ACTA SCIENTIFIC MEDICAL SCIENCES

Volume 2 Issue 6 September 2018

Editorial

Omega-3 Fatty Acids in Cardiovascular Diseases: Need for Well Designed Clinical Trials in Different Population

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Received: July 19, 2018; **Published:** August 01, 2018

Cardiovascular diseases (CVDs) remain one of the unbeatable challenges to human in developing countries. Despite the knowledge of prevalent risk factors and therapeutic advancement in the management of CVDs, a worldwide recommendation about the dietary modifications has not yet been established. Research during the last few decades concluded the significant role of fatty acids such as saturated fatty acids (SFA), trans fatty acids (TFA) and polyunsaturated fatty acids (PUFS) in the pathophysiology of CVDs. While SFA and TFA are present in fried food, PUFA is present naturally in vegetable oils/animal fat. Fatty fish is the richest sources of omega-3 fatty acids, eicosapentaenoic acid (EPA; 20:5) and docosahexaenoic acid (DHA; 22:6). Potential beneficial effects of fish oil containing EPA and DHA against cancer, autoimmune diseases and neurodegenerative diseases were experimentally proved as well. But the beneficial effects in large population based clinical trials are scant. Nevertheless, the mixed responses produced in many clinical trials, a uniform dietary recommendation which can render beneficial effect against chronic inflammatory disease including CVD has not yet been derived. Hence there is great paucity for well-designed trials across the world.

The fatty acids such as SFA and TFA were associated with formation and progression of CVDs. Population-based cohort study in the Norwegian population supports that TFAs intake increases the risk of coronary heart disease (CHD) and sudden cardiac death [1]. Replacing the TFAs with PUFA could reduce the event up to 39% [2]. Despite the experimental evidences, no conclusive clinical evidences were obtained so far to support the association of high intake of SFA and incidence of CHD [3]. However, based on large randomized trials a permanent reduction or replacement of dietary saturated fats with unsaturated fats is suggested [4].

Association of TFAs and SFAs with CVDs can be ascribed to the endothelial dysfunction resulting from an increased synthesis of soluble cell adhesion molecules which can favour the formation of atherosclerosis [5]. Furthermore, increase in dietary SFAs, cholesterol or TFAs can increase the production of interleukin (IL)-6 and tumour necrosis factor-alpha (TNF-α). These pro-inflammatory cytokines can either induce inflammation or interfere in the activity of desaturases. Such decreased activity of desaturases will result in the poor conversion of essential fatty acids, linoleic acid or alpha-linolenic acid to higher PUFA such as arachidonic acid (ARA)/EPA/DHA [6]. In addition to the increased pro-inflammatory mediators, TFAs can release the C-reactive protein and soluble tumour necrosis factor receptor 2. Both can augment the progression of atherosclerosis.

The association of omega-6 PUFA such as ARA with the CVD can probably due to the pro-atherogenic effect of excess eicosanoids (prostaglandin F-2alpha, thromboxane-A2 and leukotiene-B4, -C4, -D4 and E4) produced from the cyclooxygenase -2 or lipoxygenase pathway. Epidemiological studies in the native population of Netherlands, Canada, Alaska and Eskimos in Greenland established the beneficial protective effect of high consumption of fish/sea food against CVD [7]. Most of the studies in the Asian region were conducted in Japanese population that emphasized an increased consumption of fish associated with a profound decrease in the incidence of CVDs [8,9]. The mortality rate from CVD was found lower in those consuming ≥3 servings of sea food/week in Japanese population [10]. Further, it can be concluded that the protection against CVD is better in people who consume moderate amount i.e. 1 - 2 servings of sea food/week, than those of little or no sea food intake. A cross-sectional study in Chinese population found lower serum concentration of omega-3 fatty acids in CHD patients than patients with cardiovascular risk factors [11].

The main properties of EPA and DHA (1:1.2 ratio) beneficial against CVDs are antiarrhythmic, anti-inflammatory, antioxidant and antihypertensive among others. These effects are mediated through the down regulation of nuclear factor–kappa B and pro-inflammatory cytokines gene expression in mononuclear blood

cells. They can inhibit various signalling pathways including calcium-calmodulin-dependent protein kinase II in cardiomyocytes which may contribute to the antiarrhythmic effect. They are effective in lowering the triacyl glycerol level (at 4 g/day) by inhibiting the lipogenesis in hepatocytes. Presence of vitamins, high-quality protein and other essential nutrients in fish and seafood can also contribute the anti-atherogenic effects. Fish protein provides arginine for endothelial nitric oxide synthase to produce nitric oxide in endothelial cells which cause vascular relaxation and lowering of blood pressure. However, the effect of omega-3 fatty acids on the serum cholesterol level is debatable.

Despite the experimental evidences, many clinical trials and meta-analysis conducted on omega-3 fatty acids (EPA and DHA) during the last decade suggested a mixed response against CVD protection. The major reasons for such inconsistent results were analysed to be variation of relative EPA/DHA ratio, population heterogeneity for metabolizing the omega-3 fatty acids, other co-morbidities that increase the risk for CVD in the cohort selected for the trials or interaction of omega-3 fatty acids with drugs used in the management of CVD. Furthermore, certain pit falls that encrypted in the trials such as similarities in the consumption placebo (e.g. olive oil), consumption of fish meal in both treated and control groups, lack of long term follow-up of the study or short duration of the study with supplementation of low doses of omega-3 fatty acid were also needing to be considered. Nevertheless, the results, American Heart Association in their class II recommendation list suggest 2 fishy meals/week for the beneficial effect [12]. The cut off values of risk factors such as triacyl glycerol, total cholesterol and blood pressure are not available in different populations may hamper the CVD management. No previous studies could establish the beneficial serum/plasma or RBC membrane phospholipid level of omega-3 fatty acid in population during their supplementation. The prevalent risk factors of CVD are found varying among populations even among urban verses rural; the need for well-designed clinical trials in CVD patients using omega-3 fatty acid alone and in combination with the conventional cardiovascular drugs with monitoring the plasma or RBC level of omega-3 fatty acid is warranted.

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