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The Effects of Akkermansia *Munciniphila* on Serotonin and Fetuin-A Hormone Levels and Some Biometric Parameters in Obese Patients

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Abstract

The objective of the present study is to determine the anti-obesity effects of Akkermansia munciniphila on some biometric measurements. 40 patients were divided into two groups, each with 20 patients; G1 group consumed the probiotic of *A. munciphila* and G2 consumed placebo capsules. The results showed significant effects on the body weight ($p\leq 0.001$), which was reduced by a range of -2.29 to -0.7, whereas non-significant differences were observed in the Waist circumferance . The study also showed significant differences ($p\leq 0.001$) between the two groups in the levels of cholesterol (287 vs. 285 mg/dl) , whereas the level of Triglyceride significantly decreased in the treated patients ($p\leq 0.001$). No significant differences were observed in the concentration of fat. There were also significant differences in the levels of fetuin-A ($p\leq 0.020$) and serotonin ($p\leq 0.039$). The consumption of the probiotic of *A. muciniphila* was proved to be beneficial for human health, while further studies are needed to explore more effects.

Keywords: Serotonin, body weight, lipid profile, Obesity, Probiotics, Fetuin-A.

دراسة تأثير استهلال المعززات الحيوية على مستوى هرموني السيروتونين والفيوتين A مع بعض المؤشرات الحيوية لدى عينه من مرضى السمنة

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الخلاصة :

تهدف الدراسة لتحديد مدى تأثير استهلاك المعززات الحيوية على بعض الهرمونات والمؤشرات الحيوية لدى عينه من مرضى السمنة حيث اجريت هذه الدراسة في مركز بحوث وعلاج السمنة في كليه طب الكندي جامعه بغداد (للفترة من شهر كانون الاول 2019 الى شهر شباط 2020 شارك في هذه الدراسة 40 مريضه من الاناث بعمر يتراوح بين (18−45) سنه , تم الاعتماد على المعايير العالمية لتحديد مرضى السمنة (BMI ≤30) وتم تقسيم العينة الى مجموعتين مجموعه الدراسة مكونه من 20 مريض ومجموعه السيطرة 20 مريض ايضا المجموعة الاولى استهلكت المعززات الحيوية A.municiphila ولمده 3 اشهر ومجموعه السيطرة استهلكت كبسول وهمي .اظهرت النتائج نزول الوزن بمقدار 2.29 كغم قياسا بمجموعه السيطرة وكذلك اظهرت الدراسة انخفاضا واضحا في مستويات (الكوليسترول,والدهون الثلاثيه,ومستويات السكر في الدم) اما بخصوص تأثر استهلاك المعززات الحيوية على هرموني (fetuin−Aو serotonin) كانت النتائج علاقه طرديه ما بين انخفاض الوزن مع انخفاض مستوى الهرمونات

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Introduction

Akkermansia muciniphila (*A. muciniphila*) colonizes in the mucosal layer of the gut and is able to modulate the basal metabolic functions[1]. Many studies were suggested that *A. muciniphila* is consistently correlated with obesity. The causes of the beneficial impact of *A. muciniphila* treatment on obesity has been increasingly highlighted, having been proved by a variety of animal models and human studies. *A. muciniphila* was characterized as a beneficial player in body metabolism . It was considered to be the next generation of microbiota to have advantageous effects on human health [2]. The abundance of *A. muciniphila* was related with a healthy intestine, whereas the decrease of its numbers was inversely linked to several diseases [3]. IBD patients (ulcerative colitis and Crohn's disease) showed decreased *A. muciniphila* [4]. A reduced amount of these bacteria was also observed in patients with acute appendicitis.. Muciniphila was also shown to have an inverse relationship with severe appendicitis [5]. Some analysis of obese children reported substantial decreases in number of *A. Muciniphila* [6]. Obesity is described as an extreme increase of fat that poses a health risk. It is measured by body mass index (BMI), which involves dividing the weight of a person (in kilograms) by the square of its height (in meters). An individual with a BMI of 30 or more is usually considered obese and a person with a BMI equal to or greater than 25 is considered overweighed. Overweight and obesity are significant risk reasons for a kind of chronic diseases, including diabetes, diseases of hypertension and cancer [7]. Pathophysiology of overweightness and metabolic disorders are complex, beginning from the environmental and genetic mismatch. Obesity is a pro-inflammatory syndrome that shows a key role in many diseases' development. These include type 2 diabetes, high blood pressure and dyslipidemia. Gastro intestinal tract (GIT) is inhabited by a complex ecosystem — the gut microbiota — which is dependable for regulating important health-care functions including protective, structural, and histological ones [8]. Probiotics are food elements or supplements with living microorganisms that can have active effects on the host's health [9]. Certain strains were reviewed due to possible therapeutic deficiency effects on the host, with possible benefits for weight control and diabetes control [10]. Fetuin –A is a serum protein that is discharged by adipocytes and hepatocytes and has the function of controlling hepatic metabolism. Research clarified the role of Fetuin –A in reducing metabolic dysfunction by binding the insulin receptor and inhibiting auto-phosphorylation of tyrosine kinase A [11]. Several studies showed that the level of Fetuin –A is decreased through weight loss [12]. Serotonin-1 is defined as a diacytelase which relies on nicotinamide adenine dinucleotide. The key function of serotonin is the modulation of energy balance. It has a positive effect on the homeostasis of glucose and the response to insulin [13]. Serotonin-1 is a chemical variable that is generated by nerve cells and transfers signals between them and other body cells. Dopamine is found primarily in the digestive tract, but it is also present inside the central nervous system and in blood platelets [14]. Serotonin is formulated from tryptophan, a basic amino acid. This amino acid has to arrive the body within the diet and is commonly found in foods like nuts, cheese, and red meat [15]. The absence of tryptophan can result in reduced serotonin levels. The present research determines hormone levels of serotonin-1 and fetuin A as well as the anthropometric markers in obese patients following administration of *A. Muciniphila* [16]. The aim of this study is the determination of the effects of probiotic supplement on body weight reduction , hormone levels and biochemical parameters among obese females .

Materials, methods, and patients

This study was performed with the participation of 40 female patients who were visiting the center of obesity treatment in Al-Kindy medical college, Baghdad University, between December 2019 and February 2020.The age range of the participants was 18-45. BMI value was determined by dividing weight to height . All obese patients had BMI $\geq$ 30.

The participants were divided into two groups; G1 consisted of 20 patients who consumed *A. municiphila* probiotic two times per day, whereas G2 consumed placebo capsules. Both groups followed a similar diet as determined by physicians in Al –Kindy obesity center.

Personnel information was recorded for all participants. After an overnight fasting, a blood sample was taken from each patient. Both blood and serum samples were obtained and stored at -70 ° C before the assay. Manufacturer instructions were followed for all analyses.

Statistical analysis

The data were analyzed using the SPSS statistical package for the Social Sciences (SPSS, version 20.0 for windows, Chicago, IL, USA). Shapiro–Wilk normality test was used to determine whether the studied parameters followed a Gaussian distribution. Categorical variables were expressed as proportions, which were compared using the Chi-square test ($\chi 2$) [17].

Results

Effects of *A. municiphila* on the Fasting blood sugar

The results showed a significant decrease in ($P \leq 0.012$) sugar levels (from 135 to 126 mg/dl) compared with that of the placebo group. The study also showed a highly significant ($p \leq 0.001$) decrease in cholesterol level in the intervention group (from 287 to 285 mg/dl), whereas the control group demonstrated increased levels (from 290 to 295 mg/dl), as illustrated in Figure-1.

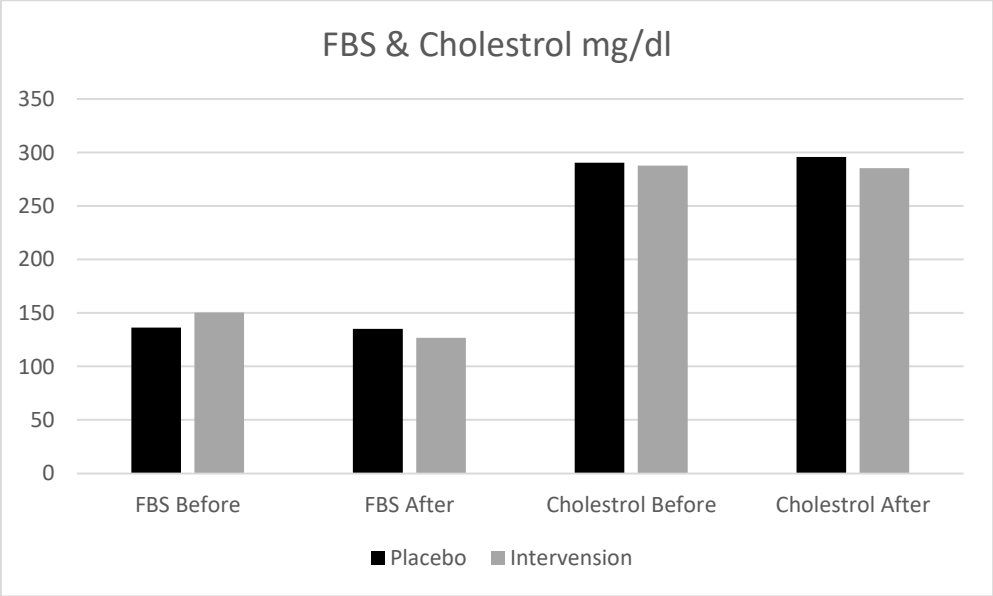

Figure 1-Effects of the probiotic on the level of cholesterol and Fasting Blood sugar Effect of *A. municiphila* on HbA1C concentration.

The results showed a significant ($p \leq 0.075$) decrease in the level of Hba1c in the blood of the treated group (from 8.02 to 7.79 mg/dl) while the placebo group showed an increase (from 7.82 to 8.25 mg/dl), as illustrated in Figure-2.

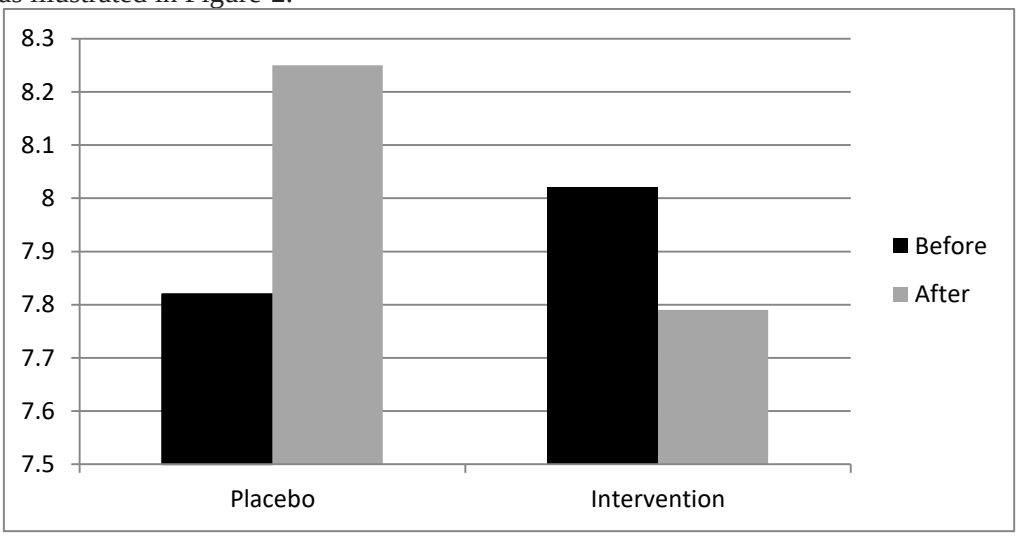

Figure 2-Effects of *A. municiphila* on the level of HbA1C (%)

Effects of *A. munichiphila* on serotonin level

The serum level of serotonin was significantly ($p \leq 0.039$) increased in the intervention group (from 6.80 to 6.95 ng/ml) compared with the placebo group which showed a decreased level (from 6.27 to 6.20 ng/ml), as shown in Figure-3.

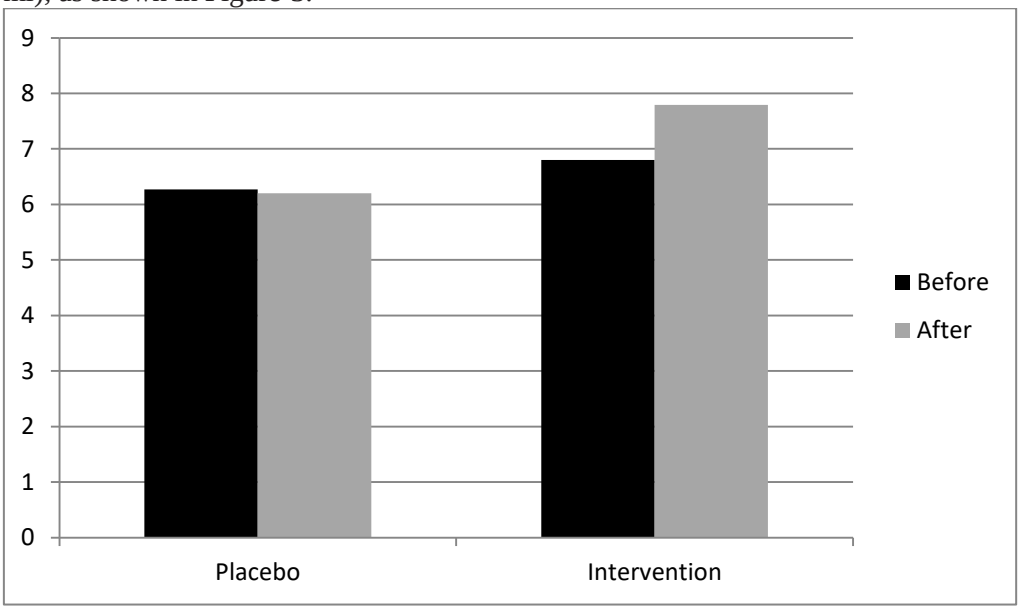

Figure 3-Effects of *A. municiphlia* on the serotonin levels (ng/m).

Effects of *A. municiphila* on Fetuin-A level

In this study, the intervention group also showed increase in the levels of Feutin-A (form 121 to 104 pg/ml) with a high significant difference ($p \leq 0.020$), whereas the placebo group had increased levels (from 140 to 143 pg/ml), as shown in Figure-4

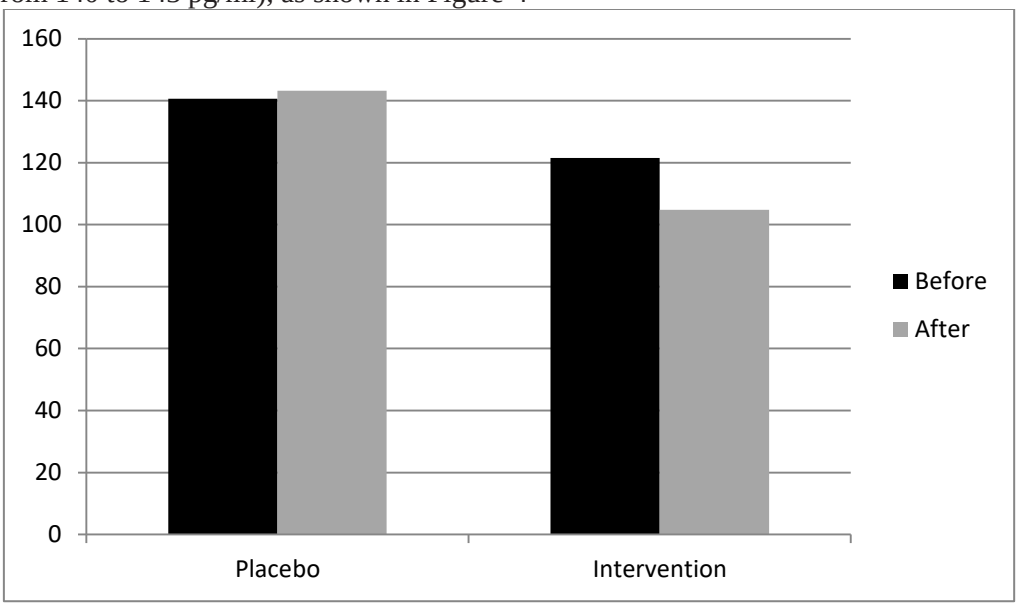

Figure 4-Effects of *A. municiphila* on Futein level (pg/ml)

Effects of *A. municiphila* on the body weight and W.C

The study showed a significant ($p \leq 0.001$) decrease in body weight (from 75.16 to 73-01 kg), while the placebo grouped showed an increase (from 82.02 to 83.70 kg) , . The study also showed an insignificant decrease in the measurement of waist circumference in the treated group (from 98.60 to 96.32 cm^2), while the control group showed a reduction (from 101.9 to 100.69 cm^2), as shown in Figure- 5.

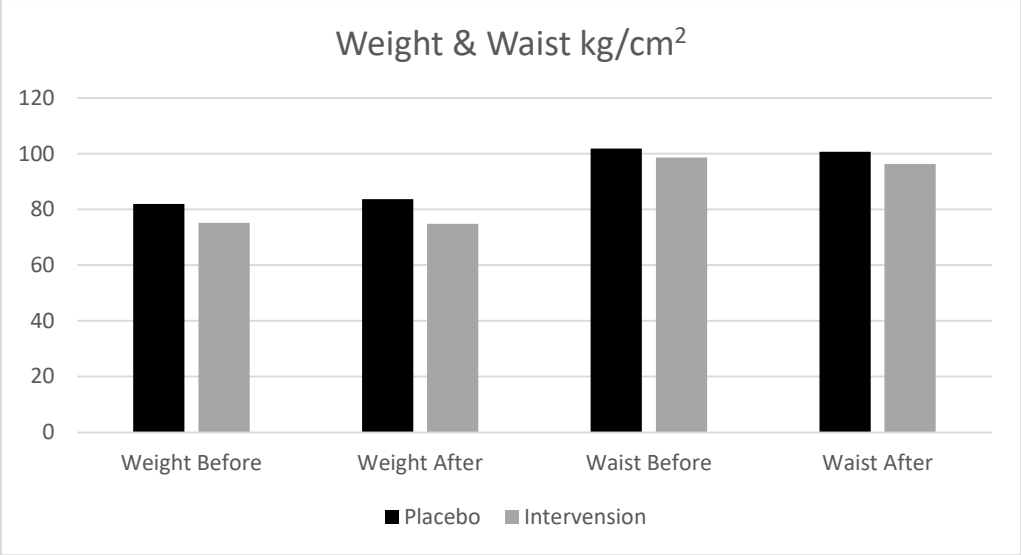

Figure 5-Effects on the body weight and waist circumference

Effects of *A. municiphila* on the levels of triglyceride and protein

The study also showed an insignificant decrease in the level of triglyceride in the intervention group (from 70.05 to 70.16 ng/dl), whereas it was elevated in the placebo group (from 72.26 to 73.90), as demonstrated in Figure-6.

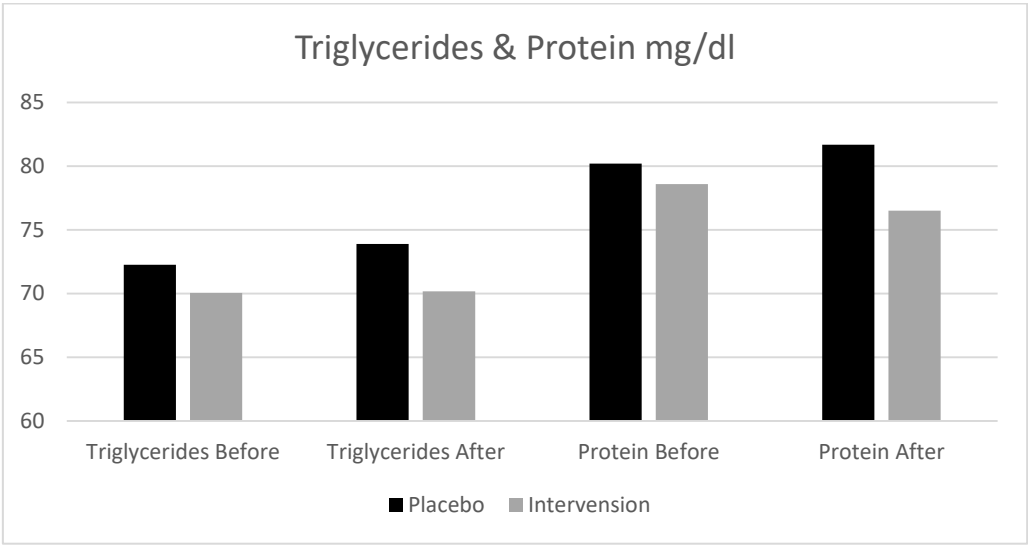

Figure 6-Effects of probiotics on Triglyceride and protein level.

Discussion

The relationship between the host and *A. muciniphila* was identified as colonization by the bacteria due to increased gene expression linked to immune response [18]. *A. muciniphila* plays an important role in regulating metabolic endotoxemia and metabolism of the adipose tissue [19]. An additional study reported that *Muciniphila* had an effect on the expression of the genes involved in cellular lipid metabolism [20]. Some work identified the role of *A. muciniphila* on obesity and Diabetic Miletus In 2014, a study investigated the impact of *A. muciniphila* on insulin sensitivity and metabolic disease and showed that the proliferation of these bacteria contributed to a decrease in body weight [21]. In 2017, a study found that bile acid metabolism, body weight, insulin level and inflammatory markers were organized by the intestinal microbiota [22]. The reduction in body weight was also confirmed via similar research, such as that of Wu *et al* 2015 , who found that body weight loss was greater in the monitoring group than that in the intervention group. Consequently, the impact of probiotic supplementation decreased on the body weight improved by excluding the (Lee et al.)report from

meta-analysis by [1.42, 0.69] kg [13]. Another research reported a body weight loss by 3.6 kg [14]. Another study by Minami *et al.*, 2018 [15], suggested increased body weight loss and cholesterol levels after probiotic use. A drop in the levels of total cholesterol and triglycerides as well as in body weight was registered by Wu *et al.*, 2015 [23]. This finding was in accordance with the research conducted by Nam *et al*. in 2018. The association between obesity and serotonin level in the midbrain was found to be negative with BMI of obese subjects ($r = -0.3126$, $p = 0.0496$), and positive with BMIs of non-obese subjects ($r = 0.2327$, $p = 0.0053$), and these slopes were substantially different. The abovementioned research provided specific details on the association between obesity and the level of the intestinal hormone [24]. Another study, in 2017, found that mice, in which the TPH1 encoding gene had been ablated when feeding a high-fat diet (Tph1-/-), had a dramatically decreased weight gain as well as lower body fat, blood glucose, and fasting insulin rate. They also demonstrated better glucose tolerance and insulin sensitivity along with protection against non-alcoholic fatty liver disease [25]. the result of this study was agree with study was done in 2013 by Alajeeli et al they was provide the positive effect of probiotic on the body weight [26]. also Al-ani & Al-ShahwanyA ,2018 was reported that ability of probiotic to regulation of hormone level [27] .finally study by Sabaa Taher,2016 was registered beneficial role of milk with probiotic to regulation of body immunity and gut health against the parasites [28].

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