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Review

Cardiovascular diseases: Traditional and non-traditional risk factors

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Abstract

Cardiovascular disease (CVD) is responsible for more number of deaths worldwide. The muscles and vessels of heart and blood transporting roads become vulnerable portion in most of the CVD. The role of hypertension and cholesterols of different density triglycerides in induction and progression of cardiovascular disease is discussed in this present review. Besides this the potential biomarkers such as homocysteine, fibrinogen, D-dimer and thrombin/anti-thrombin III complex, interleukin and serum amyloid in prognosis is also discussed in this review.

Key words: Cardiovascular disease, Diabetes, Fibrinogen, HDL, LDL

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Cardiovascular diseases (CVD) which mainly include coronary heart disease (CHD), stroke, rheumatic heart disease (RHD) and cardiomyopathy represent the leading cause of death worldwide[1]. In the early 20th century, CVD was responsible for less than 10% of all deaths worldwide, but it increased to 30% by 2001. Countries like low and middle-income have 80% deaths due to CVD. By 2020, CVD will become the leading cause of death and disability[2] in low and middle-income countries. In a year, mortality of CVD accounts ~ 9%[3]. CVD includes a wide range of disorders which includes diseases of the cardiac muscle and of the vascular systems. Potential risk factors for CVD include hypertension, tobacco use, physical inactivity, elevated low-density lipoprotein cholesterol, diabetes and a cluster of interrelated metabolic risk factors[4]. Framingham Heart Study in 1961 was the first to introduce the concept of risk factors which links the presence of high cholesterol, tobacco usage, hypertension and diabetes mellitus to future CVD[5]. Mostly CVDs are due to atherosclerosis as well as due to infections.

Traditional risk factors

Although earliest research has recognized hypertension, diabetes and hypercholesterolemia as traditional CVD risk factors, several researchers have reported their absence in a considerable portion of individuals experience clinical vascular events. Indeed, up to half of those having their first clinical vascular events does not have traditional CVD risk factors[6]. However, these findings may not be relevant to all populations, researchers from the FHS report that 50% of the patients with CHD had levels of total cholesterol (TC) ≤240 mg/dl and 20% had TC <200 mg/dl[7].

Data from the Women's Health Study (WHS) confirmed those three quarters of coronary events happen in 27,939 women without a high level of LDL cholesterol (<160 mg/dl) and 45% happen in women with normal LDL cholesterol (<130 mg/dl)[8]. When numerous large studies of CVD were reviewed, as one would expect, most individuals had one or more traditional risk factors[9]. Conversely, one fifth had none of the traditional risk factors. In

addition, among cohort individuals who did not suffered CHD, the rates of traditional cardiovascular risk factors were also relatively high[10]. Given these findings, new research has focused on ways of enhancing our ability to predict CVD. However, many of these show promise and most widely used in routine clinical practice.

Hypertension and cardiovascular disease

In its Sixth Report, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (1997) defines categorical hypertension as a BP ≥140 mmHg systolic or ≥90 mmHg diastolic or current use of antihypertensive drugs. Several observational studies have confirmed clearly a powerful relationship between high BP and CHD[11-13]. This relationship holds for both men and women and younger and older persons. Occasionally those with high BP are at higher risk of CHD[14].

Diabetes and cardiovascular disease

Risk for all forms of CVD, is increased significantly in patients with type 1 and type 2 diabetes mellitus[15,16]. The mortality rate in non-diabetic patients was less compared to diabetic patients who experienced CHD[17,18]. Hyperglycemia is considered to be the potential risk factor while it is not dependant on the normally observed characters in diabetics like obesity and dyslipidemia. Good glycemic control decreases risk for microvascular complications of diabetes. However, in diabetic patients, significant control of glucose has not been reducing the macrovascular disease (CHD), although a trend toward benefit has been observed[19].

Total cholesterol, low-density lipoprotein cholesterol and cardiovascular disease

Cholesterol is synthesized almost in all cells and considerable amounts of it can be absorbed from the diet. According to the lipid hypothesis, unusually high cholesterol levels (hypercholesterolemia), or higher concentrations of LDL cholesterol have been recognized as principle lipid risk factors[20]. Various studies have confirmed that blood TC levels have an exponential role on cardiovascular and total mortality, with the association more evident in younger subjects. In old age people, the effect of higher cholesterol on health is indeed larger[21].

Several studies have consistently confirmed that CHD risk and TC had a dose-response relationship. The Multiple Risk Factor Intervention Trial (MRFIT) screened >300,000 men and established a curvilinear relation between TC and age-adjusted CHD death rate; in MRFIT screeners with a TC level of ≥240 mg/dL, relative risk (RR) for CHD, compared with those with TC <182 mg/dL, the death rate was 3.4[22]. Conversely, except TC, there are factors influencing the risk of CHD risk was clearly established by studies of 25 years of follow-up in the Seven Countries Study (SCS)[23], in which a dose-response association between TC and CHD mortality rate was observed.

Studies across different populations demonstrate that those with higher cholesterol levels have more atherosclerosis and CHD than do those who having lower levels (Keys et al., 1984). The positive association between proportion of serum cholesterol and onset of first or consequent CHD attack, due to elevated LDL cholesterol, was observed; the higher the level, the greater the risk[24]. Prospective data recommended that the risk of CHD at lower cholesterol levels and this evident has disappeared in larger studies[24,25]. Population with very low serum cholesterol e.g. TC <150 mg/dL (or LDL cholesterol <100 mg/dL) witness the almost absence of clinical CHD throughout the life[26,27].

The association between the elevated LDL cholesterol to the onset of CHD observed to be a multistep process[28]. Atherogenesis, the fatty streak, having macrophages filled with cholesterol, is the first stage and most of them derived from LDL cholesterol. The fibrous plaques, scar tissue over lipid rich core, are the second stage. Other risk factors also contribute to plaque growth. The third stage is demonstrated the onset of plagues, prone to rupture and luminal thrombosis formation, of unstable. Plaque rupture is responsible for most acute coronary syndromes (ACS) [29,30] .

Triglycerides, very low-density lipoprotein cholesterol and cardiovascular disease

Triglyceride (TG) is an ester formed from a glycerol molecule, provided OH group each with and make up the majority of fats, which was later properly utilized by digestion. Lipids cannot be absorbed by the duodenum in TG form and it is absorbed as fatty acids, monoglycerides and some diglycerides, once the TG have been digested. In the human body, high levels of TG in the bloodstream have been linked to atherosclerosis and CHD.

Several observational studies and analysis published in the earlier years largely support TG as an independent risk factor for CHD. These studies

have been performed in populations over a wide spectrum of ages in a number of countries with quite different rates of CVD[31-34]. Traditionally, CHD events due to elevated TG were predicted in univariate analysis, after adjustment for other covariates, including plasma glucose and HDL cholesterol, to which it is strongly and inversely correlated[35]. Yet, even after adjustment for HDL cholesterol, detailed assessment of population-based prospective studies has disclosed an independent effect of TG on CHD events[36]. Coupled with the knowledge that combined hyperlipidemia promotes CHD to a significantly greater extent than either high LDL cholesterol or TG alone[37].

Very low-density lipoprotein (VLDL) cholesterol is a type of lipoprotein formed by the liver, which enable movement of fats and cholesterol within blood stream. It is accumulated in the liver from cholesterol and apolipoproteins, which converted in the bloodstream to LDL cholesterol. VLDL cholesterol transports endogenous products (such as TG, phospholipids, cholesterol and cholesteryl esters) where chylomicrons transport exogenous (dietary) products.

The most likely candidates for atherogenic TG-rich lipoproteins (TGRLP) are remnant lipoproteins. These lipoproteins include small VLDL cholesterol and lipoproteins of intermediate-density i.e., IDL. The atherogenicity of remnants was well supported by several reviews[38-40]. In several clinical studies elevation as well as their specific identification of remnants was noticed to be strong predictors of CHD[41-42].

High-density lipoprotein cholesterol and cardiovascular disease

HDL cholesterol is one of the 5 major groups of lipoproteins cholesterol, which enable lipids like cholesterol and TG to be transported within the water based blood stream. In healthy persons, about thirty percent of blood cholesterol is carried by HDL cholesterol. An increased level of HDL cholesterol protect against CVD while lowering which cause enhanced heart disease risk. When measuring cholesterol, some contained in HDL particles is considered as guardians of the cardiovascular health of the body, in contrast to "bad" LDL cholesterol.

Strong epidemiological evidence links low serum HDL to increased CHD morbidity and mortality[43,44]. High HDL cholesterol levels conversely convey reduced risk. Various epidemiological data taken as a whole suggest that a 1 percent decrease in HDL cholesterol is associated with a 2–3 percent increase in CHD risk[44]. Low HDL cholesterol, based on epidemiology studies, to be an independent risk factor for CHD and it holds after correction for other risk variables in multivariate analysis.

In fact, in prospective studies[45,46], HDL cholesterol usually the risk factor of CHD risk having high correlation with CHD risk. Adult Treatment Panel II (ATP II) at <35 mg/dL were noticed as a low HDL cholesterol, one of several major risk factors used to modify the therapeutic goal for LDL cholesterol. The definition of low-HDL cholesterol was set to be the same for both genders because the level of HDL cholesterol would impart the same risk for men and women.

Non-traditional risk markers

The epidemiological and basic science search for better understanding of the etiology of CVD has produced numerous serum markers as candidates for representing “nontraditional” risk. Several are part of the progression of inflammation - a process, now understood to be central to atherosclerotic disease[47]. Candidates have included homocysteine, plasminogen activator inhibitor-1 (PAI-1), fibrinogen, D-dimer and thrombin/antithrombin III complex; and various inflammatory markers such as CRP, interleukin (IL), serum amyloid A (SAA), MMP and adhesion molecule. However, many of these markers show promise, most are not used in routine clinical practice and the predictive power of many has not been confirmed.

Homocysteine

It was clearly understood from the literatures[48,49] that the role of homocysteine as oxidative stress indicator. As a mediator of one carbon metabolism, homocysteine, levels are associated with CVD[50-52]. It was suggested[53] (Humphrey et al., 2008) that, the level of homocysteine moderately increase the risk of CVD by 20%. Ueland et al.[54] and Van Guldener et al.[55] reported that, the one type of CVDs, like stroke and deep vein thrombosis can be reduced by reducing the level of homocysteine by 3-5 mol/L in serum.

Plasminogen activator inhibitor-1 (PAI-1)

PAI-1 is the key fibrinolysis regulator. Jugo et al.[56] based on the bivariate analysis, stated that, the PAI-1 was directly correlated with carotid intima-media thickness, BP, Body Mass Index (BMI), LDL and total cholesterol, glomerular filtration and triglycerides. Zhuang et al.[57] reported that, the patients with acute ischemic stroke had significant

amount of t-PA, while level of PAI-1 was reduced significantly. Existence of negative correlation between t-PA and PAI-1 was revealed and significant difference in activities of t-PA and PAI-1 was observed in control group, acute, convalescent and chronic groups. Tofler et al.[58] revealed that, those with CVD have higher level of PAI-1 (29.1 ng/ml) compared to those without (22.1 ng/ml) CVD. It was also observed from his experiment that, an antigen level of PAI-1 and t-PA was in strong linear relationship with CVD incidence.

Fibrinogen

Fibrinogen (Fg), the precursor of fibrin, coagulation factor described first in 1836 by Buchanan. The hematological changes such as increase in viscosity of plasma, aggregation of erythrocytes, thrombogenesis of platelets are due to increase in level of Fg[59]. Meade et al.[60], based on the epidemiological studies, stated that the risk of CVD such as ischaemic heart disease, thromboembolism and stroke increase with respect to the increase in concentration of plasma Fg.

D-dimer

The fibrin degradation marker, D-dimer, one of the important marker associated with CVD. Lind et al.[61] in his longitudinal cohort study on 719 patients with oral anticoagulant revealed the association of CVD with higher level of D-dimer. Fruchter et al.[62], based on data from clinical and laboratory, proposed D-dimer as prominent prognostic marker of short and long term survivors subjected to acute exacerbation. He also noticed the changes in the mean D-dimer level in non-survivors (3.18 mg/L and survivors (1.45 mg/L).

Interleukin

Interleukin-6, the potent prognosis indicator in serum, used as a tool for the early diagnosis of CVD based on clinical trials[63]. Reichert et al.[64] suggested from his study with 942 coronary heart disease (CHD) revealed that the polymorphism in IL-6 c.-174 CC genotype was found to be the independent risk marker of CHD. Similarly, Buraczynska et al.[65] provided an information that, the patients with diabetic (Type-2) having an allele of C IL-6 G(-174)C are highly susceptible to CVD.

Conclusion

Studies implicate urbanization, westernization of diet and increasing rates of smoking, obesity, and diabetes contributes to disease pathogenesis. The steps taken towards the control of CVD during the past decades reduced mortality related to CVD. Potential risk factors for CVD include hypertension, tobacco use, physical inactivity, elevated low-density lipoprotein cholesterol, diabetes and a cluster of interrelated metabolic risk factors[4]. However, many patients never acquired adequate control over the CVD risk factors even when these factors have been identified. Besides the growing prevalence of obesity and type 2 diabetes mellitus (Type -2 DM) threatens to decline the improvements in CVD that have been achieved. The increased incidence of obesity has contributed to significant increase in the prevalence of other important CVD risk factors, including hypertension, dyslipidemia, insulin resistance, and type 2 DM[4]. Various studies have confirmed that blood cholesterol are primarily important component that leads to CVD and its associated mortality evidenced in younger subjects. A high level of HDL cholesterol seems to protect against CVD and low HDL cholesterol levels increase the risk for heart disease. Non-traditional risk markers includes homocysteine, coagulation markers such as plasminogen activator inhibitor-1 (PAI-1), fibrinogen, D-dimer and thrombin/anti-thrombin III complex; and various inflammatory markers such as CRP, interleukin (IL), serum amyloid A (SAA), MMP and adhesion molecule. Pharmacologic therapies are now available to address individual CVD risk factors and are being evaluated, including endo-cannabinoid receptor antagonists, peroxisome proliferator inhibitor are regulating the activity of glucagon-like peptide-1[4].

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