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Metabolic Effects of Probiotic Supplementation in Diabetic Hemodialysis Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors contributed equally to this work, read and approved the final manuscript.

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ABSTRACT

Aims: To evaluate the effects of probiotic supplementation in diabetic hemodialysis patients on metabolic profile and level of inflammation.
Study Design: Single blind, placebo controlled clinical trial.
Place and Duration of Study: Dialysis unit of internal medicine department, Tanta University, Egypt in a period between 1 st of January 2019 to 31 th march 2019.
Methodology: 60 hemodialysis and diabetic patients were included. They were divided into two groups of equal numbers (Probiotics group and control group). Probiotic supplements were added to the Probiotics group, as regarding CBC parameters, lipid, iron profile, renal functions, HbA1c, serum albumin and CRP; we compared the base line values and values after the end of study in both groups.
Results: There was significant increase in hemoglobin in study and control group at the end of study P value <0.001 in study group and P value <0.001 in control group, also significant decrease in CRP in study group P value <0.001, significant decrease in HbA1c in study group P value 0.001 and significant increase in serum albumin in study group P value 0.039.
Conclusion: Although probiotics significantly improved the inflammation and glycemic control in diabetic hemodialysis patients, it had no significant effect in lipid and iron profile.

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Keywords: Diabetes; hemodialysis; inflammatory markers; C reactive protein (CRP); hemoglobin A1C (HbA1c); albumin.

1. INTRODUCTION

Chronic kidney disease (CKD) is a common worldwide public health problem and its prevalence is estimated to be 8–16% worldwide [1]. CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more, irrespective of the cause [2].

The risk to develop CKD increase in females than males, hyperuricemia, hypertension, cardiovascular disease, old age and smoking [3]. Also in diabetes which consider the leading cause of end-stage renal disease (ESRD) in the world [4].

CKD is important risk factor for infectious complication, (as pneumonia, sepsis, bacteremia and urinary tract infections), cardiovascular complication, atherosclerosis, dyslipidemia, thyroid dysfunction, bone mineral diseases, hypertension and anemia [5-9].

The epidemic of diabetes mellitus and its complications poses a major global health threat. The International Diabetes Federation (IDF) estimated that 1 in 11 adults aged 20–79 years (415 million adults) had diabetes mellitus globally in 2015 [10]. This estimate is projected to rise to 642 million by 2040, and the largest increases will come from the regions experiencing economic transitions from low-income to middle-income levels [10].

IDF listed Egypt among the world top 10 countries in the number of patients with diabetes. In 2013, the IDF estimated that 7.5 million individuals have diabetes and around 2.2 million have pre-diabetes in Egypt [11].

Some studies supposed that pathogenesis of diabetic nephropathy occur through inflammatory process and endothelial dysfunction using high sensitive C-reactive protein (CRP), hemoglobin A1C (HA1C), homocysteine and micro albuminuria as markers of these inflammatory process and endothelial dysfunction [12,13].

Probiotics may act as biological agents that modify the intestinal microbiota and certain cytokine profiles that used in many studies on humans studying their effect on gastro intestinal tract (GIT) and Immune system [14-15].

There are some studies that investigated the effect of probiotic in improving metabolic profile of diabetic hemodialysis patients as glucose homeostasis and few biomarker of inflammation and oxidative stress [16], without any significant side effects in the treatment group, but possible translocation, permanent colonization and some gastro intestinal upsets but are rare event [17-18], but none was conducted in Egypt.

2. MATERIALS AND METHODS

The present study carried out on 60 hemodialysis patients with diabetes from department of internal medicine Tanta University Hospital, the duration of the study will be 3 months started from 1st of January 2019 to 31th of March 2019.

The study population will be divided into 2 groups:

Group I: 30 patients will receive the study agent (5 million of lactobacillus delbruekii and lactobacillus fermentum daily for 12 weeks) beside the appropriate weight based dose of erythropoietin stimulating agent (ESA) and anti-diabetic agents.

Group II: 30 patients will receive placebo tablets, beside the appropriate dose of ESA and anti-diabetic agents.

Inclusion criteria: Patients with diabetic end stage renal disease (ESRD) on hemodialysis with (hemoglobin) <11 gm.

2.1 Exclusion Criteria

Intact PTH> 300 pg/ml,Vitamin B12 or foliate deficiency,Urea reduction ratio <65%,intolerance to Lactobacillus,recent retinal or cerebral hemorrhage and risk factors for hemorrhage as active peptic ulcer disease,patients with psychological problems that interfere with their ability to comply with the study requirements, pregnancy or breast-feeding,presence of systemic hematological disease or known haemoglobinopathy,infection or malignancy within the last 3 months.

2.2 Methods

Full history taking, clinical examination, Full blood count, Transferrin saturation, intact parathyroid hormone level, Serum calcium,

phosphorus, albumin, C-reactive protein, Hemoglobin A1C and Lipid profile. These laboratory tests are evaluated at the beginning and at the end of study.

2.3 Statistical Analysis of the Data

Statistical analysis and presentation of data was conducted using SPSS (Statistical Package for the Social Sciences) version 22 computer program. Categorical data were presented as numbers and percentages and Pearson's Chi-Square test was applied to investigate the association between categorical variables. For continuous data, they were tested for normality by Shapiro-Wilk test. For normally distributed data, they were expressed as mean ± standard deviation. For non-normally distributed continuous data, they were expressed as median and interquartile range (25^{th} -75^{th} percentiles). For comparison of the independent study and control groups at the time of admission before the intervention, Independent T and Mann-Whitney U tests were used for normally distributed and non-normally distributed data respectively. Whereas, for comparison of continuous data in both the study and control groups before and after the intervention, paired T and Wilcoxon Signed Rank tests were applied according to the nature of data distribution. Level of statistical significance was considered at P <0.05.

3. RESULTS

3.1 Base-Line Characteristics of Study Groups

Sex characters of study participants showed that: in the group Ⅰ (probiotic group) males were represented by 40% and females by 60%. In group Ⅱ (placebo group): males were represented by 60% and females 40%.There was no statistically significant difference between the two groups.

Age characters of study participants showed that, the mean age of the group Ⅰ was 57.7 ± 11.4 years; the group Ⅱ was 50.9 ± 16.9 with no statistically significant difference was found between the two groups.

Virology characters of group Ⅰ showed that 36.7% was HCV negative and 63.3% was HCV positive, the group Ⅱ was 56.7% HCV negative and 43.3% was HCV positive with no statistically significant difference between the two groups.

There were no statistically significant differences between the two groups at beginning of study as regard to CBC, Lipid profile ,CRP, S.albumin and HA1c(Tables 2,3,4).

There was significant change in hemoglobin in both groups at the end of study being (9.48+0.59) before and (10.6+0.4) after study with P value <0.001 in group Ⅰ and (9.75+1) before and (12+0.43) after study with P value <0.001 in group Ⅱ and there is no significant changes in MCV, MCH, reticulocytic count, platelet count, total leucocyte count, neutrophil count and lymphocyte count before and after study in both groups (Table 5).

A comparison between group Ⅰ and control group at start and end of study according to CRP, HbA1c, albumin, there was a significant decrease in CRP in group Ⅰ (mean rank =16.16) before and (mean rank =12.20) after study and P value <0.001 also there is significant decrease in HA1c in group Ⅰ (mean rank =17.11) before and (mean rank =10.21) after study with P value 0.001.

There is significant increase in s.albumin in group Ⅰ (mean rank =8.69) before and (mean rank =19.53) after study with P value 0.039 (Table 7).

4. DISCUSSION

This study was conducted on 60 patients 30 patients received probiotic supplementation with appropriate dose from erythropotien and anti-diabetic agents as a group Ⅰ(probiotic group) and 30 patients as a group Ⅱ(placebo group) didn't receive probiotics but received erythropotien, placebo tablets and anti-diabetic agents.

As regard to demographic data of two groups there was no statistically significant difference between two groups ,but due to effect of randomization males account 40%from (probiotic group) and 60%from (placebo group)but females were 60%from (probiotic group) and 40%from (placebo group)also HCV positive patient were 63.3% from (probiotic group) and 43.3%from (placebo group)and as regard to age the mean age of (probiotic group) was (57.7 ± 11.4) years and (50.9 ± 16.9) years in (placebo group), this demographic data is agreed with the demographic data in a study conducted by Soleimani, Alireza et al. [16] ; but mean age was higher than our study in a randomized, double-

blind, clinical trial conducted by Arani, Navid Mazruei et al. [19].

In our study there was significant difference in both groups in hemoglobin level at the end of the study (9.5±.6) before and (10.6±.9) after study with P value <0.001 in (probiotic group)and (8.5±1) before and (12±1.7) after study with P value <0.001 in (placebo group)and there is no significant changes in MCV, MCH, Reticulocytic count before and after study in both groups, this changes in hemoglobin level was similar that occurred in the study of Shariaty, Zahra et al. [20] this trials showed that there was increase of hemoglobin level in both study groups but not reach level of significance in both groups, this difference between this study and our study may resulted from low base line hemoglobin level in our study in both groups compared with hemoglobin level in Shariaty, Zahra et al. [20] trials also in our study participant received a weight based dose from ESA but in Shariaty, Zahra et al. [20] trials participant received fixed dose of ESA(12,000 units of erythropoietin alfa

Table 1. Comparison between the studied groups according to demographic data

			Groups		Tests of significance	
			group Ⅰ N=30	**group Ⅱ** N=30	Test statistic	P value
Age (year)	Minimum		27.0	22.0	t=1.822	0.074
	Maximum		75.0	74.0		
	Mean		57.7	50.9		
	SD		11.4	16.9		
Gender	Female	N	18	12	X^2=2.40	0.121
		%	60.0%	40.0%		
	Male	N	12	18		
		%	40.0%	60.0%		
HCV	Negative	N	11	17	X^2=2.411	0.121
		%	36.7%	56.7%		
	Positive	N	19	13		
		%	63.3%	43.3%		

Table 2. Comparison between the studied groups according to complete blood count at beginning of the study

CBC		Groups		Tests of significance	
		group Ⅰ N=30	**group Ⅱ** N=30	Test statistic	P value
Hemoglobin(gm./dl)	Mean	9.5	9.8	t=1.27	0.209
	SD	.6	1.0		
MCV(fl)	Mean	82.5	85.4	t=1.45	0.152
	SD	8.0	7.6		
MCH(pg.)	Mean	28.5	28.2	t=0.291	0.722
	SD	2.6	3.7		
Reticulocyte count%	Median	1.2	1.3	Z_{mw}= 0.245	0.807
	IQR	.9-1.9	.8-2.1		
	Mean rank	31.05	29.95		
platelet(cell/mm^3)	Mean	224733.3	210506.7	0.793	0.431
	SD	54442.6	81866.4		
MPV	Mean	9.1	8.9	t=1.507	0.137
	SD	.6	.6		
Total leucocyte count (cell/mm3)	Mean	5842.0	5399.0	0.774	0.522
	SD	2748.0	2574.9		
neutrophil(cell/mm3)	Mean	52.4%	54.8%	0.649	0.519
	SD	14.4%	13.4%		
lymphocyte(cell/mm3)	Mean	32.2%	35.8%	1.34	0.157
	SD	9.1%	10.5%		

per week), not changed throughout the study, this causes may be accepted to us due to lack of large trials that investigate the effect of probiotic supplementation on different parameter of complete blood count in diabetic patients on hemodialysis.

Our study show no significant changes in lipid profile in both probiotic group and placebo group these findings is agreed with results of study conducted by Soleimani, Alireza et al. [21] that show there was no significant changes in total cholesterol, triglycerides, HDL, LDL between study participants *On other hand* according to Kooshki, A., Tofighiyan, T., Miri, M. [22] clinical trial; there was a significant decrease in cholesterol in probiotic group (p value=0.001) and no significant changes in triglycerides level between two groups ,also there was significant decrease in LDL levels in study group (P value =0.001)compared with placebo group.

This difference between Kooshki, A., Tofighiyan, T., & Miri, M. [22] study and both our study and study of Soleimani, Alireza, et al [21] may be from the total caloric intake was restricted in Kooshki, A., Tofighiyan, T., & Miri, M. [22] study in synbiotic group (1850 ± 475 k.cal per kg) and study was conducted on hemodialysis participant with average BMI (23.45 ± 5) without diabetes.

Table 3. Comparison between the studied groups according to iron profile and lipid profile count at beginning of the study

Before intervention		Groups		Tests of significance	
		group Ⅰ pre	**group Ⅱ** pre	Test statistics	P value
Transferrin saturation %	Mean± SD	20.8±6.7	19.3±7.1	t=0.862	0.392
S.iron (mcg %)	Median	.60	.70	Z_{mw}=1.51	0.131
	IQR	.28-.80	.30-1.36		
	Mean rank	27.10	33.90		
Cholesterol (mg/dl)	Median	156.0	164.0	Z_{mw}=0.718	0.473
	IQR	124.0-185.0	148.0-223.0		
	Mean rank	28.88	32.12		
Triglyceride (mg/dl)	Median	113.5	137.0	Z_{mw}=0.370	0.711
	IQR	109.0-234.0	109.0-232.0		
	Mean rank	29.67	31.33		
HDL(mg/dl)	Median	28.0	30.5	Z_{mw}=0.942	0.346
	IQR	24.0-37.0	25.0-44.0		
	Mean rank	28.38	32.62		
LDL(mg/dl)	Median	100.0	99.0	Z_{mw}=0.296	0.767
	IQR	73.0-129.0	86.0-155.0		
	Mean rank	29.83	31.17		
VLDL(mg/dl)	Median	23.5	26.0	Z_{mw}=0.681	0.496
	IQR	20.0-30.0	21.0-35.0		
	Mean rank	28.97	32.03		

Table 4. Comparison between the studied groups according to CRP, S. albumin and HbA1c count at beginning of the study

Before intervention		Groups		Mann-Whitney U test	
		group Ⅰ pre	**group Ⅱ** pre	Z_{mw}	P value
CRP(mg/dl)	Median	20.0	22.0	0.853	0.394
	IQR	17.0-22.0	16.0-28.0		
	Mean rank	28.58	32.42		
HbA1C (%)	Median	8.8	7.5	0.385	0.70
	IQR	6.5-12.0	6.3-12.0		
	Mean rank	31.37	29.63		
S.albumin (g/dl)	Median	3.4	3.5	1.688	0.091
	IQR	3.2-3.5	3.1-4.0		
	Mean rank	26.72	34.28		

Table 5. Comparison between the studied groups at start and end of study according to complete blood count

		Groups							
		Group Ⅰ (N=30)				Group Ⅱ (N=30)			
		Before	After	Test statistic	P^1 value	Before	After	Test statistic	P^2 Value
Hemoglobin(gm./dl)	Mean	9.48	10.6	7.33	<0.001*	9.75	12.0	12.9	<0.001*
	SD	.59	.40			1.0	0.43		
MCV(fl)	Mean	82.5	82.7	0.490	0.628	85.4	84.9	1.16	0.253
	SD	8.0	7.1			7.6	7.7		
MCH(pg.)	Mean	28.5	28.7	0.408	0.686	28.2	28.5	0.421	0.677
	SD	2.6	2.2			3.7	2.9		
Reticulocyte count%	Median	1.2	1.2	1.04	0.299	1.3	1.4	0.263	0.793
	IQR	.9-1.9	.9-2.0			.8-2.1	.8-3.1		
	Mean rank	6.20	3.50			13.68	15.32		
platelet(cell/mm3)	Mean	224733.3	220933.3	1.09	0.281	210506.7	207433.3	0.188	0.852
	SD	54442.6	57985.7			81866.4	45383.9		
MPV	Mean	9.1	9.0	1.58	0.124	8.90	8.89	1.85	0.073
	SD	.6	.8			.63	.63		
Total leucocyte count (cell/mm3)	Median	5210.0	5210.5	1.36	0.173	4945.0	4945.0	1.05	0.293
	IQR	4200.0-7780.0	4200.0-7650.0			3440.0-7030.0	3440.0-7030.0		
	Mean rank	4.25	2.00			2.75	3.88		
neutrophil(cell/mm3)	Mean	52.4%	52.1%	1.44	0.161	54.8%	55.1%	1.96	0.059
	SD	14.4%	14.6 %			13.4%	13.3%		
lymphocyte(cell/mm3)	Mean	32.2%	31.6%	5.45	1.89	35.8%	36.1%	1.86	0.072
	SD	9.1%	9.4%			10.5%	10.2%		

$P^{1:}$ For comparison of the group Ⅰ before and after the intervention
$P^{2:}$ For comparison of the group Ⅱ before and after the intervention
Test statistic: paired T test and Wilcoxon-Signed Rank test
**significant at p<0.05*

Table 6. Comparison between the studied groups at start and end of study according to iron and lipid profile

		Groups							
		Group Ⅰ (N=30)				Group Ⅱ (N=30)			
		Before	After	Test statistic	P^1 value	Before	After	Test statistic	P^2 Value
Transferrin saturation %	Mean	20.8%	20.63%	0.491	0.627	19.3%	19.9%	1.56	0.129
	SD	6.7%	6.8%			7.1%	7.6%		
S.iron (mcg %)	Median	.60	.49	0.402	0.688	.70	.80	1.03	0.299
	IQR	.28-.80	.30-.90			.30-1.36	.50-3.0		
	Mean rank	16.38	14.82			15.17	15.82		
Cholesterol(mg/dl)	Median	156.0	156.0	1.63	0.102	164.0	193.0	1.24	0.214
	IQR	124.0-185.0	124.0-186.0			148.0-223.0	140.0-200.0		
	Mean rank	2.0	3.0			13.33	16.18		
triglyceride(mg/dl)	Median	113.5	158.5	1.41	0.157	137.0	149.5	1.14	0.254
	IQR	109.0-234.0	109.0-243.0			109.0-232.0	108.0-270.0		
	Mean rank	1.0	1.5			16.09	15.16		
HDL(mg/dl)	Median	28.0	29.0	0.260	0.795	30.5	30.5	1.89	0.059
	IQR	24.0-37.0	25.0-37.0			25.0-44.0	25.0-44.0		
	Mean rank	17.13	13.50			1.0	2.5		
LDL(mg/dl)	Median	100.0	121.5	0.751	0.453	99.0	107.0	0.754	0.459
	IQR	73.0-129.0	81.0-140.0			86.0-155.0	72.0-130.0		
	Mean rank	15.08	15.82			15.79	15.12		
VLDL(mg/dl)	Median	23.5	22.5	0.136	0.892	26.0	26.0	0.228	0.820
	IQR	20.0-30.0	20.0-33.0			21.0-35.0	22.0-33.0		
	Mean rank	3.5	2.67			14.85	14.20		

P^1: For comparison of the group Ⅰ before and after the intervention

P^2: For comparison of the group Ⅱ before and after the intervention

Test statistic: paired T test and Wilcoxon-Signed Rank test

Table 7. Comparison between the studied groups at start and end of study according to CRP, HA1c and albumin

		Groups							
		group Ⅰ (N=30)				group Ⅱ (N=30)			
		Before	After	Test statistic	P^1 value	Before	After	Test statistic	P^2 Value
CRP(mg/dl)	Median	20.0	10.0	3.53	<0.001*	22.0	23.0	1.33	0.182
	IQR	17.0-22.0	7.0-19.0			16.0-28.0	15.0-35.0		
	Mean rank	16.16	12.20			7.88	7.35		
HbA1C%	Median	8.8	6.4	3.31	0.001*	7.5	8.5	0.668	0.491
	IQR	6.5-12.0	5.0-7.5			6.3-12.0	6.3-11.0		
	Mean rank	17.11	10.21			8.0	9.33		
S.Alb (gm/dl)	Median	3.4	3.5	2.069	0.039*	3.5	3.5	1.57	0.116
	IQR	3.2-3.5	3.1-3.8			3.1-4.0	3.0-3.6		
	Mean rank	8.69	19.53			11.84	12.36		

P^1: For comparison of the group Ⅰ before and after the intervention
P^2: For comparison of the group Ⅱ before and after the intervention
Test statistic: Wilcoxon-Signed Rank test
**significant at p<0.05*

Our study showed that no significant effects of probiotic supplementations in diabetic hemodialysis patient on urea, creatinine level, calcium , phosphorus, potassium, sodium and PTH level in both group of study this finding is agreed with trial of Arani, Navid Mazruei et al. [19] In which there was no significant changes in creatinine level and BUN in the study group.

Also our results were in agreement with Soleimani, Alireza, et al. [16] study that showed no significant differences on creatinine and BUN in study groups and also showed no significant differences was detected in Na & K level in both group.

Our study results were against Borges Natália A et al. [23] clinical trial in which there were significant differences in Pre-dialysis urea and potassium levels in probiotic groups (P value 0.05)(P value 0.02)respectively ,but no significant differences in Predialysis urea and creatinine ;this study supposed theoretically that introduction of probiotic bacteria in a uremic environment may exacerbate the damage to gut mucosa including potassium channels that have increased expression in a CKD patients to compensate progressive loss of renal function and decreasing of potassium loss through the damaged kidneys .

In our study there was significant decrease in CRP between two study groups; (mean rank =16.16) at base line and (mean rank =12.20) after study and P value <0.001 in Probiotics group.

Also there was significant decrease in HA1c in Probiotics group (mean rank =17.11) before and (mean rank =10.21) after study with P value 0.001.

Albumin increase significally in Probiotics group (mean rank =8.69) before and (mean rank =19.53) after study with P value 0.039.

This results were agreed with result of Soleimani Alireza et al. [16] this study showed a significant decrease in CRP in probiotic group (P value 0.04) compared to placebo group and also showed significant decrease in HA1c in probiotic group (P value 0.01) compared to placebo group, but the increase in albumin in probiotic group not reach level of significance; this result was agreed with the results in Soleimani Alireza et al [21] there was significant decrease in CRP in probiotic group (P value < 0.001) and significant decrease of HA1c (P value 0.01) and fasting blood glucose and insulin level.

In Haghighat Neda et al. [24] study a double-blind, clinical trial showed that Synbiotics group had significant decrease in CRP compared to the placebo (p = 0.005).

Also our study is in agree with Natarajan Ranganathan et al. [25] Study that reported a significant decrease in CRP level in probiotics group compared with placebo group.

This result was against Borges Natália A et al. [26] Pilot Study that showed no statistically significance decrease in CRP in probiotic group (P value0.44) but this study was conducted on small number of participant 21 HD Patients 11 participant only received probiotic supplements.

Our limitations include a small number of included patients and a Short period of the study, lack of strict dietary flow up to the patient, multi drugs taken by the patients and difficulty to equalize doses of these drugs taken by the hemodialysis patient with diabetes for proper studying effect of probiotics in those type of patients and lacking to multi centric clinical trials on this drugs on diabetic patients on HD for proper comparing the results of our study with others especially effect on complete blood count parameters , so we recommend that further multicentric clinical trials on large number and for longer period .

5. CONCLUSION

The probiotic group showed significant decrease in CRP and significant increase serum albumin at the end of the study emphasizing the anti-inflammatory effect of the used drug, also probiotic group showed significant decrease in HbA1c at the end of the study emphasizing the role of the used drug in glycemic control.

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CONSENT

Informed written consent was obtained from all patients after a full explanation of the benefits and risks of the study. Privacy of all patients' data is granted by a special code number for every patient file that includes all investigations.

ETHICAL APPROVAL

The protocol was approved by the local ethics committee to conduct this study and to use the facilities in the hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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