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Effects and safety of exercise combined with medication and diet in treatment of diabetes and comorbidity

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Objective The role of exercise in the prevention and treatment of chronic diseases is widely accepted and regular physical exercise may play an irreplaceable role beyond traditional medicine and drug treatments. However, current guidelines do not provide details on the characteristics of exercise programs which are aimed to be carried out concomitantly to drug treatments. Moroever, the safety of combined exercise and drug treatments has rarely been considered.
The future of exercise is medicine research will likely need to focus on questions such as how to build customized exercise programs for different patients in the context of individual physiological responses to exercise? When combining drug and concomitant exercise treatment, what is the optimal exercise prescription in terms of timing, intensity and duration? Does exercise only have an additive effect or may exercise actually reverse or even cancel out some of the expected effects induced by the drug treatment? What is the role of diet in exercise interventions? Does a given exercise program affect the lipid and glucose metabolism to the same extent?
In this report, we will present different randomized clinical trials conducted in our research group to tackle some of the abovementioned questions. This particularly includes patients with comorbidity conditions (prediabetes and non-alcohol fatty liver disease,NAFLD), as well as patients with type 2 diabetes (T2D).
Methods Two different randomized trials are included, both of which were conducted in China (ChiCTR-IOR-16008469 and ISRCTN 42622771). The ChiCTR-IOR-16008469 study was a randomized crossover trial. The aim of this study was to assess whether the duration between metformin administration and high-intensity cycling (HIIT) affects the glucose metabolism. T2D patients performed a single session of HIIT (~25 minutes) at 30 (EX30), 60 (EX60), and 90 (EX90) minutes following breakfast and metformin administration in a randomized order. Subjects' diurnal glucose metabolism was assessed between 8:00 a.m. and 4:00 p.m. (Metf) of each exercise day as well as on a control day. Furthermore, insulin was assessed both before and immediately after each exercise bout. The ISRCTN42622771 trial was a four arm randomized trial. Six-hundred and three patients from seven clinics were recruited, out of which 115 individuals aged 50-65-year fulfilled the inclusion criteria (impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) and NAFLD) and were randomly assigned (1:1:1:1) to either of the four groups: aerobic exercise (AEx, n = 29), diet intervention (Diet, n = 28), aerobic exercise plus diet intervention (AED = 29), or no intervention (NI = 29). The study spanned over anaverage period of 8.6 months (7-11 months). Progressive supervised aerobic exercise training (60-75% intensity) was carried out 2-3 times/week in 30-60 min/sessions, and the diet intervention consisted of a lunch with 38% carbohydrate and diet fibre of 12g per day, while the remaining meals were freely chosen but with supervised nutrition intakes. The hepatic fat content (HFC) assessed by 1H MRS, glycated haemoglobin (HbA1c) and insulin sensitivity were assessed by conventional methods.

Results In study 1, we found that in diabetes patient glucose levels significantly decreased in all exercise settings, irrespective of the timing. However, whenHIIT was performed at 30 minutes post-metformin administration, the peak glucose was lowered, thereby further stabilizing the postprandial glucose fluctuation. The risk for hypoglycemia at different times to exercise after metformin administration was highest in EX90 (22.2%) compared to EX30 (3.7%) and EX60 (7.4%). While the lactate level was 19% higher in EX60 and 8% higher in EX90 compared to EX30. Compared with Metformin, the decrease in insulin was larger in EX30 and EX60 (both p < 0 001). These results indicate that timing of exercise is an important factor to consider when prescribing exercise as adjuvant to metformin therapy for T2DM patients.

In study 2, we showed that in patients with morbidity (prediabetes with NAFLD), HFC was significantly reduced in the AEx (–24.4%), diet (–23.2%), and AED (–47.9%) groups, as opposed to the 20.9% increase in the NI group (p=0.006, p=0.002, and P<0.0001, respectively).Importantly, HFC decreased to normal levels (<5.6%) in ten (44%) out of 23 participants in the exercise plus diet group and nine (41%) out of 22 participants in the diet group, while the in the exercise group it decreased only in three (14%) out of 29 participants. Further, all intervention groups showed improvements ininsulin sensitivity (AEx 33%, p=0.023, Diet 37%, p=0.012, and AED 34%, p=0.029) but only the AED group significantly decreased HbA1c (-4.4%, p=0.01) compared with the NI group (1.9% and -0.6%). However, after controlling for the change of body weight as well as for the duration of the intervention and baseline values, the significant differences in HbA1cand insulin sensitivity between the groups disappeared. Furthermore, based on HbA1c IFG or IGT, no significant remission and progression from prediabetes to diabetes were observed between the intervention and NI.

Conclusions The results derived from these two trials imply that: 1) the combined effects of exercise and metformin therapy on T2D should take into account that both exercise and metformin are likely to affect the lactic metabolism because T2D is considered as a redox disease. For the acute effect of exercise combined with metformin therapy, exercising at 30 minutes post-metformin administration appeared to be optimal for reducing glucose fluctuation. To avoid the risk for hypoglycemia and lactases with the combined treatment, selecting optimal timing may be the first and easiest step towards personalized exercise medicine. Thus, when exercise is recommended to diabetic patients, the timing of exercise may be an important consideration so that the therapeutic effects of metformin are not compromised. However, further studies are warranted to elucidate the long-term effects of combining metformin and exercise on glycemic control and lactic metabolism as well as the underlying mechanisms. 2) Aerobic exercise training combined with a fibre-enriched diet can aid reduce HFC more effectively than either exercise or increased fibre intake alone in pre-diabetic patients with NAFLD. However, the effect on glycaemic control and insulin sensitivity is not substantial. Therefore, it remains to be addressed why the same intervention protocol did not show the similar effect on the HFC and glycaemic control/insulin sensitivity in the same subjects. When these questions being uncovered, the combined intervention could be considered as an integral part of lifestyle interventions for patients with a cordiality condition for an increased risk of developing T2D.