Chapter 3
Aims and Objectives

3. AIMS AND OBJECTIVES
Cardiovascular and metabolic diseases are elevating public health concerns in India and worldwide. Diabetes is considered as a chronic inflammatory disease and insulin resistance is a well-known feature of type 2 diabetes. Endothelial dysfunction and insulin resistance in cardiovascular and metabolic disorders are often co-morbid states.

The vital role of insulin in vascular endothelium is to activate the production of NO whereas in metabolic tissue the primary function of insulin is to stimulate the glucose disposal. Both vascular and metabolic of insulin shares Phosphatidylinositol 3-kinase– dependent insulin-signaling pathway. Obesity associated chronic inflammation is well-perceived for its role in insulin resistance and T2D.

Pro-inflammatory cytokines including interleukin-6 (IL-6) has emerged as one of the central mediators that link obesity-associated chronic inflammation with insulin resistance. The products of IL-6 signaling pathway such as SOCS-3, IKK and mTOR causes proteasomal degradation of IRS in insulin signaling pathway, which leads to insulin resistance. Studies have shown inflammatory molecule including IL-6 induce vascular insulin resistance in ECs.

Complex gene-environment interactions lead to development of diabetes and cardiovascular disease. Growing body of evidences suggests potential role of epigenetic modification such as DNA methylation in development of cardiovascular diseases. More over persistent epigenetic changes might further extend risk of development of cardiovascular diseases.

Knowledge of epigenetic mechanism due to cross talk between inflammation (IL-6) and glucose metabolism (insulin signaling) is very scant. Hence, we hypothesize that IL-6 induced vascular insulin resistance might be associated with epigenetic changes.

Thus, our study was focused to improve the current understanding on:

1. Whether genome undergoes changes in DNA methylation pattern in vasculature during insulin resistance caused by inflammation?
2. What are the promoter/target genes affected during these pathophysiological conditions of inflammation governing angiogenesis?
3. Whether inflammation induced insulin resistance in endothelial cells modulate angiogenesis?
4. To study epigenetic based signaling mechanisms under the conditions of vascular insulin resistance