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Clinical utility of C-reactive protein, NON-HDL cholesterol and lipid ratios in patients with stroke

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ABSTRACT

Stroke is a non–communicable disease of increasing socioeconomic importance in elderly populations. Just after the onsets of stroke in humans a range of inflammatory cells are activated. Evidence from observational studies indicates that high-sensitivity C-reactive protein (hsCRP), a peripheral marker of inflammation, is the strongest predictor of stroke. The various lipid ratios and non-high-density lipoprotein (non-HDL) cholesterol have not been as widely studied in association with stroke. The present study was therefore designed to evaluate the association of hsCRP, non-HDL cholesterol and lipid ratios with the scenario of risk of stroke. Hundred patients were recruited for the study, of which, fifty belongs to control and fifty were test group. Among the patients with complication, there was a significant elevation in the levels of hsCRP, non-HDL cholesterol and lipid ratios when compare with control. Detection of hsCRP, lipid ratios and non-HDL cholesterol are significant in patients with stroke and is important to stratify post stroke patients into risk groups.

Key words: High-sensitivity C-reactive protein, Stroke, Non-high-density lipoprotein cholesterol, Lipid ratio.

INTRODUCTION

INDIA is the country of fabulous wealth and varied heritage. On the other hand the existing diseases in the Indian society are quite awesome and threatening. Hence it is mandatory to control the intensity of the diseases and their dangerous predisposing factors in order to save India from becoming the capital of these diseases. India, already the diabetes capital of the world with 32 million persons with diabetes, is projected to have 69.8 million in 2025. The count of "hypertensive" individuals is expected to rise from 118 million in 2000 to 214 million in 2025 (Kearney *et al.*, 2005). Stroke is a major cause of death and long–term disability and has potentially enormous emotional and socioeconomic consequences for patients, their families, and health services. According to World Health Organization (WHO), stroke was the second commonest cause of worldwide mortality in 1990 and the third commonest cause of mortality in more developed countries.

The epidemiological data that support the role of high-sensitivity C-reactive protein (hsCRP) as a predictor of vascular disease are consistent across different study populations. High concentrations of hsCRP have been shown to be associated with increased risk of developing cerebrovascular disease. Studies included were for an association between hsCRP and stroke (Ridker *et al.*, 1997; Ford and Giles, 2000; van Exel *et al.*, 2002; Rost *et al.*, 2001; Curb *et al.*, 2003; Cao *et al.*, 2003; Cesari *et al.*, 2003). Although the total cholesterol (TC) to high-density lipoprotein (HDL) cholesterol ratio, low-density lipoprotein (LDL)

cholesterol to HDL cholesterol ratio and triglycerides TG to HDL cholesterol ratio are a predictor of CVD, which contains both an atherogenic and an antiatherogenic lipid component (Stampfer *et al*., 1991; Kinosian *et al*., 1994; Criqui and Golomb, 1998), these various lipid ratios have not been as widely studied in association with stroke. The present study also analysed non-high density lipoprotein (non-HDL) cholesterol for stroke, which was proposed as a risk marker for coronary heart disease (CHD) and as a secondary target of therapy (National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2002). However, there were spare data about non-HDL cholesterol and stroke.

MATERIAL AND METHODS

Patients

The total number of patients included in this study was 100, all registered for a medical check-up at the RMC Neuro Center, Trichy and Ramakrishna Nursing Home, Trichy, between April 2006 to September 2007. At the time of admission or entrance all patients responded to a standardized questionnaire covering many personal details (such as smoking habit, alcohol intake, physical activity, food habit, family history, and medical information) organised by trained interviewers. The study population consisted of 50 patients (test group) with a mean age of 60.5±8.8 years; the control group included 50 patients with mean age of 55.1±6.4 years.

Biochemical parameters and Assay

Samples for the analysis of lipid profile were obtained in the fasting state. The venous blood samples were drawn into pyrogen-free blood collection tubes without additive. The serum was collected after centrifugation at 3500 rpm for 3 minutes and then stored at in a refrigerator until analyzed. Samples were collected from the lab for further analysis. TC and TG were assayed by routine enzymatic methods using an auto analyser. HDL cholesterol was measured using the same enzymatic method after precipitation of the plasma with phosphotungstic acid in the presence of magnesium ions. For cost reasons, LDL cholesterol values have long been estimated using the Friedewald formula: [TC] " [total HDL cholesterol] " 20% of the TG value = estimated LDL cholesterol. The VLDL cholesterol is estimated as one-fifth of the TG. The concentration of hsCRP was measured in serum by the latex-enhanced immunoturbidimetric method. The value of TC to HDL cholesterol ratio, LDL cholesterol to HDL cholesterol ratio and TG to HDL cholesterol ratio was calculated by TC/HDL cholesterol, LDL/HDL cholesterol and TG/HDL cholesterol respectively. Non-HDL cholesterol value has calculated as TC " HDL cholesterol.

Statistical analysis

Statistical analysis was performed with SPSS 12 statistical software package. Data were recorded on a pre-designed proforma and managed on spreadsheet. All the entries were checked for any error. Descriptive statistics for quantitative variables were computed by mean and standard deviation. Means in the two groups were compared by Student's t-test. In this study, $p<0.05$ has been considered as statistically significant. The relative risk (RR) is the ratio of the proportions of cases having a positive outcome in two groups. RR was calculated by using MedCalc easy-to- use statistical software between test group and control.

RESULTS

Clinical characteristic of the patients were shown in the Table 1. The prevalence of diabetes, hypertension, hypercholesterolemia, hypertriglyceridemia, high LDL cholesterolemia low HDL cholesterolemia, atherogenic dyslipidemia and metabolic syndrome were higher in test group than the control. The present study demonstrates that considerable variability is observed between control and test group. Table 2 shows the comparison of baseline values of blood pressure and biochemical parameters examined in two groups of patients. There were a significant increase found between test group and control in diabetes ($p<0.09$), systolic blood pressure ($p<0.007$) and diastolic blood pressure ($p<0.06$). Among the patients with complication the baseline mean hsCRP concentration increased significantly ($p<0.001$) than the control.

From the results, there were a significant increase of TC ($p<0.004$) and LDL cholesterol ($p<0.003$) levels in test group than the control. Significant increases ($p<0.002$) were noted in the mean levels of non-HDL cholesterol in test group when compare with control. There were no significant found between test group and control in TG, TG to HDL cholesterol ratio and VLDL cholesterol levels. Significant decreases ($p<0.01$) were noted in the mean levels of HDL cholesterol in test group than the control. There were a significant increase found in TC to HDL cholesterol ratio ($p<0.001$) and LDL cholesterol to HDL cholesterol ratio ($p<0.008$) in test group when compare with control.

Table 1: Clinical characteristic of study patients

	Control (n=50)	Test group (n=50)
Age	55.1±6.4	60.5±8.8
Elders = 65 years (%)	3	20
Sex M/F	29/21	35/15
Food Habit - Veg/Non-Veg (%)	4/96	8/92
Cigarette Smoking - Ever/Never (%)	22/78	36/64
Alcohol Consumption - Ever/Never (%)	6/94	20/80
BMI (%)	2	16
Obesity (%)	2	12
Physical Activity - Low or Lack (%)	84	96
Diabetes (%)	20	38
Hypertension - SBP or DBP (%)	32	54
Hypercholesterolemia (%)	20	34
Hypertriglyceridemia (%)	26	34
Low - HDL cholesterolemia (%)	40	58
High - LDL cholesterolemia (%)	14	22
Atherogenic Dyslipidemia (%)	2	14
Metabolic Syndrome (%)	6	34

Table 2: Baseline mean levels of the blood pressure and biochemical parameters examined in serum samples of all patients

	Control	Test group
Systolic BP	123±11.1	131.4±17.5
Diastolic BP	81.2±7.7	84.4±9.5
C-reactive protein	0.9±0.4	2.3±1.4
Glucose	114.7±21.8	125.3±33.5
Total Cholesterol	166.1±30.8	184.7±32.1
Triglycerides	137.6±71.4	156.1±74.8
High-density lipoprotein cholesterol	40.1±6.8	37.0±5.0
Low-density lipoprotein cholesterol	98.9±26.9	115.3±28.9
Very low-density lipoprotein cholesterol	27.8±14.7	31.8±17.2
Non-high-density lipoprotein cholesterol	126.2±28.1	147.9±33.4
TC to HDL cholesterol ratio	4.2±0.7	5.0±1.4
LDL cholesterol to HDL cholesterol ratio	2.5±0.6	2.9±1.0
TG to HDL cholesterol ratio	3.5±1.9	4.2±2.5

The RR of hypercholesterolemia was found to be 1.70 (95 % CI 0.86 to 3.34). The RR of hypertriglyceridemia was found to be 1.03 (95 % CI 0.71 to 2.39). The RR of high LDL cholesterolemia was found to be 1.57 (95 % CI 0.66 to 3.72). The RR of HDL cholesterol was found to be 1.45 (95 % CI 0.95 to 2.19). The RR of hsCRP was found to be 4.16 (95 % CI 1.87 to 9.27). RR for hsCRP was higher when compare with the lipid profile.

DISCUSSION

High concentrations of hsCRP have been shown to be associated with increased risk of developing cerebrovascular disease. Ridker and colleagues, (1997) analysed data from the Physicians' Health Study (PHS) by using a prospective, nested case-control design, and indicated that the baseline concentration of hsCRP in apparently healthy men could predict the risk of first ischaemic stroke. However, ischaemic brain injury is characterized by acute local inflammation and raised hsCRP concentration (Beamer *et al.*, 1998), as well as increases in other inflammatory cytokines (Fassbender *et al.*, 1994). Moreover, raised concentrations of hsCRP have crucial prognostic implications in patients with acute ischaemic stroke (Di Napoli *et al.*, 2001; Di Napoli and Papa, 2002). The major risk factors for stroke and CVD, such as smoking, diabetes, and hypertension, are associated with higher hsCRP levels (Mendall *et al.*, 1996; Tracy *et al.*, 1997).
The Framingham Study (FS) followed 591 men and 871 women for 12–14 years and showed that raised plasma hsCRP concentrations independently predicted the risk of future ischaemic stroke and transient ischaemic attack (TIA) (Rost *et al.*, 2001). Curb and colleagues, (2003) examined the Honolulu Heart Program (HHP) cohort by use of a prospective, nested case-control study with 20 years of follow-up, and suggested that high concentrations of hsCRP in middle adulthood was an important risk factor for thromboembolic stroke in healthy men. The Cardiovascular Health Study (CHS) followed 5,417 individuals age 65 years or older for 10.2 years and showed that hsCRP was an independent risk factor for ischaemic stroke (Cao *et al.*, 2003). However, the Health, Aging, and Body Composition (Health ABC) study did not find a significant association between hsCRP and risk of incident stroke, but their follow-up period of 3.6 years was relatively short (Cesari *et al.*, 2003). These relationships could potentially explain the associations that have been found between hsCRP level and stroke or mortality. In a recent prospective cohort study found that baseline serum hsCRP level was an independent predictor for future ischemic stroke and all-cause mortality in an apparently healthy population (Shinji *et al.*, 2008).

A prospective cohort study in women found that TC to HDL cholesterol ratio was significantly associated with increased risk of ischemic stroke (Kurth *et al.*, 2007). Because the pathophysiology of ischemic stroke may be similar to that of CHD, a high TC to HDL cholesterol ratio and LDL cholesterol to HDL cholesterol ratio may be an unrecognized risk factor for ischemic stroke. The present study results are consistent with the possibility of increased risk in those with the highest levels of TC to HDL cholesterol ratio and LDL cholesterol to HDL cholesterol ratio, but not TG to HDL cholesterol ratio.

The present study found that there was a significant increase of stroke with the increase of non-HDL cholesterol levels. Non-HDL cholesterol was the strongest statistical predictor of stroke followed by TC. This is in agreement with two recent studies that have identified non-HDL cholesterol as a strong predictor for CHD (Pischon *et al.*, 2005) and overall CVD (Ridker *et al.*, 2005). It has been previously shown in the Women's Health Study (WHS) that non-HDL cholesterol is highly correlated with apolipoprotein B100, and both are of equally strength in prediction vascular events (Ridker *et al.*, 2005). Another study found that the multivariable-adjusted hazard ratio of ischemic stroke was 2.45 for non-HDL cholesterol (Kurth *et al.*, 2007). However, with regard to risk detection, non-HDL cholesterol may be preferred since it can be easily calculated by subtracting HDL cholesterol from TC.

CONCLUSION

Based on part of these data, inclusion of the measurement of hsCRP as one of the strategies to assess stroke patients seems a reasonable approach for identifying high-risk individuals. However, with regard to risk detection, TC to HDL

cholesterol, LDL cholesterol to HDL cholesterol ratio, and non-HDL cholesterol may be preferred since it can be easily calculated from the values obtained on a routine lipid profile. The findings of the present study, ignoring the subtype of stroke all patients were considered as the complicated with stroke. Additional studies are needed to investigate this issue.

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