Coronary Stent Placement in Patients With Diabetes

The number of patients with type 2 diabetes mellitus (DM) has been greatly increasing worldwide, and the clinical impact of abnormal glucose metabolism has been recognized in the management of coronary artery disease (CAD). Even though there has been recent advancements in intracoronary interventional devices, patients with DM have a particularly high risk for restenosis and target lesion revascularization than those without, up to 30–50%. The primary mechanism for this increased risk of restenosis has been attributed to diffuse and accelerated neointimal proliferation within the stented segment in the era of the bare-metal stent (BMS).

Stent implantation causes arterial injury, which can initiate neointimal growth, a process that involves platelet deposition, thrombus, inflammation, migration and proliferation of vascular smooth muscle cells (VSMCs), and extracellular matrix formation. Initially, platelet deposition and activation occur at the injury site, leading to the release of cell-signaling molecules, such as platelet-derived growth factors. The cell-signaling molecules induce expression of cell surface receptors that bind to circulating inflammatory cells. The activated inflammatory cells secrete molecules that bind to specific receptors on VSMCs, causing mitosis (ie, cell proliferation) and an inflammatory response.

Pioglitazone Revisited to Illuminate Contemporary Vascular Reparative Therapy in the Era of Drug-Eluting Stents

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increase in the cellular mass in the neointima, eventually leading to in-stent restenosis (ISR) in some cases, especially in diabetic patients. Further, endothelial dysfunction has been noted in type 2 DM, and is associated with atherothrombosis progression and neointimal proliferation after coronary stenting. A wide range of systemic pharmacological interventions has been attempted to reduce the incidence of ISR, and peroxisome proliferator-activated receptor-γ (PPARγ) agonists, the thiazolidinediones, has been evoked as a savior. Several clinical trials demonstrated treatment with pioglitazone is effective in decreasing ISR and the need for revascularization after BMS implantation in patients with DM, in addition to insulin-sensitizing effects through adiponectin. Preclinical studies demonstrated that pioglitazone can exert its anti-inflammatory, antiproliferative and anti-migratory effects on all these processes. Pioglitazone can reduce the number of monocytes and macrophages infiltrating and decrease the serum levels of interleukin-6 (IL-6), matrix metalloproteinases (MMP)-1 and -9 and monocyte chemoattractant protein-1 (MCP-1). Thus, these effects can inhibit the migration and proliferation of VSMCs, neointimal hyperplasia and extracellular matrix formation during the vascular remodeling processes. In addition, pioglitazone has been reported to improve endothelial dysfunction independently of the observed benefits on insulin sensitivity (Figure).

Pioglitazone and MicroRNA-Based Strategy in the DES Era

Drug-eluting stents (DES) significantly reduce restenosis compared with BMS in a wide range of patient populations. Even still, DM continues to be associated with an increased risk of restenosis and unfavorable clinical outcomes. Although in-stent neointimal suppression after DES seems similar between DM and non-DM patients, large and eccentric plaque accumulation at the culprit lesion in DM patients may hamper adequate stent expansion and longitudinal lesion coverage, which may lead to late DES failure. If only targeting to reduce neointimal proliferation, there seems no need to consider additional pharmacological intervention in the era of DES.

As suggested from pathological studies, suppression of neointimal growth via DES is accompanied by delayed healing post-DES implantation, such as lack of re-endothelialization and persistent fibrin deposition and inflammation, leading to further deterioration of endothelial function of the coronary vasculature in type 2 DM. Drugs concurrently used with DES do not discriminate between proliferating VSMCs and endothelial cells (ECs). This lack of discrimination delays re-endothelialization and vascular healing, which potentially increases the risk of late thrombosis following DES implantation.

In this issue of the Journal, Hong et al report that pioglitazone improved brachial artery flow-mediated dilatation (baFMD) and adiponectin as well as enhanced microRNA 24. MicroRNAs (miRs) are recently identified endogenous, non-coding, single-stranded RNAs of 18–22 nucleotides that constitute a novel class of gene regulators. In most cases, miRs negatively regulate the expression of protein-coding genes by promoting degradation or suppressing translation of target miRNAs and modulating various biological functions. Santulli et al. recently reported their attempt to specifically reduce proliferation of VSMCs, but not ECs after vascular injury using miR-facilitated gene delivery. Contemporary vascular reparative therapy via pioglitazone may open the gate for novel microRNA-based strategies as a therapeutic approach to specifically inhibiting vascular restenosis while preserving endothelial function.

References