Effects of Exercise on ACE2

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TO THE EDITOR: Obesity has been shown to increase the risk for more severe coronavirus disease 2019 (COVID-19) courses and higher mortality, particularly among younger (age < 50 years) hospitalized patients (1). In addition to obesity, conditions that are typically associated with lower physical activity (higher age, hypertension, diabetes, coronary heart disease, and chronic obstructive pulmonary disease) are associated with worse clinical outcomes from COVID-19 (2). Regular physical exercise promotes immune defense and decreases susceptibility to pathogenic microorganisms, including viruses. Under the time pressure of the current COVID-19 pandemic, rapid scientific discoveries together with clinical observations have provided several potential drug targets. However, so far, neither vaccines nor effective and safe pharmacotherapies against the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exist. Therefore, nonpharmacological strategies, particularly moderate exercise, should be considered as approaches to reduce the SARS-CoV-2 infection–related burden. Whether physical exercise affects propagation of SARS-CoV-2 or the course of COVID-19 is currently unknown.

Cellular entry of SARS-CoV-2 requires angiotensin-converting enzyme 2 (ACE2) (3). ACE2 is a membrane-bound enzyme that is released into the circulation via ectodomain shedding (3). Variation in circulating ACE2 protein may result from genetic factors, differential gene expression in various tissues and/or ectodomain shedding influenced by diseases (including COVID-19), medications, or exercise (3). In addition, ACE2 plays an important role in regulating angiotensin II. So far, it has not been fully understood how the balance between the membrane-bound ACE2 receptor and its soluble form is maintained, and whether this balance may contribute to COVID-19 susceptibility is not known.

Indeed, targeting ACE2 holds promise as a way to prevent COVID-19 in exposed individuals or at least to attenuate severe disease courses. Higher endogenous ACE2 serum concentrations may predispose individuals to severe COVID-19 outcomes. Evidence obtained before the COVID-19 pandemic indicates that intensive aerobic physical exercise acutely increases plasma concentrations of ACE2 in humans (4). It remains unclear whether and how these short-term exercise effects translate into long-term changes to ACE2 serum concentrations.

We therefore tested the hypothesis that physical exercise causes chronic alterations in ACE2 serum concentrations. In the context of a previously reported, randomized, double-blinded, placebo-controlled physical-training intervention of 4 weeks, we evaluated putative changes of vastus lateralis *ACE2* mRNA expression and ACE2 serum concentration over baseline in healthy young men with or without concomitant treatment with the antioxidant vitamins C and E, given orally (5). In this post hoc analysis, we found a significant increase in

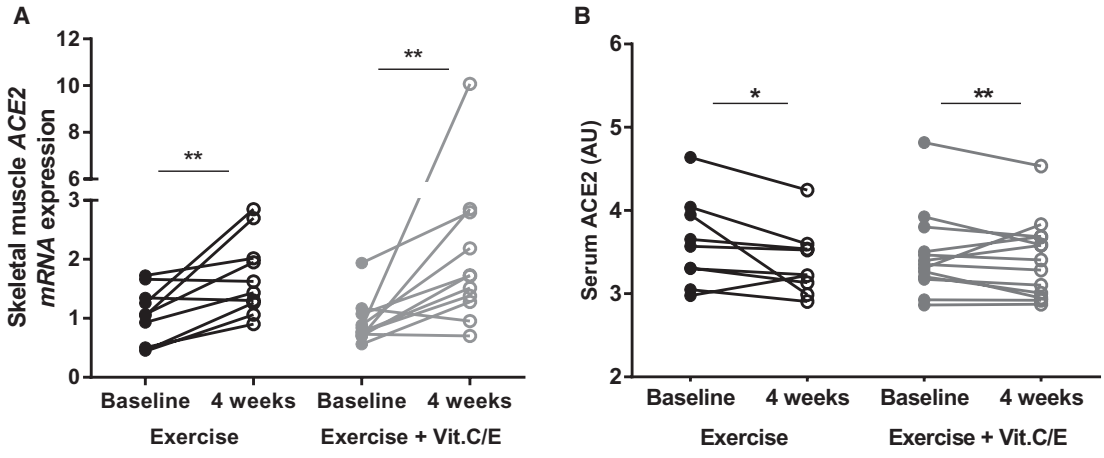

Figure 1 Effects of a 4-week intensive exercise intervention on angiotensin-converting enzyme 2 (*ACE2*) mRNA expression in skeletal muscle and ACE2 serum concentrations. Twenty-one healthy young men took part in a supervised exercise program over 4 weeks, as previously reported (5). Eleven participants received, in addition to the exercise intervention, 1,000 mg of vitamin C and 400 IU of vitamin E orally (Exercise + Vit.C/E). (**A**) *ACE2* mRNA was measured using the QuantStudio 6 Flex Real-Time PCR System (ACE2: Hs00174179_m1; 18S rRNA: Hs99999901_s1; Life Technologies). Skeletal muscle biopsy specimens were obtained under local anesthesia from the right vastus lateralis muscle and were immediately snap-frozen in liquid nitrogen. (**B**) ACE2 serum concentrations were measured using the Olink Cardiovascular II panel Proseek analysis service. Results are expressed in the form of relative quantification (normalized protein expression) and are logarithmically related to protein concentrations but cannot be converted to absolute protein concentrations. Interpretations are therefore relative and not absolute. Immediately before each skeletal muscle biopsy, blood samples were obtained in the fasted state between 8 AM and 10 AM after an overnight fast. Serum aliquots were stored for further analyses at –80°C. The study was approved by the ethics committee of the University of Leipzig, Leipzig, Germany. The study was registered at ClinicalTrials.gov: identifier NCT00638560. * $P < 0.05$; ** $P < 0.01$ compared with baseline.

skeletal muscle *ACE2* expression, which was independent of the treatment with antioxidants (Figure 1A). Baseline circulating ACE2 levels were not different between the treatment groups ($P=0.13$). The intensive exercise program led to significantly reduced ACE2 serum concentrations, which were most pronounced in the group receiving antioxidant supplementation (Figure 1B). The discrepancy between higher muscle *ACE2* expression and lower circulating ACE2 in response to the training program indirectly suggests that skeletal muscle does not play a crucial role in determining ACE2 serum concentrations. In addition, we are aware that *ACE2* mRNA measurements do not necessarily reflect ACE2 protein levels in either the skeletal muscle or the serum. We acknowledge the limitation that the muscle biopsy material was not sufficient to perform ACE2 protein analyses.

Taking these factors together, we report here that physical exercise induces expression of *ACE2* in skeletal muscle but leads to lower circulating ACE2 levels that may potentially impact SARS-CoV-2 pathogenicity. Whether increased *ACE2* expression following exercise also occurs in the lung, heart, or other tissues more relevant to individual COVID-19 outcomes and whether exercise modifies susceptibility to SARS-CoV-2 and the severity of COVID-19 should be systematically investigated in larger cohorts. Our findings may have practical implications, especially for people with increased susceptibility to SARS-CoV-2 infections, in whom a lack of physical exercise may serve as a modifiable risk factor.

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