Exercise Effects on Gut Dysbiosis, Intestinal Permeability and Systemic Inflammation in Patients with Type 2 Diabetes: A Pilot Study

Evasio Pasini1*, Giovanni Corsetti2, Deodato Assanelli3, Cristian Testa4, Claudia Romano2, Francesco S Dioguardi5 and Roberto Aquilani6

1Cardiac Rehabilitation Division, Maugeri Scientific Clinical Institutes, Italy
2Division of Human Anatomy and Physiopathology, Department of Clinical and Experimental Sciences, University of Brescia, Italy
3Division of General Medicine, Azienda Ospedaliera Spedali Civili di Brescia, Italy
4Laboratory of clinical microbiology and virology Functional Point, Italy
5Department of Clinical Sciences and Community Health, University of Milan, Italy
6Department of Biology and Biotechnology, University of Pavia, Italy

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*Corresponding author: Evasio Pasini, Cardiac Rehabilitation Division, Maugeri Scientific Clinical Institutes, IRCCS Lumezzane, Lumezzane, Brescia, Italy. Tel: 0039-030-825313 Email: evpasini@gmail.com

Abstract

Exercise plays a significant role in the prevention of the diabetes. Recent data propose that dysbiosis of intestinal microbiota composition contributes to development of Type 2 diabetes (T2D). Moreover, dysbiosis alters intestinal endothelium permeability causing the "Leaky gut syndrome" (LGS). We measured in 15 selected patients with standard medical cures for stable T2D the effects of 6 months of endurance, resistance and flexibility training on the gut microbiota composition and intestinal permeability. At baseline, T2D patients had high biochemical parameters (glycaemia, HOMA index, HbA1c, C-Reactive Protein [CRP]) with dysbiosis (elevated concentration of M ycetes) and altered intestinal permeability (measured by faecal Zonulin). After chronic exercise, glycaemia, HOMA index, HbA1c and CPR were reduced as well as faecal presence of M ycetes spp and Zonulin. This pilot study showed that selected patients with T2D had intestinal dysbiosis with overgrowth of M ycetes, presence of LGS and low grade inflammation. Interestingly, chronic exercise significantly reduced all these parameters.

Keywords: Exercise; Diabetes; Microbiota; Dysbiosis; Zonulin; Leaky gut syndrome

Introduction

Evidences show that exercise plays a significant role in the prevention of the diabetes and control of glycaemia as well as in the diabetes-related organ complications [1]. Furthermore, recent data propose microbiota composition as possible potential environmental contributor to development of T2D [2]. Indeed, gut dysbiosis influences fundamental intestinal functions as epithelium permeability, causing the "Leaky gut syndrome" (LGS) [3]. As consequence, LGS heavily influences gut functions including digestive, absorptive and endocrine activities that, in turns, may influence glucose metabolism. Moreover, LGS activates inflammation allowing translocation of microorganisms from the intestinal lumen to the blood circulation. Interestingly, recent papers show that physical activities could modify gut microbiota [4,5]. Recent evidences suggest that a useful method for assessing the alteration of intestinal permeability is the dosage of Zonulin in the patient's stools [6]. Thus, the aim of this study was to evaluate the role of chronic exercise on the gut flora composition and intestinal permeability in patients with stable T2D.

Materials and Methods

This research was a controlled open-label trial. Research protocol was approved by the Ethics Committee of Spedali Civili di Brescia, and performed in accordance with the Declaration of Helsinki. We selected non-smokers 15 males patients with mean age of 69±1.3 years with a controlled diet of 7949kJ (1900
Table 1: Biochemical measurements before (T0) and after exercise training (T1). Data are expressed as mean±sd.

|                         | T0            | T1            | p   |
|-------------------------|---------------|---------------|-----|
| Glucose (mg/dl) (nv=70-100) | 139±10.1      | 129±9.5       | <0.05 |
| HbA1c (%) (nv=4-6)       | 7.0±0.2       | 5.8±0.3       | <0.05 |
| HOMA index (nv=0.22-2.5) | 4.58±0.6      | 3.52±0.7      | <0.05 |
| CRP (mg/dl) (nv=0-5)     | 6.1±1.0       | 9.1±1.3       | <0.05 |

Table 2: Gut flora composition (Genus/Species-x 10^5cfu/ml) and Zonulin concentration (ng/ml) faecal concentration before (T0) and after exercise training (T1). Data are expressed as mean±sd.

| Genus/Species | T0            | T1            | p   |
|---------------|---------------|---------------|-----|
| Lactobacillus spp (nv>150) | 99.8±39.4     | 119±48.9      | ns  |
| Bifidobacterium spp (nv>200) | 220.5±52.3    | 246.6±69.1    | ns  |
| Enterococcus spp (nv<150)    | 0.6±2.2       | 0             | ns  |
| Streptococcus spp (nv<150)   | 0             | 0             | ns  |
| Bacteroides spp (nv>150)     | 162.1±33.3    | 185.0±55.6    | ns  |
| E. Coli (nv<150)             | 160.1±56.6    | 138.0±63.0    | ns  |
| Candida spp (nv = 0)         | 8.0±9.2       | 4.6±5.0       | ns  |
| Mycetes spp (nv = 0)         | 310±42        | 191.5±45      | <0.001|
| Campylobacter spp (nv = 0)   | 2.0±3.2       | 3.2±7.8       | ns  |
| Clostridium Difficile (nv = 0) | 0±1.5        | 0.1±0.8       | ns  |
### Discussion

This pilot study showed that selected patients with T2D had intestinal dysbiosis with overgrow of mycetes, presence of "Leaky gut syndrome" and chronic inflammation. Interestingly, chronic exercise significantly reduced all these parameters. Previous studies show that dysbiosis is present in T2D patients [9,10]. In line with these data, we found a massive presence of mycetes and candida in T2D patients, and inflammatory index. It is well known that gut mycetes stimulate systemic inflammation. Indeed, mycetes activates the innate immune receptor C-Type Lection Dectin-1. In detail, Dectin-1 is a cell receptor which reacts with B-1,3-glucans which is presents in the fungi wall. In turns, Dection-1 stimulates intracellular caspase recruitments domain-containing protein 9 with consequent local and generalised activation of inflammation due to inflammatory cytokine production and consequent stimulation of T helper 17 [11]. Notably, systemic inflammation is present in diabetic patients and it is consider one of the possible pathophysiological cause of this metabolic syndrome [2]. In addition, local intestinal inflammation could induce altered intestinal importability with consequent loss of gut fundamental functions. Indeed, for the first time in these patients, we found increased Zonulin's faecal concentration suggesting the presence of "Leak gut syndrome". Indeed, Zonulin is the proteins that physiologically modulates the intracellular intestinal cells tight junctions [6]. Traditionally, the functions of intestinal tract is the digestion and absorptions of the ingested nutrients. However, recent evidences show that intestine regulates the immune and endocrine system by producing specific inflammatory molecules and/or hormones. In addition, it regulates the trafficking of macromolecules and/or microorganism between intestinal lumen and blood influencing systemic inflammation. It is intuitive that maintenance of intestinal im permeability and functions is crucial to maintain global metabolic body homeostasis avoiding the presence of "Leak gut syndrome" and the consequence malfunction.

It is known that exercise controls glycaemia and inflammation but here, for the first time, we showed that exercise decreases gut mycetes colonisation and the presence of "Leak gut syndrome" in T2D patients, likely improving important intestinal functions. The mechanisms by which exercise modified gut flora and reduced is not known yet. Recent data shows that exercise influences microbiota by several mechanisms. Indeed, exercise may modify bile acids profiles [12] and/or faecal short chain fatty acids (SCFAs) as butyrate [13]. Exercise may also interact with gut immunological function increasing intestinal immunoglobinulin A (IgA), decreasing number of lymphocytes-B and CD4+T cells, and influencing gene expression of cytokines as IL-6, IL-4, IL-10 and TGF-B [14]. Exercise can also modify microbiota because is able to reduce intestinal transit time [15].

We think that our data, although preliminary, could have important clinical implications. Indeed, for the first time, we showed that patients with T2D have heavy intestinal mycetes colonisation and LIS, and chronic exercise can reduce these alteration. This likely could improving intestinal function which influence nutrients metabolism, hormonal production and absorption of oral drug-administered. So, exercise, with or without a specific therapies able to cure of intestinal microbiota, could be an important step for tailored therapy allowing traditional therapy and patients metabolism to function more properly.

This study has some limitations. We used a selective culture medium to identify bacteria and mycetes instead of molecular biology techniques. Indeed, we don't want to provide a "faecal finger print" of patients. We won't identify saprophytes and some minor intestinal pathological and mycetes species capable of stimulating inflammation without gastrointestinal symptoms [7]. This is a pilot study with a limited number of selected patients. We have in progress a large scale study to confirm these results.

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