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# ASSOCIATION OF RISK FACTORS FOR DEVELOPMENT OF CORONARY ARTERY DISEASE AND NUTRITIONAL AND IMMUNE STATUS ON THE RECOVERY FOLLOWING CORONARY ARTERY BYPASS SURGERY

By

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## DECLARATION BY THE CANDIDATE

The work described in this thesis was carried out by me under the supervision of Prof. Sagarika Ekanayake (Department of Biochemistry, Faculty of Medical Sciences, University of Sri Jayewardenepura), Dr. Aruna Kapuruge (Cardio-thoracic unit, Sri Jayewardenepura General Hospital, Nugegoda) and Prof. Chandanie Wanigatunge (Department of Pharmacology, Faculty of Medical Sciences, University of Sri Jayewardenepura) and a report on this has not been submitted in whole or in part to any university or any other institution for another Degree/ Diploma.

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Signature of the candidate

## CERTIFICATION BY SUPERVISORS

We certify that the above statement made by the candidate is true and that this thesis is suitable for submission to the University for the purpose of evaluation.

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We certify that the candidate has incorporated all corrections, additions and amendments recommended by the examiners.

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# ABBREVIATIONS

| | |
|---|---|
| **ABTS** | 2,2'-azino bis 3-ethylbenzthiazoline-6-sulfonic acid |
| **ACS** | Acute coronary syndrome |
| **ACTH** | Adrenocorticotrophic hormone |
| **ALT** | Alanine amino transferase |
| **AMI** | Acute myocardial infarction |
| **AST** | Aspartate amino transferase |
| **AT-1** | Angiotensin type-1 |
| **AUC** | Area under the curve |
| **BHT** | Bed head ticket |
| **BMI** | Body mass index |
| **BMR** | Basal metabolic rate |
| **BU** | Blood urea |
| **CABG** | Coronary artery bypass graft |
| **CAD** | Coronary artery disease |
| **CHD** | Coronary heart disease |
| **CRP** | C - reactive protein |
| **DM** | Diabetes mellitus |
| **DYS** | Dyslipidemia |
| **EDTA** | Ethylenediaminetetraacetic acid |
| **eNOS** | Endothelial nitric oxide synthase |
| **ET-1** | Endothelian-1 |

| | |
|---|---|
| **FT3** | Free tri-iodothyronine |
| **FT4** | Free tetraiodothyronine |
| **G-6-PD** | Glucose-6-phosphate-dehydrogenase |
| **Hb** | Hemoglobin |
| **HDLc** | High density lipoprotein cholesterol |
| **HPA** | Hypothalamic-pituitary-adrenal |
| **HPLC** | High performance liquid chromatography |
| **HR** | Hazard ratio |
| **HTN** | Hypertension |
| **ICAM-1** | Intercellular adhesion molecule-1 |
| **ICU** | Intensive care unit |
| **IHD** | Ischemic heart disease |
| **IL-6** | Interleukin-6 |
| **iNOS** | Inducible nitric oxide synthase |
| **LAD** | Left anterior descending |
| **LCX** | Left circumflex |
| **LDLc** | Low density lipoprotein cholesterol |
| **LOD** | Limit of detection |
| **Lp(a)** | Lipoprotein (a) |
| **MAC** | Mid arm circumferences |
| **MCP-1** | Monocyte chemotactic protein-1 |
| **MI** | Myocardial infarction |

| | |
|---|---|
| **NEFA** | Non-esterified fatty acids |
| **NF-κB** | Nuclear factor kappa B |
| **NO** | Nitric oxide |
| **NYHA** | New York Heart Association |
| **PAI-1** | Plasminogen activator inhibitor -1 |
| **PE** | Petroleum ether |
| **RBP-4** | Retinol binding protein 4 |
| **RCA** | Right coronary artery |
| **ROC** | Reactive operative characteristic |
| **ROS** | Reactive oxygen species |
| **SCr** | Serum creatinine |
| **sICAM-1** | Soluble Intercellular adhesion molecule-1 |
| **SPR** | Solid phase receptacle |
| **TAC** | Total antioxidant capacity |
| **TB** | Total bilirubin |
| **TC** | Total cholesterol |
| **TEAC** | Trolox equivalent antioxidant capacity |
| **TF** | Tissue factor |
| **TFPI-1** | Tissue Factor Pathway inhibitor 1 |
| **TG** | Triglyceride |
| **TGF-β** | Transforming growth factor β |
| **TNF-α** | Tumor necrosis factor- alpha |

| | |
|---|---|
| **TSH3** | Thyroid stimulating hormone - 3rd generation |
| **UA** | Uric acid |
| **VCAM-1** | Vascular cell adhesion molecule-1 |
| **WBC** | White blood cells |
| **WC** | Waist circumference |
| **WHO** | World Health Organization |
| **WHR** | Waist to hip ratio |

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# Association of risk factors for development of coronary artery disease and nutritional and immune status on the recovery following coronary artery bypass surgery

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## ABSTRACT

Cardiovascular diseases are the major cause for mortality of men and women worldwide. In Sri Lanka 40% of proportional mortality is due to cardiovascular diseases. Coronary Artery Disease (CAD) is a major disease categorized under Cardiovascular Diseases. One of the most common treatment modes for CAD is Coronary Artery Bypass Graft (CABG). Though the risk factors (conventional and emerging) related to development of CAD are documented in Sri Lanka, the data pertaining to Sri Lankans needs to be analysed with its association with severity of the disease and the need for surgery (CABG). In addition data with regard to the effect of nutritional or immune capacity on the recovery of patients undergoing CABG is not available in Sri Lanka. The objectives of this study were to determine the association between CAD risk factors, disease severity and recovery following CABG and to determine the effect of nutritional and immune status and other factors on recovery following CABG.

Conventional risk factors, demographic data, anthropometric data and data related to current food consumption were collected using an interviewer administered questionnaire from patients awaiting CABG. Pre and post-operative blood samples were collected to analyse biochemical [lipid profile, thyroid profile, cortisol, lipoprotein (a), C-reactive protein, liver functions, blood urea, serum creatinine and uric acid],

C-reactive protein, liver functions, blood urea, serum creatinine and uric acid], nutritional [albumin, vitamin A, vitamin E, ferritin, total antioxidant capacity (TAC)] and immune (interleukin-6 [IL-6]) parameters. The pre and postoperative information related to bypass surgery were collected. The severity of CAD was measured by Gensini score. Recovery was correlated to the number of days of stay at ICU and hospital. EuroSCORE II was used to predict mortality following cardiac surgery.

Patients (n = 102) awaiting CABG surgery were enrolled for the study. The mean age for presenting for CABG was 57 years. Around 60% of individuals were urban dwellers. The percentage distribution of hypertension, diabetes mellitus and dyslipidemia were 70.6%, 53.9% and 87.3% respectively. The percentage of hypertensive females were significantly (p=0.000) higher compared to the male patients. The current or previous alcohol users and smokers among males were 25.5% and 44%. From the total 53.9%, had a family history of CHD. A significantly high (p=0.001) possibility of developing CHD was observed in females who had a family history of CHD. An association between the severity of CAD and EuroSCORE II with above parameters was not observed.

The percentages of overweight, obese I and obese II categories are comparatively higher in females (80%) than males (53.8%). All females had their waist circumference > 80cm while 97.1% of females had their waist: hip ratio > 0.8. Mid arm circumference of both males and females were higher than normal reference range (< 24 cm).

The females had significantly high concentration of total cholesterol (p=0.001), low density lipoprotein cholesterol (p=0.02) and also high density lipoprotein cholesterol (p=0.02). Lipoprotein (a) concentration was not significantly different between males and females. Around 2/3 of patients had Lp(a) concentration >30mg/dL. Lipoprotein (a)

concentration of individuals diagnosed as dyslipidemic (males-46.9 ± 36.4 mg/dL, females-54.1 ± 42.0 mg/dL) and non dyslipidemic (males-48.6 ± 40.3 mg/dL, females-51.5 ± 41mg/dL) were not significantly different. Another CHD risk marker, CRP concentration (6.8 ± 8.2 mg/L) was slightly higher than normal reference (< 6 mg/L) prior to surgery and increased following surgery (214.3 ± 57.1mg/L). The average fibrinogen was 290 ± 60.7 mg/dL, also within normal range.

Pre-operative AST, ALT, total bilirubin, uric acid, blood urea and creatinine concentrations were 36.8±14.6 IU/L, 29.4±16.6 IU/L, 12.2±5.8 IU/L, 353±123 μmol/L, 5.6±3.0 μmol/L and 102.3±33.6 μmol/L respectively and were within the normal ranges. Post-operative concentrations of ALT (40.1±28.1 IU/L), total bilirubin (17.5±10.9 IU/L), uric acid (381±125.7 μmol/L) and creatinine (117±42.3 μmol/L) were also within the reference ranges. However, post-operative AST (83.4±51.6 IU/L) and blood urea (7.7±3.2 μmol/L) were significantly high.

Free T3, T4 and TSH were 3.9±1.0 pmol/L, 15±3.3 pmol/L and 3.0±3.7 μUI/ml respectively. Subclinical hypothyroidism among males is 16.4% with no hypothyroid individuals. Among females 8.6% were hypothyroid and 11.4% were subclinically hypothyroid.

The cortisol (111.1±43.4 ng/ml) was within the normal reference range at the time of measurement. Pre-operative vitamins A (70.3±32.2 μg/dL) and E (9.3±4.9 μg/dL) were significantly low post-operatively [A (45.9±19.0 μg/dL, p= 0.000) and E (7.8±2.8 μg/mL, p=0.006)]. Serum ferritin (138.7±137.5 μg/L) was within the normal range prior to surgery. Pre-operative albumin (47.0±3.7 g/L) was significantly higher than post-operative (42.5±3.3 g/L) concentration. Pre-operative total antioxident capacity (TAC) was 6.5±1.3 μg TEAC /10μl with low postoperative (6.2±1.2 μg TEAC /10μl)

concentration. The severity of coronary artery disease measured by Gensini score for dyslipidemic and non dyslipidemic males were 51.4±23.5 and 51.5± 27.8 respectively. The Gensini score had significant positive correlations with cortisol (r= 0.307, p=0.005) and with ferritin (r=0.2, p=0.005). There was no significant correlation between conventional risk factors, other biochemical, nutritional and immune markers with severity of CAD. Pre-operative IL-6 (17.1±73.3 pg/mL) increased postoperatively (255.4±214.7 pg/mL). Pre (p=0.008) and post (p=0.01) operative TAC and post-operative IL-6 (p=0.006) was significantly high in patients who developed infections during hospital stay. Pre-operative TAC can predict incidence of post-operative infections with 56% sensitivity and 74% specificity, 5.9 µg TEAC /10µl as cut-off value. Similarly post-operative TAC also can predict the incidence of post-operative infections with 78% sensitivity and 45% specificity at 6.6 µg TEAC /10µl as cut-off value. Odds ratios (OR) elevation of pre-operative albumin (1.2, 95% CI 1-1.3), post-operative IL-6 (1, 95% CI 0.9-1.0) and pre-operative TAC (0.6, 95% CI 0.39-0.98) concentrations associated positively with individuals who have developed infections when compared to individuals with no infections.

According to the surgical procedures the highest numbers of grafts performed were 3 and 4 grafts with 44.6% and 41.6% of patients respectively. Cardiac surgery risk model, EuroSCORE II was 1.4±0.7%. EuroSCORE II had positive significant correlations with Gensini score (r= 0.4, p=0.006) and ICU stay (r=0.3, p=0.04) only. The average hospital and ICU stay was 16.6±14.4 and 5.4±2.5 days respectively. Post-operative infections developed in 27.3% of the patients.

In conclusion, among the conventional risk factors, dyslipidemia was the most frequent risk factor among both males and females. There was a higher possibility (26%) of

contribution for CHD if the parents had CAD compared to siblings. Animal food intake was within the recommended intake once diagnosed as having CHD. Almost 75% of the study sample was obese and 97% of females had W: H ratio above the recommended values and indicate the need for life style change. Even though the lipid profile parameters were within the normal range the lipoprotein (a) was high irrespective of risk factors indicating that this can be considered as a good marker for identification of individuals susceptible for CHD in Sri Lankan population following further studies.

Among the patients a moderately high percent of individuals with subclinical hypothyroidism and hypothyroidism were present. Serum cortisol and ferritin concentrations above 141 ng/mL and 160 µg/L were indicative of increased severity of CAD as calculated by Gensini score and could be used as markers to assess the severity of CAD. No correlations were observed with risk factors, other biochemical, nutritional and immnulogical parameters and severity of CAD.

Interleukin-6 and TAC can be considered as markers for predicting development of post-operative infections. EuroScore II correlated with severity of disease and the duration of ICU stay. In addition pre-operative TAC, post-operative IL-6 and EuroSCORE II could be considered as predictors of prolonged hospital stay following surgery.