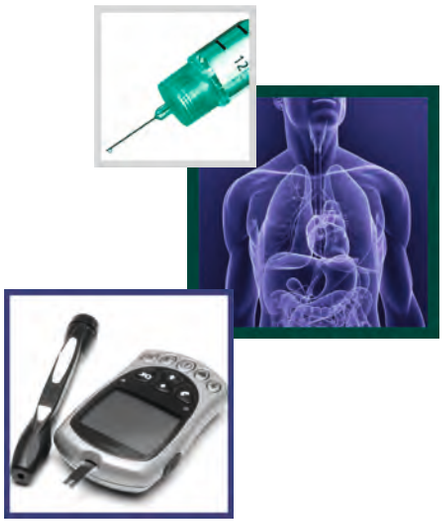

Complex relationship between metformin and exercise in diabetes treatment: should we reconsider our recommendations?

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"Given the frequency at which exercise and metformin are prescribed together, it is surprising how little is known about how these treatment modalities interact."

Exercise and metformin have been used together to lower blood glucose for over half a century. Today, they represent two of the primary therapeutic approaches for managing Type 2 diabetes. Given the frequency at which exercise and metformin are prescribed together, it is surprising how little is known about how these treatment modalities interact. For example, to what extent the glucose-lowering effects of metformin and exercise are additive when used together is not well understood. On the other hand, growing concerns regarding 'glucocentric' approaches to diabetes management has resulted in further recognition of the importance of other modifiable risk factors for cardiovascular disease [1]. One such risk factor is exercise capacity (also known as cardiovascular fitness or aerobic fitness), which is considered as one of the strongest predictor of mortality in people with and without diabetes [2]. While exercise interventions can be specifically designed to improve exercise capacity in people with diabetes [3], little is known about the impact of other diabetes therapies on this important risk factor.

What do we know about combining exercise & metformin?

■ Do metformin & exercise affect each other?

Early studies examining the effects of metformin and other biguanides on the capacity to exercise have primarily focused on lactate concentrations, which were known to increase with exercise intensity and with medications from this class [4]. Studies generally suggest that the small increases in lactate observed with metformin persisted during exercise of various intensities but were not further accentuated [5,6].

In recent years, studies have found that metformin can affect submaximal exercise by increasing heart rate or ratings of perceived exertion [5,6]. Heart rate and perceptions of exertion are often used to prescribe exercise intensities. Consequently, patients taking metformin could reach a targeted heart rate or perceived exertion with lower workloads. This could in turn have a small but significant impact on their energy expenditure or fitness gains. Perhaps even more concerning could be a decrease

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in physical activity behaviors if exercise becomes less enjoyable.

On the other hand, metformin has been shown to activate AMPK and studies in rodents have shown that other AMPK activators, such as AICAR, can increase exercise capacity [7]. While this has not been shown in humans with metformin, an increase in fat oxidation during exercise has been consistently observed [5,6,8,9], which could theoretically lead to reduced dependence on muscle glycogen and prolonged endurance. In addition, metformin has been shown to improve exercise tolerance (i.e., Duke score) in nondiabetic women with clinically defined angina, and this was attributed to improved endothelial function [10].

Resistance training is also recommended for people with Type 2 diabetes [11]. Resistance training, such as exercising with weight machines, relies largely on anaerobic energy production. Significant reductions in muscle concentrations of ATP (-23%) and phosphocreatine (-34%) have been observed after 10 weeks of metformin treatment [12]. Whether these changes translate to a reduced ability to perform resistance training exercises is not well understood.

Exercise has the potential to affect many drugs through its effects on blood flow, absorption, excretion and metabolism. Although metformin is not metabolized by humans, changes in blood-flow distribution during exercise could affect the metformin pharmacokinetics. In addition, both exercise and metformin activate AMPK in overlapping tissues and it is not clear how this affects metformin pharmacodynamics. In our most recent study we were surprised to observe that plasma metformin concentration were elevated on exercise day compared with rest days [6]. However, more detailed studies are needed to better understand these findings.

In summary, metformin and exercise can affect each other in multiple ways. However, to date, the magnitude of the observed effects in humans have been relatively small and it is unclear to what extent they have meaningful long-term impacts on people with diabetes.

■ Are the glucose-lowering effects of metformin & exercise additive?

Generally, the higher the baseline glycated hemoglobin (A1C), the greater the anticipated A1C reduction from medications [13] or exercise [14]. Consequently, it could be expected that the effects of exercise on glycemic control may be lower in those who have already improved their glycemic control with metformin. In addition, since exercise and metformin activate partially overlapping pathways (e.g., AMPK), improvements in glycemic control resulting from combining metformin and exercise may be even less than expected. Perhaps it should not have been a surprise when the Indian Diabetes Prevention Program reported that the combined lifestyle and metformin intervention was no more effective at lowering the risk of developing diabetes than either intervention alone [15]. However, the reasons for the complete absence of additive effects of metformin and lifestyle in this study are not understood and may be related to the population, a floor effect as well as physiological factors mentioned above.

Insight on the interactions between the effects of metformin and exercise were recently highlighted in two similar short-term studies. In the study by Sharoff *et al.*, the 2–3 weeks of metformin use virtually eliminated the insulin sensitizing effect of a single bout of exercise [9]. Furthermore, we have shown that in some conditions the combination may in fact be less effective at lowering the glycemic response to a meal than metformin alone [6]. A recent study has also suggested that the insulin sensitizing effect of 12 weeks of combined exercise training with metformin may be reduced compared to exercise or metformin alone in people with prediabetes [16].

Should we reconsider our recommendations?

At this point, there is insufficient evidence to suggest exercise and metformin should not be prescribed together as part of a first-line therapeutic approach to the management of diabetes. Even though the glucose-lowering effects of exercise and metformin may not be additive, there is no evidence to suggest their combination exposes patients to a greater risk of lactic acidosis, hypoglycemia or diabetes complications, nor to suggest that metformin has a meaningful negative impact on exercise capacity or participation. Nevertheless, there may be strategies to help patients and practitioners better use these treatment modalities together.

The current approach in many countries, such as Canada [17], is to prescribe metformin almost immediately after the diagnosis of diabetes, leaving little time for lifestyle interventions to exert their full effect. This approach seems justified, even for patients with relatively good glycemic control, due to the poor long-term adherence that plagues most

lifestyle interventions. However, there is evidence that metformin is not nearly as effective in older participants or in those with lower BMIs, and that the effect of lifestyle intervention is much stronger in these subgroups [18], probably due to the greater likelihood of increasing physical activity [19]. Consequently, an older, leaner individual with Type 2 diabetes who has no orthopedic limitations to physical activity and relatively good glycemic control would probably get greater benefits from additional support for lifestyle changes rather than from early addition of metformin.

The timing of meals and exercise is often considered when determining the appropriate use of other therapies such as insulin secretagogues or insulin. However, since the combination of metformin and exercise does not lead to hypoglycemia, little attention has been devoted to examining the impact of meal timing. It's important to note that the studies demonstrating a negative interaction between exercise and metformin on glucose metabolism have been conducted in conditions of near normoglycemia. One study was conducted 3 h after a small breakfast in people with very well-controlled diabetes [6] and the other was conducted in the fasting state in nondiabetics [9]. In these conditions, the combination of metformin and exercise increased glucagon [6] or hepatic glucose output [9] to a greater extent than exercise alone. Perhaps exercising soon after a meal would reduce this exaggerated counterregulatory response.

The discussion above has mostly focused on physiological interactions between metformin and exercise. However, it is important to remember that lowering hyperglycemia can be an important motivator for lifestyle changes. The following questions need to be considered by patient and their healthcare providers. Are patients who reach glycemic targets through medication less inclined to perceive the need to make significant lifestyle changes? Are patients who see fewer improvements in glycemic control after exercise less likely to continue engaging in those behaviors? Although speculative and not applicable to all patients, the unintended consequence of early metformin prescription could be to reduce the likelihood of adopting or maintaining exercise, thereby missing out on a very long list of other benefits of exercise.

In summary, the effectiveness of two of the primary treatment modalities for Type 2 diabetes can be influenced by many factors and recent studies exemplify the importance of further examining how these treatments can affect each other. A recent systematic review on the effects of physical activity on A1C in Type 2 diabetes identified 23 studies with a total of only 933 participants randomized to structured exercise groups [14]. This illustrates the relatively small capacity to conduct exercise studies compared with other diabetes therapies. Future pharmaceutical studies need to more directly consider how their medications interact with exercise, a recognized cornerstone of diabetes therapy.

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