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Effect of exercise and dietary intervention on serum and adipose tissue metabolomics in patients with insomnia: a 6-month randomized-controlled trial

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Objective Objectives: Insomnia is common in modern society, with a prevalence between 10-20% among adults. Insomnia is associated with numerous adverse health outcomes and carries a heavy burden for health-care system. Accumulating evidences have shown that lifestyle interventions such as exercise and dietary modification could benefit sleep by mitigating symptoms of insomnia. However, the metabolic profile change in people with insomnia following exercise or diet intervention is not clear.

Methods Methods: Seventy-two Finnish men (age: 51.5 + 10.2 years; body mass index, BMI:29.3 + 3.9 kg/m²) with chronic insomnia symptoms participated in this study. They were then randomly assigned into three groups: exercise (n = 24), diet group (n=24) or control group (n = 21). Nordic walking or other aerobic exercise was performed 30 to 60 minutes per session, one to five sessions per week, at the intensity level of 60%-75% of estimated maximum heart rate. Specific individualized diet programs are developed after baseline assessments of each participant's current dietary intakes (based on three-day food diary) and body weight. Blood samples were collected in the morning between 7:00 and 9:00 a.m. after overnight fasting. In addition, subcutaneous adipose tissue biopsies were obtained from a subgroup of 20 subjects. Gas Chromatography Time-Of-Flight Mass Spectrometry (GC-TOF-MS) method was used to investigate the serum and adipose tissue metabolites. Sleep was assessed by using a non-contact sleep monitoring system. Multivariate analysis and univariate analysis were used for metabolomics data analysis.

Results Results: Sleep onset latency (SOL), wakefulness after sleep onset (WASO), and sleep efficiency (SE) were all significantly changed ($p < 0.05$) after 6-month exercise intervention, and total sleep time (TST), SOL and SE were significantly changed ($p < 0.05$) after 6-month diet intervention. A total of 223 known metabolites in serum and total of 154 known metabolites in adipose tissue were detected. Eleven metabolites were affected by exercise and eight metabolites were affected (Variable importance in the projection, VIP > 1 from (orthogonal) partial least-squares-discriminant analysis (OPLS-DA) and $p < 0.05$ from *t* test) by diet in adipose tissue. Among the metabolites detected in serum, there were 17 metabolites affected by exercise, 21 metabolites by diet and 13 changed in the control group (VIP > 1 and $p < 0.05$). We found that in the exercise group, in serum, change of shikimic acid correlated with change of WASO ($r = -0.479$, $p = 0.038$) and SE ($r = 0.462$, $p = 0.047$), change of Cystathionine correlated with change of TST ($r = -0.545$, $p = 0.016$) and SE ($r = -0.6$, $p = 0.007$), while in adipose tissue, change of cholesterol ($r = -0.822$, $p = 0.023$) and Behenic acid ($r = -0.833$, $p = 0.02$) correlated with change of SE. In diet group, change of leucine correlated with change of WASO ($r = -0.655$, $p = 0.001$) and change of SE ($r = 0.499$, $p = 0.013$), change of Linoelaidic acid correlated with change of WASO ($r = -0.519$, $p = 0.009$) and change of SE ($r = 0.506$, $p = 0.012$), change of L-Allothreonine ($r = -0.460$, $p = 0.024$) and Erythrose ($r = -0.441$, $p = 0.031$) correlated with change of BMI, change of L-Rhamnose correlated with change of TST ($r = -0.480$, $p = 0.018$) in serum, while

change of glycylproline correlated with change of SOL ($r = -0.845$, $p = 0.034$) in adipose. In addition, change of acetanilide correlated with change of TST ($r = -0.772$, $p < 0.01$), change of palmitoleic acid correlated with change of BMI ($r = -0.491$, $p = 0.038$) in serum but not association in adipose tissue was observed in control group.

Conclusions Conclusion: Several metabolites related to energy metabolism are altered after exercise and dietary intervention in people with insomnia. The change of these metabolites may explain partly the underline mechanisms of improvement of sleep quality through lifestyle interventions.