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PDE5 inhibition ameliorates visceral adiposity targeting the miR-22 / SIRT1 pathway: evidence from the CECSID trial

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Background: Visceral adipose plays a significant role in cardiovascular risk. PDE5 inhibitors (PDE5Is) can improve cardiac function and insulin sensitivity in type 2 diabetic patients (TD2M).

Purpose: To investigate whether PDE5Is affect visceral adipose tissue (VAT), specifically epicardial fat (EAT), and what the mechanism involved using microarray-based profiling of pharmacologically modulated miRNAs.

Methods: a randomized, double-blind placebo-controlled study was designed in TD2M. 59 diabetic patients were randomized to receive 100 mg/d Sildenafil or Placebo for 12 weeks. Fat biopsies were performed in a subgroup of patients. In a parallel animal study, db/db mice were randomized to 12 week Sildenafil or vehicle and VAT was collected. Main outcomes and measures were anthropometric and metabolic parameters. VAT quantification through cardiac magnetic resonance imaging (CMR), array of circulating 2005 miRNAs, qPCR and flow cytometry of VAT.

Results: Compared to Placebo, Sildenafil reduced waist circumference (p=0.024) an EAT by CMR (p=0.005). Microarray analysis identified some miRNAs differentially regulated by Sildenafil, among which a downregulation of miR-22-3p, confirmed by real-time qPCR (p<0.0001). Sildenafil’s modulation of miR-22-3p was confirmed in vivo in HL-1 cardiomyocytes. An up-regulation of SIRT1, a known target of miR-22-3p was found both in serum and subcutaneous fat in Sildenafil-treated subjects. Compared to vehicle, 12-week Sildenafil treatment downregulated miR-22-3p and upregulated SIRT1 gene expression in VAT from db/db mice, shifting adipose tissue cell composition toward a less inflamed profile.

Conclusions: Treatment with PDE5Is in human and murine models of diabetes improve VAT targeting SIRT1 through a modulation of miR-22-3p expression.

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AMP-activated protein kinase activation partially restores the anti-contractile effect of perivascular adipose tissue in male offspring of obese dams

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Introduction: Maternal obesity pre-programmes offspring to develop obesity and associated cardiovascular disease although the underlying mechanism is currently unknown. Perivascular adipose tissue (PVAT) can improve vascular function and insulin sensitivity in type 2 diabetic patients (TD2M). However, whether AMPK activation within PVAT partially restores anti-contractile capability at both ages, remains to be determined.

Purpose: We aimed to determine the mechanisms by which an obesogenic maternal diet pre-programmes detrimental vascular changes in her offspring.

Methods: 6 week old female Sprague-Dawley rats were fed a 10% fat diet (controls) or an obesogenic, high fat diet (HFD; 45% fat) for 12 weeks before mating, during pregnancy and lactation. At 6 weeks of age. PVAT-denuded mesenteric arteries from pups, with or without exogenous PVAT, were preincubated with glucosamine had no effect on PVAT-denuded vessels but simultaneous AMPK activation within PVAT partially restored anti-contractile capability at both ages.

Conclusions: The diminished anti-contractile effects of PVAT in offspring of HFD dams can be mimicked by incubation of PVAT with glucosamine and partially restored by AMPK-activated protein kinase activation within PVAT.

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Peroxisome proliferator activated receptor (PPAR) alpha/gamma agonist aleglitazar attenuates tumor necrosis factor (TNF) alpha-mediated inflammation and insulin resistance in human adipocytes

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Background: Adipose tissue inflammation is a mechanistic link between obesity and the related sequelae, including insulin resistance and type 2 diabetes. Co-ligands of peroxisome proliferator activated receptor (PPAR) α and γ, combining in a single molecule the metabolic and inflammatory-regulatory properties of α and γ agonists, are promising therapeutic strategy to antagonize adipose tissue inflammation.

Methods: Human Simpson-Golabi-Behmel syndrome adipocytes were treated with aleglitazar or the selective agonists for either PPARα or γ, fenofibrate or rosiglitazone, for 24 h before stimulation with TNF-α. Conditioned media were then tested for MCP-1 by ELISA, the mRNA expression for MCP-1 as well as other pro-inflammatory cytokines were investigated by RT-PCR, the activation status of insulin signaling with regard to activation of mitogen-activated protein (MAP) kinases was assessed by Western analysis with antibodies recognizing the phosphorylated (activated) forms of each kinase.

Results: Aleglitazar, at concentrations as low as 10 nM/mL, reduced the stimulated expression of several pro-inflammatory mediators including interleukin(II)-6, and chemokine (C-X-C motif) ligand 1 (CXCL1), as well as the expression and release of monocyte chemoattractant protein(1)(MCP-1). Correspondingly, functional monocyte migration assays revealed that aleglitazar reduced monocyte migration, an effect that was consistent with suppression of MCP-1 secretion. Under the same conditions, aleglitazar reversed the TNF-α-mediated suppression of insulin-stimulated serine/threonine phosphorylation and decreased the TNF-α-induced secretion of inflammation-associated cytokines, two major switches in insulin-mediated metabolic activities also restoring glucose uptake in insulin-resistant adipocytes. These effects were associated with the prevention of activation of serine and threonine kinases involved in the inflammatory-mediated expression of MCP-1, and with a prevention of insulin resistance, involving the p38 mitogen-activated protein.

Conclusion(s): Aleglitazar reduces adipose inflammation and dysfunction in insulin signaling in activated adipocytes. Such effects appear to be mediated, at least in part, by interference with the activation of p38 MAPK. Although the extent of aleglitazar effect was never superior to those of PPARα and γ agonist combination, these data suggest that aleglitazar may benefit diabetic and obese patients, and deserves further investigation.