8. Summary:

Cardiovascular diseases (CVD) are the leading cause of mortality worldwide. There are several predominant factors that influence disease promotion and severity. Geographical location and demographic profile are one of the important factors for the disease outcome. Stresses, sedentary lifestyle and abnormal energy metabolism cause sustained hyperglycemia, hypertension and insulin resistance. Compelling evidence suggest that diabetes has a distinct relation with different cardiovascular disorder. Diabetes is also now epidemic worldwide.

In the current study occurrence, severity and mechanism of CVD has been studied in adult individuals-patients. There are different hematological and biochemical parameters like LDH, CPK, CPK-MB which were studies in the trop-T + ICU admitted patients. Prior the investigation all regulatory norms and ethical clearances were approved from the competent authority. Study results show the serum SGOT and LDH in female cardiac patients were found to be significantly higher in both trop T- or trop T+ patients. The present multiple comparison ANOVA test suggests that most of the risk factors and serum markers of female cardiac patients were impaired significantly ($p<0.001$) than that of male patients. It is noticed that the parameters are more severely impaired in trop-T+ ($p<0.001$) than the trop-T- ($p<0.05$-0.01) patients. The malondialdehyde (MDA) and NPSH levels were found to be higher in case of serum samples of cardiac patients. In rat experiment mean body weight of animals did not significantly change in different nutritional groups. However, the reno-somatic index (kidney weight/100g bw)

decreased significantly both in lipid or fructose fed rat group. Cholesterol and triglyceride notably increased in lipid fed and urate decreased in either diet group. The oxidant component; MDA and antioxidant enzyme catalase and SOD1 activities significantly increased/impaired in rat liver and heart of lipid-fed group.

In the patients oxidative stress markers like MDA, antioxidant components like NPSH, SOD, catalase, GPx were tested and measured. Human samples were also tested for the study of inflammatory markers like CRP, TNF a, IL-6 etc. In other several in-vitro experiment with human blood samples and animal tissue slices other important parameters like NO, NOS, Insulin, glucose transporter and stress induced protein dermcidin gene and protein expression were studied for the understanding of the mechanism of diabetes and diabetes associated CVD disorder . Occurrence of a high level dermcidin isoform-2 in CVD demonstrates a possible regulation on cytokines expression. It was found that incubation of 120 nM of dermcidin isoform-2 (DCN-2) to the normal neutrophil solution for 2 h resulted in the increase of synthesis of TNF-α from 3.829 ± 1.53 pg/ml to 20.7 ± 6.9 pg/ml and IL-6 from 3.27 ± 1.52 pg/ml to 47.07 ± 3.4 pg/ml. Cytokines were determined in CVD patient blood with TNF-α level 18.3-27.3 pg/ml, median value 21.863 pg/ml and IL-6 23.54-52.733 pg/ml, median value 42.163 pg/ml. Treatment with 0.6 nM estriol, female steroid hormone estrogen for 45 min decreased the elevated cytokine level in 120 nM DCN-2 treated normal neutrophils. The expression of DCN-2 induced TNF-α synthesis in neutrophils was further determined by Western blot technique with a thickened band intensity of TNF-α in DCN-2 induced neutrophil solution. The production of

nitric oxide (NO) was also regulated with the effect of DCN-2 treatment from 1.61 nmol NO/ml to 0 nmol NO/ml. The subsequent reduction of TNF-α level due to 0.6 nM estriol treatment had shown the corresponding increase in NO level to 0.559 nmol/ml.

For the better understanding experimental rat model of high lipid and fructose fed (90 days iso-caloric) was also utilized here. Rats were investigated to evaluate some risk factors and oxidant and antioxidant status in their serum, liver and hear tissues. Present result suggest that LDH, CPK, CPK-MB, MDA, SOD, these are expressed according to the disease severity and those were also higher in the individual of trop-T + or trop-T-. These markers are also associated with the age and gender association of the disease condition. Important roles of these markers are also verified and validated in our experimental rodent model. Result from animal experiment suggests that oxidative stress and inflammatory status are the prerequisite for the diabetes and CVD. These have been suggested on the student's t test, multiple comparison ANOVA test and correlation-analysis which support the interdependence among different parameters.

Several In-vitro and mouse model study suggest that stress protein dermcidin is responsible for insulin resistance and GLUT4 and NO insensitivity which results arterial endothelial disregulation, atherosclerotic plaque formation. Role of plaque rupture, platelet aggregation has been suggested to initiate the severity of the disease. Stress induced protein dermcidin has been demonstrated with high concentration in diabetic and hyperlipidemic status. The animal experiment suggests the high lipid consumption and abnormal glucose/energy

metabolism may increase the systemic oxidative stress. Stress-induction at the onset/progression of this disease is noticed as the high-level of lipid peroxides/low-level of free-thiols in association with increase of inflammatory-markers C-reactive protein and TNF-α. DCN-2 induced decrease in the synthesis of glucose-activated nitric oxide synthase (GANOS) and lower production of NO in liver has been shown here where low NO is demonstrated to supports the expression of glucose trabsporter-4 (GLUT-4) and its translocation on liver membrane surface. This finally impairs glucose transport to organs from the extracellular fluid.

So, in brief the predominant factors of cardiovascular complications have been studied in the current investigation. Oxidative stress has been implicated for the impairment of several metabolic functions. Stress induced protein DCN has been correlated with disease pathogenesis and severity. Further studies on detail mechanistic layout of this disease will help for its better therapeutic intervention.