

## What Kind of Probucol Affects Normalizing Male Birth?

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High-density lipoprotein (HDL) cholesterol (HDL-C), induced by activation of the ATP-binding cassette transporter A1 (ABCA1)<sup>1)</sup>, has been associated with anti-atherosclerosis<sup>2)</sup>. Probucol originally gained attention as an antioxidant compound through a rubber manufacturing process. Although it significantly reduces the HDL-C level in blood by strongly inhibiting ABCA1, several anti-atherosclerotic effects have been reported. Some of these effects are contrary to prediction<sup>3)</sup>. At present, probucol is a controversial drug, with extremely difficult-to-recognize overall efficacy.

Infertility in both scavenger receptor BI (SR-BI)-deficient mice with high HDL-C levels and ABCA1-deficient mice with very low HDL-C levels were previously reported. Conversely, probucol has been reported to yield favorable effects by improving infertility in SR-BI-deficient mice with high HDL-C levels.

In this issue of the Journal of Atherosclerosis and Thrombosis, Tsujita M and colleagues investigated in detail the propagation of very low HDL [ABCA1-deficient mice and lecithin: cholesterol acyltransferase (LCAT)-deficient mice] compared with the wild-type mice as well as the effects of probucol on their propagation<sup>4)</sup>. They reported the following novel findings: first, both ABCA1-deficient and LCAT-deficient mice experienced infertility; however, the reproduction of the wild-type mice with extremely low HDL-C levels as a result of probucol was unaffected. Second, probucol normalized the decrease in male genotypes in LCAT-deficient mice even though the HDL level was decreased. Third, cholesterol turnovers in some organs were upregulated by probucol administration. With

probucol, only LCAT-null mice had marginally higher cholesterol ester levels in the steroidogenic adrenal gland and higher plasma corticosterone levels, which might possibly affect the correction of male birth.

This is the first study showing the correction of male birth using probucol under certain conditions. Based on the HDL levels, the outcomes implied that HDL-C levels in the blood were unrelated to propagation under extremely low HDL-C levels. Because no changes in propagation were observed in ABCA1-null mice that were administered probucol, it is suggested that ABCA1 itself was extremely important in the organs, and its strong inhibition would induce increased cholesterol ester levels in some organs with actions affecting the propagation. In fact, organs associated with reproduction, such as the ovary and adrenal gland, have high levels of SRBI and ABCA1<sup>5, 6)</sup>. ABCA1 has been recently reported to decrease the concentration and motility of spermatozoa in human males and is related to high ABCA1 expression in the spermatozoa<sup>7)</sup>. However, probucol has not been known to solely affect males, females, or both in propagation. Therefore, if probucol is administered to only male or female mice, the outcomes may be better, suggesting positive solutions to the problem.

Because the incidence of infertility associated with coagulation disorders has been increasing in women, this study indicated that propagation might be associated with the coagulation factor vitamin K. Further studies evaluating the effects of probucol in correcting genotype propagation and its results would contribute to the development of novel clinical treatment.

### Conflict of Interest

YU received research grants, and promotional

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