Estradiol from fatty tissue doesn't cause low testosterone in type 2 diabetic men

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It's not estrogen produced by body fat that causes low levels of testosterone in type 2 diabetic men, according to a University at Buffalo study published last month in *Diabetes Care*.

Instead, the mechanism responsible for low levels of certain sex hormones in type 2 diabetic men is more complicated than originally thought, which will have implications for the development of effective treatments. The UB researchers suggest that, based on their findings, the mechanism likely originates in the hypothalamus, the part of the brain that controls hormones influencing appetite, sleep, moods and sex drive.

In 2004, the UB researchers first identified this syndrome of hypogonadism (low testosterone) in a third of type 2 diabetic men that they studied.

At the time, the conventional wisdom was that an enzyme expressed by body fat is increased in obese people, explains lead author Sandeep Dhindsa, MD, assistant professor of medicine in the UB School of Medicine and Biomedical Sciences and senior author Paresh Dandona, MD, UB Distinguished Professor of Medicine.

"It was thought that that enzyme, in turn, increased estradiol levels in the blood, which led to suppressed testosterone levels," says Dandona.

But the connection may not be all that simple, partly because not all type 2 diabetics are obese, Dandona says.

Their current study, which included both obese and non-obese type 2 diabetic men, revealed that estradiol levels in 240 subjects with low testosterone were lower, not higher, than normal levels.

"Low testostone levels as well as low estradiol levels, which we saw in this study, both probably contribute to the markedly increased risk of cardiovascular mortality in type 2 diabetics," he says.

The UB researchers established the estradiol levels using a classical measurement method and a state-of-the-art tandem mass spectrometry measurement.

"These data establish unequivocally that elevated estradiol concentrations are not the cause of this hypogonadism syndrome," says Dandona. "We now need to look for other mechanisms for the rational understanding and treatment of this syndrome so that we can unravel the mysterious mechanisms underlying this important cause of male hypogonadism (low testosterone) and potential infertility."

Dandona and his UB colleagues have extended these observations to non-diabetic, obese adults and obese children, between the ages of 15 and 20, a quarter of whom have a similar problem with low testosterone levels.

"Low testosterone levels affect a third of male type 2 diabetics, of which there are roughly ten million in this country," says Dandona. "If we can elucidate the specific underlying mechanism, we can develop a rational treatment for this condition."

Based on previous work with experimental animals, the UB researchers are currently exploring the role of resistance to the action of insulin, known to occur in these patients, at the level of the brain to elucidate the mechanism underlying the defect in testosterone production.