Vascular aging is associated with changes in the structure and function of the vascular system and such changes contribute to the risk for the development of diabetes and associated cardiovascular diseases. Vascular senescence reflects the limited ability of vascular cells to divide and proliferate and is accompanied by specific phenotypic changes in morphology, gene expression and function. In endothelial cells, these changes result in a phenotype that is pro-inflammatory and pro-atherosclerotic. The early onset of vascular senescence is also an indicator of premature aging. Recent studies have shown that hyperglycemia-induced vascular senescence is an important contributing factor to promote the development of aging-associated cardiovascular events. Sirtuin 1 (SIRT1) is highly expressed in the vasculature and has recently been identified as an important regulator of endothelial cell senescence-like growth arrest. Metformin is the most frequently prescribed first-line oral hypoglycemic agent for the treatment of type 2 diabetes. Recent studies have demonstrated that the beneficial effects of metformin may be associated, directly or indirectly, with the activation of SIRT1.

In this study, we investigated the molecular mechanisms and protective effects of metformin against high glucose (HG) induced endothelial cell senescence and the contribution of SIRT1-dependent mechanisms. Mouse microvascular endothelial cells (MMECs) were maintained in culture under either normoglycemic (11mM glucose) or hyperglycemic (HG, 40 mM) conditions and Western Immunoblot techniques were used to determine changes in protein expression.

Immunoblot analysis reveals that MMECs exposed to HG results in a significant reduction in SIRT1 expression, but an increase in FoxO1 and p53 acetylation. HG exposure also results in a significant up regulation of p21 expression and a decrease in anti-apoptotic Bcl-2 expression. The percentage of senescence-associated β-galactosidase activity is increased with exposure to HG. The presence of metformin reduces the negative effect of HG on SIRT1 expression and protects endothelial cells from HG-induced senescence.

These data suggest that HG-induced down-regulation of SIRT1 plays a crucial role in diabetes-associated endothelial cell senescence and, furthermore, that the protective effect of metformin against HG-induced endothelial dysfunction is, at least in part, due to its effects on SIRT1 expression/activity.