IS HYPERLIPIDAEMIA A CAUSE OF PRIMARY FROZEN SHOULDER? A CASE-CONTROLLED STUDY
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ABSTRACT

BACKGROUND
The aim of this study was to evaluate the association between serum lipid profiles and primary frozen shoulder.

MATERIALS AND METHODS
This was a case-controlled study. The case group comprised 200 patients diagnosed with frozen shoulder from June 2011 to June 2016. This study was approved by MKCG Medical College, Berhampur Ethical Committee. The diagnosis was done on basis of 50% restriction of all motion of shoulder joint and x-rays of the shoulder in true anteroposterior, outlet and axillary lateral views.

RESULTS
The mean values in the patients with frozen shoulder were 6.7 months (95% CI, less than one to sixty months) for the duration of symptoms, 5.9 days (95% CI, 0 to seventy seven days) for the interval between the initial examination and blood sampling and 7.5 days (95% CI, 0 to 118 days) for the interval between the initial examination and ultrasound or MRI. Among the 300 studied patients with primary frozen shoulder, 127 had a shoulder in the freezing stage, 168 had a shoulder in the frozen stage and five had a shoulder in the thawing stage.

CONCLUSION
We conclude that elevated bad lipid levels have a significant association with primary frozen shoulder.

KEYWORDS
Hyperlipidaemia, Primary Frozen Shoulder.

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BACKGROUND
Frozen shoulder is common with a 2% to 5% prevalence. An evaluation of the risk factors for frozen shoulder is essential to an understanding of its aetiology and progression.3 Known risk factors for frozen shoulder include trauma,2,4 prolonged immobilisation,4 shoulder surgery,5 cardiac disease,6,8 diabetes,7,9,11 adrenocorticotropic hormone deficiency,12 epilepsy and Parkinson disease,13 thyroid dysfunction,14-16 autoimmune diseases,17,18 Dupuytren disease,19 genetic factors20,21 and hyperlipidaemia.22 Frozen shoulder commonly occurs in patients between the ages of forty and sixty years, but association with age has not yet been clearly evaluated.24 Patients with a frozen shoulder without diabetes mellitus and thyroid conditions and no other known aetiology are considered to have primary frozen shoulder.24

Bunker and Anthony19 focused on hyperlipidaemia as a possible risk factor for frozen shoulder after noting the similarities in frozen shoulder’s pathologic findings and those of Dupuytren contracture, which is known to be associated with hyperlipidaemia. In a later study, Bunker and Esler22 reported higher levels of serum cholesterol and triglyceride in patients with frozen shoulder than in healthy controls. Hand et al23 reporting that 17% of patients diagnosed with primary frozen shoulder had hypercholesterolaemia designated it as a risk factor; however, no control group was used in arriving at that conclusion.

Milgrom et al10 recently reported that patients with frozen shoulder did not, in their incidence of hypercholesterolaemia, differ significantly from either a control group or the regional population. Elevated serum levels of total cholesterol, triglyceride and inflammatory lipoproteins including low-density lipoprotein and non-high-density lipoprotein have not been studied for possible associations with frozen shoulder.

AIM AND OBJECTIVES
The aim of this study was to evaluate, as possible risk factors for primary frozen shoulder, all serum lipid profiles, including inflammatory lipoproteins, in an age and sex-matched case-controlled study that excluded patients with diabetes and thyroid dysfunction. We hypothesised that...
elevated serum lipid levels including inflammatory lipoproteins are associated with frozen shoulder.

MATERIALS AND METHODS
The case group consisted of 200 patients diagnosed with primary frozen shoulder from June 2011 to June 2016. The diagnosis was done on basis of 50% restriction of all motion of shoulder joint and x-rays of the shoulder in true anteroposterior, outlet and axillary lateral views.

The stages of the frozen shoulders were divided into three categories: freezing, frozen and thawing according to the results of patient's history and physical examination.\textsuperscript{5,25} The freezing stage was characterised by prominent pain and a recent progressive decrease in motion. The frozen stage was characterised by a tendency for pain to abate as motion became more severely limited. The thawing stage was characterised by a recent increase in motion accompanied by a substantial reduction in pain.

This study included only patients with frozen shoulder, no history of trauma or shoulder surgery and no evidence of rotator cuff tear who were evaluated using Magnetic Resonance Imaging (MRI) (105 patients) or ultrasonography (95 patients). Patients were excluded from this study if they had abnormal thyroid function or diabetes confirmed via blood tests or if they were receiving drug treatment or surgical treatment for previously diagnosed diabetes or thyroid disease.

Because serum lipid levels are highly affected by a person's age and sex, the control group was composed of age and sex-matched individuals who visited our health promotion center for health checkups during the same period.\textsuperscript{26,27} The control group was three times as large as the case group. The inclusion criteria for the control group were normal shoulder motion, no bilateral differences and no shoulder symptoms. The studied serum lipid profile included triglyceride (normal range, <150 mg/dL), total cholesterol (normal range, <200 mg/dL), measured low-density lipoprotein (normal range, <100 mg/dL) and high-density lipoprotein (normal range, <40 mg/dL in men and >50 mg/dL in women).

Calculated and measured low-density lipoprotein cholesterol could have different numerical values, especially when serum triglyceride is >150 mg/dL. We used the calculated low-density lipoprotein formula developed by Friedewald.\textsuperscript{28} Calculated low-density lipoprotein = total cholesterol-(triglyceride/5 + high-density lipoprotein) (normal range, <100 mg/dL). Non-high-density lipoprotein cholesterol is calculated as triglyceride-high-density lipoprotein (normal range, <130 mg/dL). Non-high-density lipoprotein cholesterol includes the bad cholesterol range from low-density lipoprotein to very low-density lipoprotein, all of which contains inflammatory apolipoprotein B particles. The dyslipidaemia criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III) guideline were used.\textsuperscript{29} A serum lipid profile examination was done after venipuncture was performed after eight-hour fasting.

Data Analysis
The odds ratios and 95% confidence intervals (95% CIs) were calculated to identify any association between serum lipid levels and primary frozen shoulder using univariate conditional logistic regression analysis. Significance was set at p<0.05. Continuous data were evaluated for total cholesterol, calculated low-density lipoprotein, measured low-density lipoprotein, high-density lipoprotein, triglyceride and non-high-density lipoprotein cholesterol. Multivariate conditional logistic regression analysis was not performed because of multicollinearity among lipid profiles with a tolerance of <0.001. All statistical analyses were performed with use of PASW Statistics, version 18.0.

RESULTS
Demographic data, serum lipid levels and the prevalence of hyperlipidaemia for 200 patients diagnosed with primary frozen shoulder and matched by age and sex to a control group of 600 patients are summarised in tables.
Univariate analyses of serum lipid levels showed total cholesterol (odds ratio, 1.010 (95% CI, 1.006 to 1.013); p < 0.001), calculated low-density lipoprotein (odds ratio, 1.008 (95% CI, 1.004 to 1.012); p = 0.001), measured low-density lipoprotein (odds ratio, 1.007 (95% CI, 1.003 to 1.011); p = 0.001), high-density lipoprotein (odds ratio, 1.015 (95% CI, 1.006 to 1.024); p = 0.001) and non-high-density lipoprotein cholesterol (odds ratio, 1.007 (95% CI, 1.004 to 1.011); p < 0.001) to be significantly associated with primary frozen shoulder. No significant association was found between serum triglyceride level and primary frozen shoulder (odds ratio, 1.001 (95% CI, 0.999 to 1.002); p = 0.451).

Univariate analyses of categorical values showed hypercholesterolaemia (odds ratio, 1.789 (95% CI, 1.366 to 2.343); p < 0.001), calculated hyper-low-density lipoproteinemia (odds ratio, 1.609 (95% CI, 1.210 to 2.138); p = 0.001), measured hyper-low-density lipoproteinemia (odds ratio, 1.643 (95% CI, 1.190 to 2.269); p = 0.003), hyper-high-density lipoproteinemia (odds ratio, 1.440 (95% CI, 1.062 to 1.953); p = 0.019) and hyper-non-high-density lipoprotein cholesterol (odds ratio, 1.645 (95% CI, 1.259 to 2.151); p < 0.001) to be significantly associated with primary frozen shoulder. No significant association was found between hypertriglyceridaemia and primary frozen shoulder (odds ratio, 0.987 (95% CI, 0.722 to 1.350); p = 0.936).

DISCUSSION

This study supports the hypothesis that elevated serum lipid levels are associated with frozen shoulder demonstrating that hypercholesterolaemia and inflammatory lipoproteinemia, particularly hyper-low-density lipoproteinemia (calculated and measured) and hyper-non-high-density lipoprotein cholesterol are significantly associated with primary frozen shoulder. Our findings were similar to the results of previous studies performed by Bunker and Esler and by Hand et al. However, Bunker and Esler also found that hypertriglyceridaemia is a risk factor for frozen shoulder; the current study could not confirm that. Because triglyceride is a lipid that is increased in diabetes and is highly correlated with blood sugar level, it may be that our contrasting findings arose as a result of different inclusion criteria.

Nonetheless, Bunker and Esler reported that serum levels of triglyceride were higher in patients with frozen shoulder even when patients with diabetes were excluded from the study groups. The differences between the findings of Bunker and Esler and those in our study seem to result from the exclusion in our study of thyroid abnormalities, especially hypothyroidism. Thyroid abnormalities, which also affect the levels of serum lipids including total cholesterol, triglyceride, high-density lipoprotein and low-density lipoprotein were not listed among the exclusion criteria by Bunker and Esler.

In our current study, both measurements of serum levels of low-density lipoprotein, a recognised inflammatory lipoprotein were significantly associated with primary frozen shoulder. Both the measured and calculated low-density lipoprotein methods have drawbacks. Although, the measured low-density lipoprotein method is influenced by triglyceride, diet and the variation in the type of manufactured measuring kits, the calculated low-density lipoprotein method is influenced by the variability of total cholesterol, high-density lipoprotein, triglyceride and the patient’s biological status. In the current study, the odds ratios of both the calculated low-density lipoproteinemia and the measured low-density lipoproteinemia were significant. Therefore, we can infer that hyper-low-density lipoproteinemia is a factor associated with primary frozen shoulder.

In the current study, the level of serum high-density lipoprotein and the presence of hyper-high-density lipoproteinemia were significantly associated with primary frozen shoulder. These are unanticipated new findings. According to a study related to coronary artery disease, a high serum level of high-density lipoprotein has been generally accepted as an anti-inflammatory factor reducing the occurrence of such diseases. However, recent studies have demonstrated that high-density lipoprotein can convert from an anti-inflammatory nature to a proinflammatory nature in acute phase responses such as to surgery or infections and can then return to an anti-inflammatory state after those acute phase reactions. High-density lipoprotein becomes a dysfunctional and proinflammatory factor in chronic systemic inflammation, such as coronary heart disease, diabetes mellitus, metabolic syndrome, chronic kidney disease, haemodialysis, systemic lupus erythematosus or rheumatoid arthritis.

Therefore, high serum levels of high-density lipoprotein in the current case group may signify that the disease process was due either to an acute phase or to chronic inflammatory status. However, in the current study, we did not evaluate C-reactive protein levels in both the study groups, which might have indicated inflammation and might have served as indirect evidence of proinflammatory...
high-density lipoprotein in the acute phase response. Therefore, the possibility of proinflammatory high-density lipoprotein as an acute phase reactant or as a factor in chronic inflammation must remain an avenue for further study. Hyper-high-density lipoproteinemia and primary frozen shoulder maybe a high-saturated-fat intake. Saturated fat can also promote proinflammatory high-density lipoprotein, which increases low-density lipoprotein oxidation and vascular inflammation. Primary frozen shoulder had a significant association with all lipid profiles in this study with the exception of triglyceride. Hypercholesterolaemia including the studied hyperlipoproteinemias due to a high-saturated-fat diet is another possible cause of primary frozen shoulder proposed by the current study and requires future investigation.

Inflammatory lipoproteins are well-known risk factors in hyperlipidaemia-related disorders. The measurement of apolipoprotein B serum level is currently the best method to evaluate the quantity of inflammatory lipoproteins. However, the level of serum apolipoprotein B is not measured routinely in most clinical circumstances because of the test’s cost. Because non-high-density lipoprotein cholesterol comprises all inflammatory lipoproteins, including intermediate-density lipoprotein, low-density lipoprotein and very low-density lipoprotein, the measurement of non-high-density lipoprotein cholesterol frequently substitutes for the measurement of apolipoprotein B.

According to our results, the serum level of non-high-density lipoprotein cholesterol was significantly associated with primary frozen shoulder demonstrating that primary frozen shoulder is associated with the serum levels of inflammatory lipoproteins that suggests that the higher levels of inflammatory lipoproteins in patients with primary frozen shoulder may have induced inflammatory changes in the shoulder capsules.

The current study had several limitations. We did not evaluate regional prevalence and ethnic differences in serum lipid profiles and could not evaluate the clinical significance of the difference in serum lipid levels between the case and control groups.

We did not completely evaluate using ultrasound or MRI, the rotator cuff status of all of the persons in the control group. However, in the current study, we did include a control group with full shoulder motion and without shoulder symptoms. Even though, the probability is very low, the current study did not completely exclude the possibility of a relationship between lipid abnormality and rotator cuff tear. Finally, because this was a cross-sectional study, we could not determine any association between serum lipid profiles and the different stages of frozen shoulder. Any time-dependent relationship between the stages of frozen shoulder and the serum lipid profiles remains to be determined.

CONCLUSION
To conclude, increase in cholesterol and lipoproteins, particularly LDL, HDL and non-HDL, non-lipoprotein, non-cholesterol lipids have significant associations with primary frozen shoulder. However, further study required to confirm whether a raised serum lipid level is a cause or a related factor of primary frozen shoulder.

REFERENCES


