SUMMARY & DISCUSSION

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Use of aspirin is well known in cardiovascular diseases, aspirin remains the cornerstone of antiplatelet therapy in patients with cardiovascular disease. Aspirin can't inhibit platelet aggregation in AMI and the use of aspirin in AMI is very little. Currently, neither the use of aspirin nor the way to restore the sensitivity of the platelets is available. We herein demonstrated a unique and simple way to resensitize the platelets. It was found that dermcidin an 11kDa protein in the circulation of AMI patients was the cause of the platelet aggregation in AMI even in the presence of aspirin and the protein showed its inhibitory effect by its binding on platelets surface and we also found that biphasic effect of aspirin might overcome the inhibitory effect of dermcidin through the production of nitric oxide.

We found the protein in cerebrovascular patients, also but in lesser amounts of concentration than that of the AMI patients. The amount of protein was also able to aggregate platelets in hemorrhagic and ischemic stroke patients. We also found the decreased concentration of insulin in the circulation of both types of stroke victims and the binding of insulin was inhibited in platelets of stroke patients. And the impairment of nitric oxide production was found in both cases. We analyzed that the dermcidin was responsible for those incidents and we reported that glucose activated nitric oxide synthase was impaired due to the presence of dermcidin in circulation of those patients and as such we found that the glucose induced decreased production of nitric oxide in hepatocytes and pancreatic cells and concomitantly we found decrease production of insulin synthesis. So, a diabetic condition was found in the stroke victims And we also demonstrated that TRIAD system low dose of aspirin, insulin and catalase were able to nullify the effect of dermcidin and inhibit platelet aggregation in AMI.

It is also known that chest pain is the distinctive feature in cardiac patients and it was also reported that the decrease nitric oxide production might be the cause of pain; so we investigated the presence of any protein in goat carotid artery endothelial cells in presence of nitro compounds, aspirin, insulin and even glucose and we found protein disulfide isomerase (PDI) from the sequence analysis. This protein might be involved in pain regulation.

The environmentally induced stress protein dermcidin was also found in low partial pressure of oxygen which might be the cause of high altitude illness and may predispose ACS. This protein was found to express in neutrophil cells in hypoxic state, in the presence of AETL and the protein was found to inhibit glucose uptake in muscle cells of mice and impaired the binding of insulin on muscle cells of mice and thus when dermcidin was injected to the tail vein of mice it was found to increase the glucose level in its circulation and as such protein was able to impair GLUT4 translocation and insulin/low dose aspirin recuperated the translocation. It was also unveiled from the FRET analysis that dermcidin inhibited the release of NO from DEA-NONOate through cGMP impairment (cGi-500 sensor was used).

In another aspect our aim was to nullify the hyperglycemia and on this aspect we prepared an orally effective insulin with milk, which could neutralize the hyperglycemia (in alloxan treated diabetic mice), so, at this point this innovation might be helpful for the patients.

So, it can be argued that it is not the aspirin, but the presence of dermcidin in the circulation of AMI subjects is the cause of failure of aspirin effect and not the higher dose but low amount of double doses of aspirin will neutralize dermcidin effect where first dose is able to produce NO which helps the removal of dermcidin from the high affinity binding sites then the second dose can inhibit aggregation by sensitizing the platelets. It was also

analyzed that insulin mediated NO might play the critical role in the atherosclerotic plaque formation in cerebrovascular disease. And it can also be inferred that different types of anti-anginal compounds, aspirin and even insulin might regulate the chest pain in ACS and AMI through the regulation of PDI protein in carotid artery endothelial cells. It can also be concluded that dermcidin might be the causative factor for the development of hyperglycemia through the insulin resistance that inturn inhibits NO formation in the circulation, as NO is proved to be the second messenger of insulin, thus dermicidin presence resulted in endothelial dysfunction and predisposing to atherosclerosis. So, dermcidin protein might create the docking of micro-environment for the endothelial dysfunction through the development of hyperglycemia slowly by hampering nitric oxide molecule, as such the protein generates cardiovascular anomaly.