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Effects of Rosiglitazone on Inflammation in Otsuka Long-Evans Tokushima Fatty Rats (*Korean Diabetes J* 2010;34:191-9)

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Thank you for your comments regarding our manuscript entitled "Effects of rosiglitazone on inflammation in Otsuka Long-Evans Tokushima Fatty rats," which was published in *Korean Diabetes J 2010;34:191-9*. The authors appreciate your constructive and helpful comments. We have responded to the questions below.

Thiazolidinediones (TZD), including rosiglitazone, are high-affinity ligands for peroxisome proliferator–activated receptors-gamma (PPAR-γ) and are used as insulin-sensitizing drugs [1]. PPAR-γ is predominantly expressed in adipose tissue, whereas the improvement in insulin sensitivity after TZD treatment occurs mainly in skeletal muscle where PPAR-γ expression is relatively low [2]. Therefore, it has been suggested that TZD improves peripheral insulin action by modulating communication signals, such as adiponectin [3], leptin [4] and tumor necrosis factor-alpha (TNF-α) [5], between fat and muscle. Another explanation is that TZD improves insulin sensitivity by promoting the redistribution of triglycerides from the liver and muscle to the adipose tissue [6,7]. Many studies have reported that PPAR-γ agonists result in lipid storage coupled with the reduced release of free fatty acids (FFA) into the circulation and also increase subcutaneous adiposity but have no effect on visceral fat mass [8].

In the studies on Otsuka Long-Evans Tokushima fatty (OLETF) rats, PPAR-α activators, including bezafibrate and rosiglitazone, greatly suppressed the expression of proinflammatory cytokines such as TNF-α, interleukin (IL)-1β and IL-6, and α-smooth muscle actin (SMA) in the pancreas [7,8]. In our study, we investigated the effects of the insulin-sensitizing anti-diabetic agent rosiglitazone on the progression of skeletal muscle inflammation in OLETF rats. We found that rosiglitazone decreased the concentrations of glucose, insulin and inflammatory cytokines in the sera of OLETF rats. Rosiglitazone also inhibited mRNA expression of inflammatory cytokines in skeletal muscle by blocking the NF-κB pathway. Therefore, our findings suggest that rosiglitazone may improve insulin sensitivity with its anti-inflammatory activity in the skeletal muscle of diabetic rats.

Our results concur with the findings of previous studies that PPAR-γ agonists can improve inflammation in peripheral tissues (including the muscle and pancreas) via the inhibition of inflammatory signaling pathways [9,10]. Recently, TZD was discovered to have anti-inflammatory effects, and its potential was reevaluated for treating diabetes. Several studies have reported that TZD including rosiglitazone decreases serum levels of inflammatory makers TNF-α, IL-6, C-reactive protein (CRP), and FFAs in an experimental model of induced type 2 diabetes in high-fat-diet albino rats [11,12]. In our study, FFA levels were lower in the OLETF group compared to the LETO group at the 40th week (Fig. 1). In contrast, we observed no decrease in FFA levels in the group treated with rosiglitazone. We still do not know why rosiglitazone did not decrease se-

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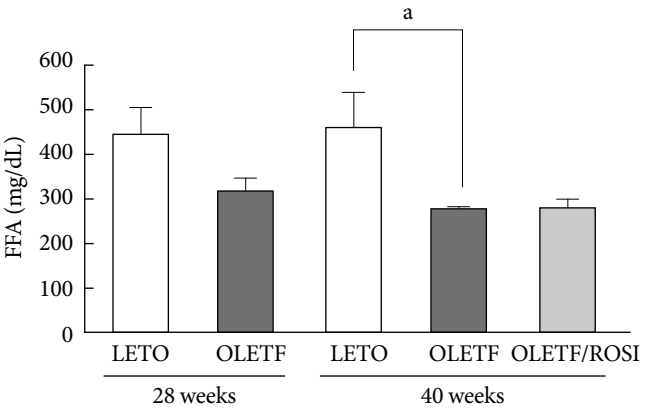

Fig. 1. Changes in concentration of serological markers in LETO and OLETF rats. Free fatty acid levels in the sera of LETO or OLETF rats were measured by colorimetric and enzymatic assay at 28 and 40 weeks. Values are represented as mean ± standard deviation. [a]$P < 0.05$ as compared to each group. ROSI, rosiglitazone; FFA, free fatty acid (From Lee JW, et al. *Korean Diabetes J* 2010;34:191-9).

rum FFA concentrations in the stage of insulin resistance of OLETF rats.

Furthermore, the anti-inflammatory effects of rosiglitazone that block the inflammatory pathway in skeletal muscle inflammation in diabetic and insulin-resistant patients without excessive FFA influx into the skeletal muscle are not clear. Due to the link between insulin resistance and inflammatory processes, we suggest that therapeutic strategies to limit inflammation and reduce levels of inflammatory markers may be a promising tool in reducing symptoms in such patients [13,14].

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