Rosiglitazone 能改善糖尿病前期之冠心症病人血管重塑生物指標

Rosiglitazone Ameliorates Biomarkers on Vascular Remodeling Among Subjects with Pre-diabetes and Coronary Artery Disease

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Background

Inappropriate vascular remodeling is common and can result in serious vascular complications among diabetes mellitus. *Matrix metalloproteinases* (*MMPs*) are a family with various catalytic enzyme activities, which will majorly determine the remodeling process of vascular matrix for the whole body. Thiazolidinedione (TZD), a synthetic activator of PPARγ, is not only an insulin sensitizer but also an activator in adipose transcriptional regulation as well as anti-remodeling process on vascular matrix tissues. Though accumulated scientific evidence supports the anti-remodeling effect on diabetes subjects, it remains uncertain whether TZD can provide similar effects on pre-diabetes with documented coronary artery disease (CAD).

Materials and Methods

In one randomized, double blind, placebo-controlled study to examine the secondary prevention of cardiovascular event of TZD among adults with pre-diabetes with angiographic documented CAD, we measured the changes of novel vascular remodeling biomarkers including *MMP-3*, *MMP-9* as well as *fetuin*, which indicating the status of arterial stiffness and calcification.

Among total 105 patients with CAD, 46 of them had pre-diabetes and were randomly assigned to receive pioglitazone 4mg (TZD group, n=23) or dummying placebo (placebo group, n=23). The median follow-up period was 2 years. Biomarkers were taken before the trial and 6 months later, respectively. Besides vascular remodeling markers, *resistin* and *adiponectin* were measured for the

modification of insulin resistance; *high-sensitivity C-reactive protein* (*hsCRP*) was also analyzed for inflammation status changes; *fetruin* was analyzed to be the marker for arterial stiffness changes. The associations between these biomarkers were analyzed to elucidate the possible interplaying mechanisms.

Results

The mean age was 66.8±0.5 years, and 84% were men with similar baseline characteristic profile including age, gender, family history, body weight, and disease severity between 2 groups. In the TZD group, insulin sensitivity profile improved significantly with decreased *resistin* (before vs. after: 3.56±2.16 vs. 2.83±1.92 ng/ml, Δ=-20.6%, $p<0.05$) and increased *adiponectin* (before vs. after: 5858±3139 vs. 20552±15980 ng/ml, Δ=+250%, $p<0.01$), which remained similar for placebo group (*resistin*: before vs. after: 2.33±1.89 vs. 2.18±1.56 ng/ml; *adiponectin*: before vs. after: 4773±2103 vs. 5372±2595 ng/ml, both $p>0.05$; respectively). The inflammatory marker like *hsCRP* (before vs. after: 3508±0.597 vs. 1671±0.597 ng/ml, Δ=-49.3%, $p<0.05$) decreased significantly. The TZD treatment, but not placebo therapy, also significantly reduced the level of traditional vascular remodeling markers, including *MMP-3* and *MMP-9* (*MMP-3*: before and after: 41.89±22.94 vs. 31.48±11.73 ng/ml, $p<0.01$; *MMP-9*: before and after: 366.2±194.6 vs. 225.6±111.8 ng/ml, $p<0.01$; respectively). Furthermore, the *fetuin* also improved after the TZD therapy (before vs. after: 186.5±44.4 vs. 159.8±31.2 μg/ml, $p<0.05$), but not the placebo group (before vs. after: 202.1±48.2 vs. 192.7±39.6 μg/ml, $p>0.05$).

In the association study, *MMP-3* and *MMP-9* were both associated the changes of inflammatory status representing by the *hsCRP* ($r=0.289$ and 0.315, both $p<0.001$), which was significantly reduced by TZD treatment instead of placebo group with standard therapy. Moreover, the insulin sensitivity associated biomarkers, including *resistin* and *adiponectin* levels, were strongly related to the arterial stiffness biomarker as *fetuin* level ($r=0.237$ and -0.276, $p=0.03$ and 0.01; respectively). These data supported the possible mechanism that TZD could stop the progression of vascular remodeling by lower the inflammatory status and improve the insulin sensitivity, finally ameliorate the vascular stiffness with additionally lower the activity of *MMPs* family enzymes.

Conclusion

In conclusion, this pharmaceutical clinical trial by treating with TZD and placebo successfully demonstrated that long-term use of TZD could ameliorate the biomarker

status of insulin sensitivity, inflammation severity and progression of arterial stiffness among those with pre-diabetes with documented CAD. An association has also been shown between the vascular remodeling markers, including *MMP-3*, *MMP-9* and the changes of the parameters mentioned above. These biological and observational results may imply a larger clinical study is necessary to prove the role of TZD in the secondary vascular remodeling prevention.