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COMMENT ON FRANCÉS ET AL.

Hepatic Cyclooxygenase-2 Expression Protects Against Diet-Induced Steatosis, Obesity, and Insulin Resistance. Diabetes 2015;64:1522–1531

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The recent study by Francés et al. (1) presented an interesting experimental study in which the authors demonstrated that constitutive expression of human cyclooxygenase (COX)-2 in hepatocytes protects against adiposity and inflammation and hence insulin resistance induced by a high-fat diet, as demonstrated by decreased hepatic steatosis, adiposity, plasmatic and hepatic triglycerides, and free fatty acids; increased adiponectin/leptin ratio; and decreased levels of proinflammatory cytokines together with an enhancement of insulin sensitivity and glucose tolerance. The authors concluded that COX-2 could be a potential therapeutic target against obesity-associated metabolic dysfunction. For this reason, we wish to share the results of two studies conducted by our research team.

In 2001, we carried out a randomized, double-blind, controlled clinical trial in which the objective was to identify the effects of COX-1 and -2 inhibition on insulin sensitivity in 21 young, healthy, nonobese male volunteers. Pharmacological COX-1 inhibition was performed with acetylsalicylic acid (ASA) at a low dose, and COX-2 selective inhibition was performed with celecoxib. After randomization, subjects received an oral morning dose of ASA 100 mg ($n = 7$), celecoxib 200 mg ($n = 7$), or placebo for the control group ($n = 7$) for 15 days. Before and after the intervention, an insulin tolerance test (ITT) was performed to assess insulin sensitivity, and the constant for the serum glucose disappearance rate (KITT) was calculated. The KITT calculated with the ITT was higher after celecoxib than at baseline (4.8 ± 0.9 vs. 4.3 ± 0.6%/min, $P = 0.04$), indicating improvement in insulin sensitivity (2).

On the basis of the results of the previous study, a randomized, double-blind, placebo-controlled clinical trial in 12 overweight or obese male volunteers was performed. Six subjects received celecoxib 200 mg and six other subjects received a placebo (control group) orally in the morning for 4 weeks. Before and after the intervention, insulin sensitivity, C-reactive protein and homocysteine levels, and metabolic profile were estimated. To assess insulin sensitivity, the euglycemic-hyperinsulinemic clamp technique was performed. The insulin sensitivity after celecoxib was significantly higher compared with the basal estimation (3.8 ± 1.2 vs. 2.8 ± 1.2 mg/kg/min; $P = 0.028$) (3).

We agree with Francés et al. (1) that COX-2 is a potential therapeutic target for the treatment of insulin resistance and that more in-depth human studies should be performed in larger populations with longer interventions and with different COX-2 inhibitors.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Francés DE, Motiño O, Agrá N, et al. Hepatic cyclooxygenase-2 expression protects against diet-induced steatosis, obesity, and insulin resistance. Diabetes 2015;64:1522–1531

2. González-Ortiz M, Martínez-Abundis E, Balcázar-Muñoz BR, Robles-Cervantes JA. Inhibition of cyclooxygenase-1 or -2 on insulin sensitivity in healthy subjects. Horm Metab Res 2001;33:250–253

3. González-Ortiz M, Pascoe-González S, Esperanzamartínez-Abundis, Kam-Ramos AM, Hernández-Salazar E. Effect of celecoxib, a cyclooxygenase-2-specific inhibitor, on insulin sensitivity, C-reactive protein, homocysteine, and metabolic profile in overweight or obese subjects. Metab Syndr Relat Disord 2005;3:95–101

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