AIMS AND OBJECTIVES

CHAPTER 2

2: AIMS AND OBJECTIVES

Obesity is markedly increasing in developing countries with elevated incidences of metabolic disorders like diabetes, CVD, hepatic steatosis, infertility and cancer. Sedentary life style, frequent intake of tran-fat, western diet and disturbed circadian rhythm leads to obesity. Excess free fatty acids induce hypertrophy and hyperplasia in adipocytes, which alter its endocrine function, elevate macrophage infiltration, inflammation which leads to peripheral insulin resistance, diabetes and CVD. Indulekha et al in 2015, reported a comprehensive study where Indians have been classified in 4 different categories based on metabolic profile and obesity, and reported increased incidence of metabolically obese phenotype, in India. They also found that levels of resistin were persistently high in all the metabolically compromised phenotypes compared to those of TNFα. There is a special consensus which has defined obesity at a new BMI$\geq$ 25 for South Asians, specifically Indians, whereas WHO has defined obesity at BMI>30 for rest of the countries.

Adipokines play a major role in energy homeostasis and elevated levels of leptin, resistin, TNFα, visfatin, IL-1β, IL-6 which govern dysregulated metabolism in adipose tissue. Among all leptin, resistin and TNFα are the main contributors towards obesity and diabetes which affects adipose tissue and alters functions of adipocytes, pre-adipocytes and macrophages.

Stem cells are becoming choice of treatment for various chronic diseases. There are different types of stem cells amongst which MSC are potential candidates being used for various therapeutic interventions. Adipose tissue is abundantly present through-out the body and contains resident stem cells called as hADSC, which are chief cells applied in the field of regenerative medicine. Since few years, extensive research is going on to understand the repercussion of obesity on metabolic profile of adipose tissue and hADSC.

It has been documented that obesity diminishes hADSC of obese Caucasians. Indians are highly vulnerable towards diabetes and CVD. There are anthropometric measurements and blood profile of obese, diabetic and metabolic syndrome Indian patients. However, till date there are no reports on ramification of obesity on hADSC of obese Indians.. Sporadic reports demonstrated altered gene expressions of leptin, adiponectin, resistin, TNFα etc. but insulin signaling has not been explored in obese Indians despite having high prevalence of diabetes.

Insulin resistance is hall mark of TIIDM and obesity. Large number of drugs are being used for the treatment of diabetes and obesity. India is traditionally rich and powerful in Ayurveda (herbal medicines). Large number of medicinal plants and their phytocompounds have been explored for treatment of metabolic disorder. Swertiamarin, a phytocompound isolated from *Enicostemma littorale* a perineal plant has been extensively studied at molecular level to prove its antihyperglycemic, hypolipidemic, antiadipogenic and insulin sensitizer efficacy.

Hence, in the present study attempt has been made to study hADSC from obese and control Indians, understand role of inflammation on obese phenotype and evaluate efficacy of phytocompound in modulating metabolically compromised hADSC of obese patients. To achieve these aims following objectives were undertaken in this thesis.

Objective 1: Comparative study of adipose tissue and hADSC in control and obese Indian population

Fist objective of the study is a pilot study performed in representative Indian population to understand the deleterious effects of obesity on adipose tissue and hADSC of obese Indians.

Objective 2: Understanding cytokine mediated insulin resistance in fate of hADSC and amelioration using insulin sensitizers

Second objective is to understand the entailing effects of TNFα and resistin on stemness and metabolic profile of hADSC independently. Also the modulatory effects of swertimarin and metformin were studied on deleterious effects of these adipokines independently.

Objective 3: Exploring the temporal expression of signaling pathways in resistin mediated insulin resistant hADSC fate

As resistin is less explored and profoundly associated with obesity and diabetes, an attempt was made in the third objective to scrutinize the temporal expressions of key signaling pathway proteins and their target genes responsible for adipogenesis and osteogenesis under the influence of resistin treated hADSC.