevalence rate of ELC in patients with CAD was 82%, and this was significantly higher than the 38.5% observed in the remaining 52 patients without CAD ($p < 0.0001$, by our calculation, Fisher's test). Sprague concluded that ELC was positively related with CAD, age and increased complications of anaesthesia [17].

Doering *et al.* compared 50 patients with CAD with 38 patients without CAD in the USA on the basis of age, weight, smoking history, diabetes and the presence of an ELC. All the above factors were correlated with CAD, but the strongest correlation was noted between CAD and ELC ($p < 0.001$) [44].

Kristensen found a positive correlation between bilateral diagonal ELC and CAD in 74 male hypertensive Danes when compared with 29 normotensive control age-matched males ($p < 0.005$) [45]. On the other hand, no genetic factor seemed to be involved in the cause and development of the ELC [45].

A very strong relationship between ELC and CAD was found in a Polish study where 72 patients out of 160 with CAD and only 23 patients out of 340 without CAD had ELC ($p < 0.00001$) [46].

In a study from Israel, Shoenfeld *et al.* found a higher prevalence (77%) of ELC in 421 patients with MI when compared with a 40% prevalence rate of 421 controls ($p < 0.05$) ($p < 0.0001$, by our calculation, Fisher's test), regardless of age [28]. Moreover, the prevalence of ELC was even higher in MI patients with diabetic retinopathy, hyper-

tension, and in Ashkenazi Jews compared with non-Ashkenazi Jews [28].

Pasternac and Sami [18] assessed 340 Canadian patients who underwent coronary arteriography; 75.6% of them had CAD. The prevalence of CAD in patients with ELC was 91.1%. This was significantly higher ($p < 0.001$) when compared with the 60.5% for patients without ELC. Of note, the positive predictive value of ELC in men was 95.7% while in women it was much lower (66.7%) [18]. The authors concluded that ELC has a high predictive value for CAD, but its absence does not rule out such a disease [18].

In a large study, Elliot suggested that ELC should be regarded as a risk factor of CAD [47]. Among 1000 patients who were admitted to large urban medical centres in St. Louis, Missouri (USA), ELC was present in 275 out of 376 patients with CAD, whereas it was seen in only 98 out of 624 patients without CAD ($p < 0.00001$) [47]. Similar results were seen in a subgroup analysis of the above study; among 205 patients who underwent coronary angiography 121 out of 148 patients with CAD had ELC [47]. In another prospective, subgroup analysis of the same study, in 112 patients who underwent cine coronary angiography only ELC and previous MI were found to significantly correlate with CAD proved by angiography ($p < 0.00001$ and $p < 0.002$, respectively) [47]. Of note, patients were considered as having CAD if coronary angiography showed $> 75\%$ stenosis of ≥ 1 major coronary artery and if they had an acute MI or history of angina [47].

Similar results were obtained in 1000 Japanese patients (573 men) [48]. The ELC was present in 58 out of 237 (24.5%) patients with CAD, a prevalence which was significantly greater than that of 35 out of 720 (4.8%) patients without CAD ($p < 0.001$) [48]. In addition, in a subgroup analysis of the above study, in 200 patients who underwent coronary angiography ELC was present in 31 out of 119 (26.1%) patients with $> 50\%$ stenosis of ≥ 1 major coronary artery but in only 3 out of 81 (3.7%) without CAD ($p < 0.01$) [48]. The ELC was also found to correlate significantly with male sex, age > 50 years, hypertension and smoking. However, in a multivariate analysis in the 200 patients who underwent coronary angiography, CAD and age > 50 years were significantly related to the presence of ELC while the other risk factors appeared to be unrelated [48]. The authors concluded that, apart from the increased prevalence of ELC with advancing age, ELC is an independent predictor for CAD in Japanese adults. Of note, the prevalence of ELC in this population is very low when compared with the results of studies in Europe and America [48].

The overall incidence of bilateral diagonal ELC in 350 non-selected patients was 45%, with

a significant increase over the age of 50 years old ($p < 0.001$) [49]. The CAD was present in 65% of patients with ELC, a prevalence that was significantly greater than that of 23% of patients without ELC ($p < 0.001$). In addition, it was shown that diagonal ELC is significantly associated with hypertension ($p < 0.01$), sex (higher incidence of ELC was observed in males (66%) than in females (34%), ($p < 0.02$)), smoking ($p < 0.05$) and hypercholesterolaemia ($p < 0.05$), but no relationship was observed with diabetes mellitus and obesity [49].

Lesbre *et al.* found a significant association ($p < 0.001$) between ELC and CAD (> 75% stenosis in ≥ 1 main coronary artery) in 172 patients [50]. Sensitivity, specificity and positive predictive value of ELC for detecting CAD were 75, 57.5 and 80.3%, respectively. The authors concluded that ELC should be considered as a marker of CAD, independently of other risk factors [50].

In an autopsy study, Cumberland *et al.* examined the relationship between ELC and severe CAD (> 75% stenosis of ≥ 1 major coronary artery) in 800 patients in the USA [51]. The authors found that the presence of ELC was significantly correlated with severe CAD ($p < 0.01$) and that the absence of ELC is a predictor of the absence of severe coronary atherosclerosis [51].

Similar results were seen in 376 postmortems (206 men) carried out in the UK [52]. The risk of death from MI in men with ELC was 2.50 whereas in women it was 3.70. In addition, the relative risk of a male with bilateral diagonal ELC having severe CAD (> 75% stenosis of a coronary artery) was 1.64 and for females it was 3.65. The sensitivity and specificity of bilateral diagonal ELC for detecting severe CAD were 62.1% and 65.9% for men and 69.2% and 78% for women, respectively. The authors concluded that ELC could be a useful sign of atherosclerosis [52].

In another necropsy study in the UK, Kirkham *et al.* found a strong association between ELC and a cardiovascular cause of death in men and women after age, height, and diabetes had been adjusted for [53].

In an Indian population, Verma *et al.* reported that bilateral diagonal ELC was significantly more pronounced in patients with documented CAD ($p < 0.001$) and that the prevalence of ELC increases with advancing age [16, 54]. Of note, the combined presence of ELC and ear canal hair represented a more sensitive index of CAD [16, 54].

In 1989, in the Copenhagen City Heart Study, 14 223 healthy persons were followed for 6.5 years in order to determine the relationship between diagonal ELC and the development of a first acute MI [55]. Of note, the right ELC was examined. After adjusting for age and sex, the authors concluded that those with ELC had a risk of acute

MI, 1.4 times greater than those without [55]. The same team 2 years later reported similar results [56]. In addition, in a recent (2014) prospective cohort study, Christoffersen *et al.* followed up the same population until 2011 [57]. The authors concluded that visible signs such as ELC, male pattern baldness and xanthelasmata, alone or in combination, are associated with increased risk of CAD and MI in the general population, independent of age and cardiovascular risk factors [57].

Miric *et al.* found that among 243 patients from Croatia, ELC was present in 72.7% of 143 with proven CAD and in 48% of the remaining 100 patients without CAD ($p < 0.001$) [58]. Additionally, ELC was more prevalent in patients older than 50 years than in younger patients [58].

In a Japanese autopsy study, where 100 men aged from 50 to 79 years old, who died free of vascular diseases or related conditions, were studied, Ishii *et al.* concluded that ELC provides a significant external marker for atherosclerosis [59].

In a prospective, cohort study which was conducted in St. Louis (USA), 108 patients were followed up for 8 to 10 years in order to ascertain whether the diagonal ELC is associated prospectively with future death or cardiac events [60]. During that time 58 deaths occurred. The prevalence of death due to acute MI, sudden cardiac death or heart failure was greater in patients with ELC whether they had CAD ($p = 0.008$) or not ($p < 0.001$) compared with patients without ELC [60]. In addition, the prevalence of cardiac events such as cardiac death, nonfatal MI, or coronary artery bypass surgery was also higher in patients with ELC whether they had CAD ($p = 0.009$) or not ($p < 0.001$) compared with those without ELC [60]. In this study, Elliott and Karrison suggested that diagonal ELC is associated with increased all-cause and cardiac morbidity and mortality [60]. Apart from the above findings, Elliott and Powel additionally demonstrated for the first time in a living population (264 patients) a graded association between the number of creased ears (i.e. unilateral or bilateral) and future coronary risk [61].

In a Brazilian study of 1464 patients (760 men), Tranchesi *et al.* found that ELC was present in 220 out of 338 patients (65%) with CAD (> 70% stenosis of ≥ 1 coronary artery documented by angiography), and this prevalence was significantly greater when compared with the 28% of 1086 patients without CAD ($p < 0.0001$) [62]. In addition, the sensitivity of ELC was 65%, the specificity 72%, the positive predictive value 42% and the negative predictive value 87% for the diagnosis of CAD. Of note, ELC was more prevalent in the white (41%) than in the non-white population (23%). However, the prevalence of ELC in both populations was significantly greater in patients

with CAD [62]. Moreover, the presence of ELC was also related to the severity of CAD. When the stenosis was present in 1 to 3 coronary arteries, the prevalence of ELC increased from 55% to 78% ($p = 0.015$) [62].

The association between ELC and CAD was found to be significant in 247 patients admitted to an acute general hospital in Dublin, Ireland [63]. The prevalence of ELC did not differ between males and females. In addition, no correlation was found between ELC and smoking, hypercholesterolaemia, hypertension, peripheral arterial disease or stroke.

Similar results were found in a non-cardiac patient population in London [64]. Motamed *et al.* reported a significant association between ELC and a history of CAD and that the ELC and CAD correlation was higher than that of CAD and other risk factors. However, the sensitivity, specificity and positive predictive value of the sign was 48%, 88% and 16%, respectively. These findings are of little clinical importance [64].

In a Croatian case-control study, Miric *et al.* found that diagonal ELC was present in 62.9% of 842 men (< 60 years old) admitted for the first non-fatal MI, and that this prevalence was greater than that of 46% of 712 age-matched controls admitted with non-cardiac diagnoses and without clinical signs of CAD [65]. The relative risk ratio (95% CI) of MI for men with ELC was 1.37 (1.25–1.5). This did not change when it was adjusted for age and other risk factors [65]. The authors concluded that dermatological signs such as baldness, thoracic hairiness and diagonal ELC indicate an additional risk of MI in men under the age of 60 years, independently of age and other established coronary risk factors [65]. One of the authors of the above study suggests that the presence of these dermatological signs (ELC, baldness, hair greying and wrinkling of the skin) in patients could be indicators of atherosclerosis [66].

Kuri *et al.* evaluated the usefulness of the ELC sign as a marker of CAD in 530 Japanese patients, aged > 40 years old, who were undergoing elective surgery [67]. The authors concluded that ELC may be a useful marker for the presence of CAD in patients for whom little or no history and investigations are available [67].

In a large study in Turkey, 3722 individuals (1250 males) were evaluated for the presence of ELC in diseases such as diabetes mellitus, hypertension, MI and CAD [68]. The authors suggested that ELC could be a valuable sign in diagnosing and screening such diseases. Of note, ELC was more pronounced in males than in females [68].

In 2004, also in Turkey, Evrengül *et al.* examined 415 patients (306 men) for the presence of bilateral ELC. There was a greater prevalence of

ELC in 296 patients with documented CAD (> 70% stenosis of 1 of the 3 major coronary arteries) by angiography (51.4%) than in 119 patients (15.1%) without CAD ($p < 0.0001$) [69]. Sensitivity of bilateral ELC was 51.3%, specificity was 84.8%, the positive predictive value was 89.4% and the negative predictive value was 41.2% for the diagnosis of CAD. The ELC was an independent variable for CAD. Of note, the presence of bilateral ELC was significantly associated not only with CAD but also with other coronary risk factors such as hypertension, male gender and smoking. There was no association between ELC, diabetes, lipidaemia and obesity. The authors concluded that bilateral ELC might be a useful sign in clinical practice [69].

In a Swedish autopsy study, 55% of 520 subjects (420 males, mean age 56) had diagonal ELC [70]. There was no significant difference between the presence of ELC in males (53.8%) and females (60%). The ELC was unilateral in 8.8% and bilateral in 91.2% of the subjects. The prevalence of ELC was 65.4% in those with CAD and 73.3% in victims of sudden cardiac death, a difference which was significant when compared with 46.1% and 57.9%, respectively in the control groups [70]. The sensitivity, specificity and positive and negative predictive values for those < 40 years old were 0.68, 0.84, 0.80, 0.72, respectively; for those between ages 40 and 50 years old, they were 0.68, 0.60, 0.63, 0.66, respectively; and for those over 60 years old they were 0.79, 0.33, 0.51, 0.61, respectively [70]. The authors concluded that ELC could be useful in screening for premature CAD in younger individuals [70]. Of note, there was a significantly greater heart weight in patients with ELC than in those without ELC ($p < 0.0001$) and in those dying from sudden cardiac death compared with deaths from other causes ($p < 0.0001$) [70].

In a Spanish study, Lamot *et al.* found a significant relation between the presence of a diagonal ELC and CAD and suggested that this sign could be useful in clinical practice, mainly among patients aged between 30 and 60 years [71].

In a recent study carried out in the USA, the relation between diagonal ELC and CAD was examined in 430 patients without history of CAD who underwent coronary angiography [72]. Severe CAD was documented when > 50% stenosis was found in ≥ 1 coronary artery in the angiography. The CAD was categorized as any CAD, significant CAD, ≥ 2 diseased vessels and ≥ 3 diseased segments. All categories of CAD were more prevalent in the group with diagonal ELC than in the group without diagonal ELC ($p < 0.001$, for all comparisons). Diagonal ELC was present in 71% of all the patients and, similarly, the prevalence of any CAD was 71% of all the patients. The prevalence of any CAD in 307 patients with diagonal ELC was

77%. This was significantly greater when compared with that of 55% of 123 patients without diagonal ELC ($p < 0.001$). In addition, sensitivity, specificity, positive and negative predictive values for diagonal ELC to diagnose any CAD were 78, 43, 77 and 45%, respectively [72]. Of note, Shmilovich *et al.* were the first to report that diagonal ELC is associated with the presence, extent, and severity of CAD and that this association remained even after adjusting for age, male gender and other risk factors for CAD [72].

The same author, in a more recent study, probably in the same population as for the above study, found that diagonal ELC is a superior predictor of CAD (> 50% stenosis of coronary arteries) than the Diamond Forester algorithm [73]. The authors suggested that, in patients with chest pain, the combination of the diagonal ELC and Diamond-Forester algorithm was a better predictor of CAD than each alone [73].

In a Chinese study of 100 patients, the prevalence of ELC in 50 patients with CAD was significantly greater than in those without CAD ($p < 0.05$) [74]. The sensitivity, specificity and positive predictive value for diagonal ELC to diagnose CAD were 61%, 58% and 59.3%, respectively [74]. The authors suggested that ELC was associated with the presence of CAD [74].

In a Chinese cohort study, among 449 consecutive Chinese patients who underwent coronary artery angiography, the prevalence of diagonal ELC was 75.2% in 250 patients with CAD, which was significantly greater than that of 46.2% of 199 patients without CAD ($p < 0.001$) [75]. Moreover, sensitivity, specificity, positive and negative predictive values for diagonal ELC to diagnose CAD in the whole population were 75.2%, 53.8%, 67.1% and 63.3%, respectively. Diagonal ELC remained a positive predictor for CAD even after adjusting for age, gender and traditional risk factors, but not for hypertension, diabetes mellitus, hypercholesterolaemia and hypertriglyceridaemia. The authors concluded that there is a significant association between diagonal ELC and CAD independent of established risk factors among Chinese people [75].

Studies showing no association between ELC and CAD

Several studies have reported no significant correlation between ELC and CAD. The first report was an American study of 211 patients undergoing coronary angiography in which no significant association between ELC and CAD was found [76].

In a letter to the editor, Burton refers to a British study which found no significant difference between the presence of bilateral ELC in 52% of 48 males with MI and in 58% of 48 age-matched controls [77].

In 1977, among 1237 Japanese-American men, the prevalence of ELC was 30% in 71 patients with any CAD (angina, coronary insufficiency and MI), 22% in 37 patients with MI and in 32% of patients without CAD. Rhoads *et al.* concluded that no significant relation was found between ELC and CAD in Japanese-American men [78, 79].

Similar results were obtained in 216 Native American Indians, where no correlation between ELC and CAD was found.

In a small controlled study (Northern Ireland) which included 23 patients with acute MI and 23 matched controls, Farrell and Gilchrist found no correlation between ELC in the occurrence of MI [80].

Jorde *et al.* reported lack of an association between ELC and coronary risk factors such as hypertension, diabetes mellitus, smoking and obesity in 686 Americans [81].

Moreover, no significant correlations were found between ELC and CAD in 100 adult Caucasian (Vermont, USA) patients (68 men) with the clinical diagnosis of aortic stenosis who underwent coronary angiography [82]. The authors concluded that ELC is of little clinical importance [82].

In 261 consecutive men who underwent coronary angiography, ELC was present in 67% of this population [83]. The prevalence of CAD in 175 men with ELC was 85% and in 86 men without ELC it was also 85%. The authors found no correlation between ELC and CAD and concluded that their association is justifiable due to the fact that ELC and CAD both increase with age [83].

In several articles, Cheng refers to a large study from China which concluded that ELC has no predictive value for CAD in 3155 persons; ELC was attributed to age [84–86].

In a prospective Irish study, among 125 consecutive patients who underwent coronary angiography, ELC was present in 65 patients [87]. The authors found no relation between ELC and age, sex, smoking, previous MI, hypertension, family history of heart disease, body mass index or angiographically defined CAD. In this context, the authors concluded that ELC is not a marker of CAD [87].

In an Austrian prospective clinical investigation, 233 patients with CAD were evaluated [88]. Eber and Delgado suggested that the presence and extent of diagonal ELC may not be regarded as a general prognostic factor for coronary atherosclerosis [88].

Kuon *et al.* assessed 670 German patients who underwent coronary angiography. The prevalence of CAD (> 70% stenosis of coronary arteries) was 55% in patients with ELC and 55.9% in patients without ELC. No significance was found. The authors concluded that although ELC is associated with age and overweight, it does not predict CAD [89].

In a subgroup analysis of the Fremantle Diabetes Study, which included 1022 diabetic patients, the prevalence of ELC was 55% [90]. Although patients with an ELC were more likely to have CAD than those without an ELC ($p = 0.019$), the sensitivity, specificity, positive predictive value and negative predictive value of ELC for detecting CAD were 60, 48, 37 and 71%, respectively. After adjusting for coronary risk factors, the authors concluded that ELC is not a predictor of CAD [90]. Similar conclusions were reached concerning diabetic retinopathy [90].

In 2009, Koracevic and Atanaskovic reported their unpublished data from a study which they had conducted 13 years before in Serbia [91]. They evaluated 78 hospitalized patients (60 men) with mean age 60.4 years. They concluded that whether or not patients had unilateral or bilateral diagonal ELC, or whether the crease was deep or superficial, it did not represent a marker of CAD [91].

Ear lobe crease and other diseases

Numerous other studies have tried to associate ELC with other diseases or coronary risk factors such as hypertension, diabetes, stroke, metabolic syndrome, peripheral arterial disease (PAD), carotid intima-media thickness (cIMT), obesity, stress and alcohol use. Park *et al.* found a strong correlation between ELC and haemorrhagic stroke [92]. More specifically, ELC was independently associated with subarachnoid haemorrhage and intracerebral haemorrhage [92]. In a recent case report, ELC was observed in a patient with sub-acute occipital infarction in the left posterior cerebral artery [93]. Others suggested or tried to correlate ELC with stress [94], anxiety [95], schizophrenia and bipolar disorder [96]. Several studies significantly correlated the presence of ELC with hypertension [28, 69, 97, 98], while others failed to find a positive correlation of ELC with hypercholesterolaemia [99]. Furthermore, others reported an association of ELC with metabolic syndrome [25, 100] or obesity [78, 79, 89]. Controversial results have been produced regarding the association of ELC with diabetic retinopathy [28, 101, 102]. Of note, a negative association was found between the presence of ELC and alcohol use in 625 white women [103]. Interestingly, in several reports the presence of ELC was significantly correlated with cIMT [104–106], whereas only one study did not reach significance [107]. Pieri *et al.* reported 2 histological lesions in the ear lobes of diabetic patients: perivascular cellular infiltration and thickening of adventitia reticularis in arterioles, precapillaries, capillaries and venules [108]. Several studies suggested using an arterialized ear lobe blood sample for the measurement of arterial O_2 pressure (pO_2) while others indicated that arteri-

alized ear lobe blood underestimates the real value [109–111]. Recent studies found a significant correlation of ELC with PAD [112, 113]. In addition, ELC was found to have a significant correlation with brachial-ankle pulse wave velocity [114], and with the cardio-ankle vascular index [115].

Comment

It is difficult to explain why there is so much variation in the studies described above. Even 41 years after the ELC sign was first described [11] there is still uncertainty regarding its relevance.

It is important to establish whether ELC is a coronary risk factor and whether this physical sign can improve vascular risk assessment. Although the majority of studies suggested an association between ELC and CAD, there are some limitations. Age, gender, race, and ear lobe shape should not be neglected if we want to evaluate the validity of ELC as a predictor of CAD. A study by Overfield and Call [19] examined 324 healthy adult subjects (70 south western Alaskan Eskimos, 167 Navajos and 87 whites). The authors found that ELC is more frequent with age in healthy adults, creasing is related to the shape of the ear lobe, and the age of onset of creasing is influenced by race [19].

The mechanisms leading to the concurrent development of ELC and CAD remain uncertain. Ethnic differences may play an important role in the prevalence of ELC. Petrakis and Koo evaluated the prevalence of ELC in various racial groups using police arrest photographs [31]. They found an age-related increase in the frequency of ELC in White, Black and Latin-American males but no increase among the Chinese and Hawaiian-Samoans [31]. It should also be considered that ELC may only predict CAD within a limited age range [17–19]. This is because the ELC is absent at birth and rarely seen in the young, whereas it is more common in the elderly [23, 24].

The presence of the ELC may be influenced by the time of the day [27]. This is because the ELC may become more apparent after sleeping and distorting the ear lobe. This factor may need to be taken into account when the prevalence of ELC is assessed.

Medication administered to treat vascular risk factors (e.g. statins) can delay, arrest or even reverse CAD progression [116], even in the elderly [117]. Does such treatment (or lifestyle measures such as smoking cessation) also affect the progression/development of ELC? If so, then studies including patients on such treatment would have some limitations. This possibility has to be considered in the light of evidence that risk factors (hypertension, smoking, hypercholesterolaemia and diabetes) are associated with an increased

prevalence of ELC, at least in some studies (as discussed above).

A large meta-analysis that investigated the possible association of ELC with CAD was recently published [118]. In this meta-analysis which included > 31,100 patients, the overall sensitivity was 62% and the specificity was 67%. Thus, 62% of patients with CAD would be expected to have ELC, while 67% of those without CAD would be expected not to have ELC. In addition, the risk of CAD is 3.3-fold higher in patients with ELC compared with those without ELC, a conclusion that suggests ELC as a marker for CAD [118].

We also need to assess any relationship between ELC and factors affecting arterial inflammation [119] or elastance [120]. Both these processes may be involved in the pathogenesis of ELC and vascular disease. Additional markers such as metalloproteinases [121] should also be considered in the pathogenesis of CAD and ELC. There is also a need to explore the relationship between various risk engines and the presence of ELC.

Conclusions

Large-scale clinical studies are needed to reach more robust conclusions regarding the clinical significance of ELC as a predictor of CAD. Future studies should consider the variables of age, race and ear lobe shape. In addition, these studies should also address whether there are common features involved in the pathogenesis of ELC and CAD, as little is known in this field. Moreover, prospective cohort studies should follow up the newly diagnosed patients with CAD and observe any changes in their ear lobes as the disease progresses. In this context, a grading system for ELC has been proposed [82].

After taking all the evidence into consideration, we cannot state with confidence that ELC represents a marker of CAD. However, we suggest that patients with ELC may benefit from being monitored more closely for the potential presence of CAD.

Conflict of interest

This review was written independently. No company or institution supported it financially. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies.

The authors declare no conflict of interest.

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