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Effects of aerobic exercise and fiber-enriched diet on gut microbiota in pre-diabetic patients with NAFLD

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Objective Compelling evidence suggests that gut microbiota can play a role in the development of the metabolic syndrome, which incorporates abdominal obesity, hypertension, hyperglycaemia and dyslipidaemia. It is known that effective lifestyle intervention (including increasing physical exercise and calorie-restricted diet) is the mainstay treatment for the majority of patients with non-alcoholic fatty liver disease (NAFLD) and prediabetes. However, the effect of aerobic exercise and dietary intervention on gut microbiota in pre-diabetic patients with NAFLD is largely unknown and needs to be elucidated. Thus, the aim of the study was to investigate whether gut microbiota composition would change after aerobic exercise training and a fibre-enriched diet intervention in pre-diabetic patients with NAFLD.

Methods We have conducted a randomized controlled trial in patients aged 50-65-year who have fulfilled the inclusion criteria (impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) and hepatic fat content >5.6%, NAFLD). The patients were randomly assigned to aerobic exercise (AEx), dietary intervention (Diet), aerobic exercise plus diet intervention (AED) or no intervention (NI) groups for an average period of 8.6 months (7-11 months). Among those participants, 78 provided fecal samples (AEx, n = 18, Diet, n = 22, AED = 21, and NI = 17). Progressive supervised aerobic exercise training (60-75% intensity) was given 2-3 times/week in 30-60 min/sessions, and the diet intervention was provided as lunch with 38% carbohydrate and diet fibre of 12g per day for 8.6-months. The hepatic fat content (HFC) was assessed by 1H MRS, glycated hemoglobin (HbA1c) and insulin sensitivity were assessed by conventional methods. Gut microbiota characterizations were determined with 16S rDNA-based high-throughput sequencing by Illumina Miseq platform.

Results The Simpson index showed that alpha diversity was significantly different in intervention groups compared with NI group after the intervention (AEx vs NI, p=0.070; Diet vs NI, p=0.014; AED vs NI, p=0.011). Simpson index had a negative trend with HFC change % after intervention (r=-0.254, p=0.053). Weighted UniFrac PCoA analysis revealed that the structure of gut microbiota in the intervention groups was significantly differed from that of NI group (AEx vs NI, p<0.01, Diet vs NI, p<0.05, AED vs NI, p<0.001). Interestingly, we found that Erysipelotrichi (which has been reported associated with NASH) was negatively correlated VO_{2max} (r=-0.274, p=0.040). At genus level, *Clostridium* and *Lactobacillus* were positively correlated with HFC change after intervention (r=0.273, p=0.038; r=0.273, p=0.041 respectively).

Conclusions The exercise and diet intervention modified the structure of gut microbiota both in alpha and beta diversity. The *Clostridium* and *Lactobacillus* is related to energy metabolism and participated in the fermentation of carbohydrate which may be partly explain the positive correlation of gut microbiota with HFC change. However, the function of specific gut microbe needs to be further studied.