Trans sexualism

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In the March issue of the *Journal of the Chinese Medical Association*, one topic addressed a very important issue about metabolic effects of cross-sex hormone therapy (HT) in transgender individuals.[1] The authors retrospectively evaluated the metabolic changes in 110 transgenders, including 65 transmasculine subjects (also: female-to-male, transman, transgender male, which refers to individuals assigned female at birth but show identify and live as men)[2] and 45 transfeminine subjects (also: male-to-female, transwoman, transgender female, which refers to individuals assigned male at birth but show identify and live as men)[2] between before and after the gender affirming hormonal therapy (HT).[1] As expected, the transmen showed the increased bad lipid profiles, such as the increased low-density lipoprotein cholesterol (LDL-C) and decreased high-density lipoprotein cholesterol (HDL-C) after androgen use and by contrast, the transwomen had a better lipid profile, such as a decreased LDL-C after the use of female HT.[1] With the aforementioned results, the authors concluded that gender-affirming HT (androgen) increased the relative cardiovascular (CV) risk in transmen.[1] Although their study did not add new information, the topic discussing the issue of trans sexualism is still worthy of discussion.

First, CV disease and chronic kidney disease (CKD) are complex diseases of multifactorial origin, which is a gender difference in the incidence and severity of the disease, and in that women, especially before menopause, have a significantly lower risk of CVD and CKD than men.[2,3] However, the gender-related disease risk may be related to different gender hormone, regardless which gender is. Evidence has shown that the increased male hormone serum levels in female population are strongly correlated with the increased risk of CVD.[4] Among these, polycystic ovary syndrome may be one of best examples.[5–7]

In their study, this hypothesis seems to be supported by their study, since according to the significant increase of LDL-C and decrease HDL-C in transmen treated with androgen, the authors concluded this androgen-related change of lipid profile may increase the CVD risk in transmen.[1] We do not want to argue this conclusion. Elevated serum levels of LDL-C have been definitively demonstrated to be a cause of atherosclerotic CVD.[8–11] Furthermore, based on the rule of "the lower the better," "the earlier the better," and "the longer the better" for the reduction of LDL-C concentration, an recognition of the critical role in the primary or secondary prevention or atherosclerotic CVD by reducing lifetime exposure to LDL-C has been much more acceptable in clinical practice,[9,10] contributing to the fact that the trends lead us to expect near-universal coverage of LDL-C reducing agents in individuals at the greatest risk.[9] Therefore, if the transmen are expected to have progressively increased serum levels of LDL-C, some strategies to interrupt this bad way may be needed. However, the questions are raised where is a way to go to obtain the maximum possible health benefits from these strategies. The first argument is "Are they the targeted individuals?" The second argument is "What are the idea serum concentrations of LDL-C to be achieved?" A systematic evidence review for the US Preventive Service Task Force raised one of important limitations about the aforementioned issues. For example, the uncertainty of thresholds (cut points) for defining elevated LDL-C concentration makes the prevalence of dyslipidemia (and diagnostic yield) difficult to interpret. The thresholds may over- or under-identify subjects, depending on age and gender. However, for trans sexualism, which gender of these should be classified?

Additionally, based on the publication of the European Society of Cardiology/European Atherosclerosis Society 2019 lipid guidelines as well as the 2017 Taiwan lipid guidelines,[12,13] evidence is strong to support the targeted levels of LDL-C as less than 55 mg/dL or even lower than 40 mg/dL, especially for very high-risk patients. However, the certain differences have been existed between western countries and Taiwan.[13] Of most importance, the discrepancy of targeted serum level of LDL-C between western countries and Taiwan is not only limited to high-risk patients but also involved in general population. In fact, there is still absent of concept whether "intensity-driven" or "target-driven" approach to reduce the risk of atherosclerotic CVD should be to follow. Many causes have been supposed to explain the above-mentioned controversies. Cost is probably not a major contributor to these differences.[9] The overlooked risk of high serum levels of LDL-C, poor compliance, nonadherence/intolerance of lipid-lowering agents, and occurrence of adverse events, regardless lipid-lowering agents-related or -unrelated may partly play a much more critical role of the enlarged gap between lowering LDL-C levels and decreased risk of atherosclerotic CVD.

Second, as shown above, it is hard to convince these transmen or even general population to accept that they with the trend of the increased LDL-C will be vulnerable to risk of atherosclerotic CVD. According to the results of their study,[1] the statistically significant increase of LDL-C in transmen from baseline with absence of transgender HT to the end (between 12 and 24 months after transgender HT) by 124.3 ± 3.7 mg/dL to 131.3 ± 3.9 mg/dL and

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 457-458.

Received February 22, 2021; accepted February 22, 2021.

doi: 10.1097/JCMA.0000000000000511.

median difference between two was only 7 mg/dL. Does this little difference contribute to any deterioration in their global health? It is difficult to reflect this statistical significance to the clinical significance, if no evidence was found for an effect of treatment on health outcomes in the transgenders. In addition, as shown before, we should keep in mind that interpretation of results from any study should be taken into consideration by looking at the actual clinical significance and should not be missed by statistical significance.[14,15]

The well-known positive correlation between higher LDL-C concentrations and higher atherosclerotic CVD risks has been definitively demonstrated to be an important issue for trans sexualism subjects, especially transmen when clinicians face these transgenders. According to their report, increasing recognition is given to the modulating lifetime exposure to LDL-C when this androgenic hormone is given. It is clear that these trends are all in the right direction, but the there is still a big challenge to deal with these transgenders, not only on an involvement of physiological changes but also on consideration of psychological supports. We are looking forward to seeing more studies focusing on this topic to enhance the global health in this transgender population.

ACKNOWLEDGMENTS

This article was supported by grants from the Ministry of Science and Technology, Executive Yuan, Taiwan (MOST 109-2314-B-075B-014-MY2 and MOST 109-2314-B-075-056), and Taipei Veterans General Hospital (V110C-082, and VGH109E-005-5). The authors appreciate the support from Female Cancer Foundation, Taipei, Taiwan.

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