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COMMENTARY

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Are we closer to providing better guidance for prescribing metformin and exercise to patients?

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Habitual exercise improves glycemia in people at risk for, or with, type 2 diabetes (T2D) (1). Although the optimal frequency, intensity, timing, duration, and mode of exercise are debatable, there is no argument that going from relatively sedentary to even modestly active lifestyles raises cardiorespiratory fitness and increases insulin sensitivity in people with prediabetes or T2D. However, the magnitude of the improvements varies across individuals (2), and it is unlikely that adopting an exercise program alone will abolish the need for antidiabetes medication. Often, that medication is metformin, the first-line agent for treatment of hyperglycemia. The net impact of combining two independently effective "medications," e.g., exercise and metformin, is often not additive, as has been noted in several studies and reviews.

In this issue of *Obesity*, Moreno-Cabanas et al. (3) assessed cardiorespiratory fitness (VO_2max), indices of fasted insulin sensitivity (homeostatic model assessment of insulin resistance [HOMA-IR]), and several cardiovascular disease risk factors (i.e., blood pressure, triglycerides, etc.) in people with metabolic syndrome, before and after exercise training and in the presence or absence of habitual metformin use. Exercise consisted of high intensity interval training 3 d/wk at approximately 43 min/session for 16 weeks. Metformin dose averaged 1,279 mg/d, in the typical range for treating individuals with prediabetes. After training, individuals taking metformin had less improvement in VO_2max and in blood pressure when compared with training alone. However, unlike some prior studies, the robust enhancement of VO_2max in the nonmedicated group did not enhance the effect of training on body composition, lipids, or HOMA-IR.

The main finding by Moreno-Cabanas et al. (3), that metformin constrains improvement to VO_2max following an exercise training program, confirms prior work (see reviews: (4, 5)). In contrast with much previous work, Moreno-Cabanas et al. report that the presence of metformin did not change the magnitude of the training responses in terms of fasting insulin sensitivity. As correctly noted by the authors, metformin is a widely prescribed, effective, inexpensive medication with few side effects. Additionally, with overwhelming evidence that exercise benefits nearly every aspect of human health, health care providers are prescribing metformin while also strongly encouraging their patients to be physically active. The context in which metformin/exercise studies are done may help explain discrepant results. There is a fundamental difference between starting an exercise regimen in people already taking metformin versus starting them together. The former illustrates how medicated patients respond to exercise in a common "real-world" situation, whereas the latter is a more controlled experimental design that also provides clinically relevant data. Both types of studies confirm that metformin impairs the cardiorespiratory responses to training (4), with a key unanswered question being the following: "what is the clinical relevance?" Moreno-Cabanas et al. (3) suggest that the smaller gain in VO_2max is inconsequential for glycemic outcomes. We believe this claim should be interpreted with caution. One reason is that several other studies do report that blunted gains in VO_2max parallel attenuated insulin sensitivity (via clamp or oral glucose tolerance test), blood pressure,

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and mitochondrial adaptations (5). Another reason is that there was a substantial difference between groups of the present work (3) in key characteristics that likely impacted results. Most notably, the metformin group had mean fasting plasma glucose (FPG) > 152 mg/dL, a value that exceeds the threshold for overt T2D. In contrast, the exercise-only group started with FPG < 105 mg/dL, a value only slightly above the normal range. A main outcome, HOMA-IR was 4.7 in the metformin group but only 3.1 in the exercise-only group, a difference that tracks with the substantial gap in FPG and indicates that, in terms of glycemic outcomes, the two groups are difficult to directly compare (however, the groups were well matched on other metabolic syndrome criteria). Does this mean participant characteristics influenced the results? This is tricky to answer, as the presence of metformin was shown to blunt VO_2max in participants who were euglycemic (6), as well as those with considerable dysglycemia (4). But whether that blunting effect contributes to clinically relevant issues may depend on participant characteristics, the order in which metformin and exercise are prescribed, and/or which outcomes are assessed (e.g., daily/nocturnal glycemia, glycated hemoglobin, oral glucose tolerance, progression from prediabetes to diabetes).

The authors (3) reasonably suggest that clinicians can keep patients on metformin while they start exercising because it will not impair clinical benefits. We agree, given there is no strong evidence that adding exercise and metformin interferes with clinical outcomes in actual patients. But we note that VO_2max is a known predictor for morbidity/mortality, and the goal of starting patients on exercise programs is to maximize well-being. From that lens, we need to provide clinicians better guidance on how to prescribe metformin and exercise to patients. Addressing the unresolved questions of how the metformin and exercise "medicines" interact is critical.O

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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