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Mini Review

Procoagulation Factors in Cardiovascular Complications Among Individuals with Familial Hypercholesterolemia

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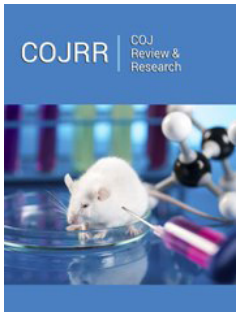

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Abstract

Familial Hypercholesterolemia (FH) is often considered to be a serious condition, causing Coronary Heart Disease (CHD) and stroke. It is generally accepted that the main cause of CHD and stroke among these people is their high cholesterol levels. However, there are too many contradictions to the theory affirming there is a direct causality between high cholesterol and Cardiovascular Disease (CVD) in these people. For instance, among individuals with FH there is no significant association between cholesterol levels and the severity of CVD. In addition, the life expectancy of individuals with FH is close to that of the population without FH. Finally, no controlled cholesterol-lowering trial in people with FH has demonstrated any significant benefit. On the other hand, studies suggest that procoagulant factors might be a critical risk factor in FH, as in patients without FH. For instance, FH individuals with CVD have high lipoprotein (a), high factor VIII and/or high fibrinogen (whereas their cholesterol does not differ) compared to those without CVD. Thus, many studies suggest that high cholesterol cannot be the cause of CVD mortality among individuals with FH. Some of them have inherited critical risk factors other than a high cholesterol. This review shows that inherited procoagulation factors may be one of the common causes of CVD in FH, not high cholesterol.

Keywords: Familial hypercholesterolemia; Cholesterol; Coagulation; Coronary heart disease; Cardiovascular disease; Lipoprotein (a); Fibrinogen; Factor VIII

Introduction

Coronary Heart Disease (CHD) and stroke among people with FH is is considered to be caused by their high cholesterol. Some studies have demonstrated that Cardiovascular Disease (CVD) is associated with high cholesterol, but many other studies have shown that the cholesterol hypothesis is not credible [1]. For example, people with low cholesterol have the same degree of risk as people with high cholesterol [2,3]. A further support of this is that the trials testing anti-CETP and anti-PCSK9 drugs did not show a lowering of total or CVD mortality although these drugs lower cholesterol much more than the statins and, in addition, do increase the supposed "good" cholesterol by about 100% [4]. In recent reviews [5,6], we have shown many contradictions to the consensus about FH and CVD. Here, we present a summary of the studies in which it is shown that only a minority of FH-people die prematurely, and that those who die have inherited various procoagulation factors, whereas their cholesterol levels do not differ from those who have a normal life expectancy.

The main contradictions

If a high cholesterol is the main cause of CVD, those with the highest values should have a higher risk compared with those with low values. In recent reviews [1-3], we show that

several studies in the non-FH population report that those with low cholesterol have the same risk as those with high values. Furthermore, five studies in FH-individuals report that cholesterol levels are not associated with degrees of various markers of risk [7-11]. It is generally believed that people with FH have a reduced life expectancy. However, this theory has been exclusively based on studies of people with FH and a family history of CVD or who already have clinical manifestations of CVD. This obviously introduces a major bias. In fact, two unbiased studies have shown that people with FH have a life expectancy comparable to the no-FH population. For instance, in the study by the Simon Broome Register group, 526 FH-individuals were followed for about four years [12]. Mortality was higher among those below age 60, but lower among the elderly. In another study, 4688 FH-individuals were followed from 1992 to 2010 [13]. During that time, CVD mortality was higher than in the general population, but total mortality was lower. Before the year 1900, the life expectancy of individuals with FH was as long as in the general population [14]. At that time, infectious diseases were the commonest causes of death. One possible reason why the life of people with FH was just as long as the life of people without FH may be that cholesterol-rich lipoproteins stimulate the immune system, a fact that has been well documented [15]. According to the cholesterol theory, cholesterol should be lowered as much as possible in individuals with FH. However, no cholesterol-lowering trial in FH has demonstrated significant benefit [6]. This is also true among individuals without FH [1-3]. Although it was claimed, for instance in a review of more than 30 statin-trials, that there was a significant benefit from the statin treatment [16], the authors only used data from twelve of the trials. When data from all trials are combined, the benefit is no longer present [1].

As the level of cholesterol in FH varies considerably, it is assumed that those individuals who suffer from CVD have higher cholesterol levels and will die earlier than those with the lowest values. Several studies have shown that age and cholesterol level in FH people with or without CVD did not differ significantly [5, 6]. Many of the participants in these studies were on statin treatment, which may have biased the results. However, five studies selected FH individuals without cholesterol-lowering treatment. Only one of these studies showed that the cholesterol level was higher in individuals with CHD [17-21]. Finally, among previous reviews on FH [5,6], ten randomized, controlled cholesterol-lowering trials that only included FH-individuals were identified. None of them succeeded in lowering CVD or global mortality, nor non-fatal CHD events. In one of them, patients with ileal bypass were compared with usual treatment [22]. Although cholesterol level was much lower in the ileal bypass group, the numbers of fatal and non-fatal events were almost identical in the two groups.

New explanations

Why do some individuals from families with FH suffer from early CHD? One possible answer is that - in addition to other classical risk factors such as smoking, diabetes, deleterious diet and others - they may have inherited other risk factors of CHD. If this is true, some of those with normal cholesterol levels in families with FH should also have a higher risk of CHD compared to the population without FH. This has indeed been shown in a study of a FH-kindred [23]. It has led to identify several other factors among FH individuals that are clearly associated with the risk of CHD. The commonest are inborn or acquired procoagulation factors and/or other thrombogenic factors, such as increased platelet aggregation. In a study of the platelet function in FH-people and non-FH people, the platelet aggregation parameters from those with FH were significantly increased [24]. Plasma fibrinogen and factor VIII levels are higher among FH people with CHD compared with those without CHD, with no difference in the levels of cholesterol [25]. In a study comparing 164 FH subjects with and without CHD (all without cholesterol-lowering treatment) with 160 subjects with “normal” cholesterol levels, the mean platelet volume was significantly higher in the FH subjects [26]. It has been shown that larger platelets are more prone to provoke formation of platelet thrombus [27]. In an analysis of DNA extracted from leukocytes in 2000 FH individuals, polymorphism in the prothrombin gene was strongly associated with CHD risk [21]. In addition, it was reported that polymorphism of the LDL-receptor - the main mechanism of high cholesterol in FH families - is associated with an increased level of coagulation factor VIII which is associated with accelerated coagulation [28].

Lipoprotein (a) [Lp(a)] is a major procoagulant factor and it is quite clear that Lp(a) is a direct cause of CHD in the non-FH population [29-31]. Obviously, Lp(a) may play the same role in FH. In a study of 388 FH individuals, the risk associated with Lp(a) was highly significant whereas the risk associated with cholesterol was non-significant [32]. In a comparison of 54 FH patients with CHD and 61 without CHD, Lp(a) was significantly higher among those with CHD, whereas cholesterol did not differ [33]. The same was found in a study of 782 FH patients with CVD and 1618 without CVD [34], and in a study of 247 FH patients with CHD and 1,713 without [35]. In the latter, cholesterol was even significantly higher among those without CHD.

Conclusion

We are showing that there is clearly little - if any-evidence that high cholesterol is the main cause of CVD in FH. In accordance, no controlled cholesterol-lowering trial in FH individuals has shown that such treatment is beneficial. It is therefore questionable to use cholesterol-lowering treatment in individuals with FH, with or without CVD. Another reason to abstain is that statins have many serious side effects [36-39]. Studies have shown that FH-individuals who suffer from CVD do have the same classical risk factors (smoking, diabetes, hypertension, deleterious diet and others) as people without FH [40]. It is likely that procoagulant factors may contribute to the additional risk associated with FH in certain families. To definitely demonstrate that procoagulation factors explain (at least partly) the risk of CVD in FH individuals, we need double-blind placebo-controlled trials testing whether anticoagulant (or antiplatelet) treatments may prevent CVD complications in FH patients.

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