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Gut Microbiota Interplay between Obesity and Non Alcoholic Fatty Liver.

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ABSTRACT

The gut microbiota is important players in the development of obesity and obesity-related disease. We aim to detect changes of fecal microbiota, frequency of fatty liver among obese adults and associated clinical; anthropological measures; biochemical and imaging studies .Twenty five obese adults randomly selected and 25 adults with normal weight serving as controls. Clinical and anthropometric evaluations were done. The fatty liver, visceral fat and subcutaneous fat were measured by ultrasonography. Quantification of Bifidobacterium, Bacteroides, Enterobacteria, and Lactobacillus in feces was done by real-time PCR. Serum hsCRP level, IL6, progranulin and LPS level were measured using ELISA. Insulin resistance was calculated by the homeostasis model. Results: Our study showed that obesity in adults was associated with a significant reduction in fecal Bifidobacteria (P<.017) and a significant increase in fecal Enterobacteria (P<.033). A significant increase in fecal Lactobacteria, Enterobacteria and Bifidobacteria in adults with fatty liver (P<.000, .041, .000 respectively). Our study showed a significant increase in inflammatory markers (progranulin, LPS, IL6 and hsCRP) in adults with fatty liver (P<.008, .016, .000 &.019 respectively).Conclusion: Intestinal microbiota might play an important part in progression of nonalcoholic fatty liver in obese adults. Modulation of gut microbiota by diet modifications or by using probiotics and prebiotics as a treatment for obesity and fatty liver disease might be the issue for further investigations.

Keywords: Fecal microbiota, LPS, Progranulin

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INTRODUCTION

Many studies explore the interdependent relationship between the host and its microbial community. They have revealed remarkable microbial influences on host metabolism, energy utilization, and storage. The gut microbiota have influence over a large number of host patho-physiological processes, including vitamin biosynthesis, inflammatory bowel disease, and colorectal cancer. The gut microbiota is important players in the development of obesity and obesity-related disease (1-4). Obesity is characterized by a low-grade inflammation and a cluster of several metabolic disorders (insulin resistance, type 2 diabetes, dyslipidemia, and hypertension) [5].

Investigations have shown that 80–90% of the bacterial phylotypes are members of two phyla: the Firmicutes (e.g. Clostridium, Enterococcus, Lactobacillus, Ruminococcus), and the Bacteroidetes (e.g. Bacteroides and Prevotella) followed by the Actinobacteria (e.g. Bifidobacterium) and the Proteobacteria (e.g. Helicobacter, Escherichia) [6, 7].

On the basis of the recent demonstration that obesity and insulin resistance are associated with a low-grade inflammation, Cani et al., have proposed several mechanisms linking gut microbiota to the development of obesity and metabolic disorders [8]. They identified the lipopolysaccharide (LPS), a membrane component of Gram negative bacteria) as the triggering factor of the early development of inflammation and metabolic diseases [8]. Bifidibacterium spp. group has been shown to reduce intestinal endotoxin levels in rodents and improve mucosal barrier function [9, 10].

We therefore tested changes of gut microbiota in obese Egyptian adults and its relation to metabolic disorders (insulin resistance, dyslipidemia, hypertension and non- alcoholic fatty liver).

MATERIALS AND METHODS

Subjects

A total number of 50 adults were recruited from the liver, obesity clinics, Medical Service Unit, National Research Centre during the period between September 2012 and December 2013. They were 25 normal weight and 25 obese adults, with age range from 19 years to 45 years old.

The study protocol was approved by the Human Ethics Committee of National Research Center, and written informed consent was obtained. Adults of both sexes were enrolled. Patients with any of the following criteria were excluded from the study: hepatobiliary diseases, chronic liver diseases including viral hepatitis malignancies, ascites, medications known to cause hepatic steatosis (such as estrogens, corticosteroids, amiodarone, and valoprate), or taking antibiotics during last 2 months, inflammatory bowel disease, human immunodeficiency virus (HIV), chronic drug or alcohol abuse.

Clinical Examination

All subjects in the study were subjected to the following: a full history taking including the complete present history, with particular emphasis on history of medication and antibiotic intake and clinical examinations, both general and systemic.

Blood pressure measured according to American Heart Association guidelines.

Anthropometric indices: Body weight measured to the nearest 0.1 kg with a balance scale and height measured to the nearest 0.1 cm. Body mass index was calculated as weight divided by height squared (kg/m2). Waist circumference (WC) was measured at the level midway between the lowest rib margin and the iliac crest. Hip circumference (HIP C) was measured at the widest level over the greater trochanters in a standing position by the same examiner; then waist to hip ratio (WHR) and waist to height ratio (WHTR) were calculated [11].

Percentage body fat was calculated by the equation:

Adult Body Fat % = (1.20 x BMI) + (0.23 x Age) - (10.8 x gender) - 5.4 [12].

Abdominal Ultrasonography

In addition to the routine abdominal ultrasound examination based on the clinical indication, ultrasonography (US) Liver size was determined by measuring distance between upper and lower borders in mid clavicular line. Liver parenchyma was examined with sagittal as well as longitudinal guidance of the probe and completed by lateral and intercostal views. The examination of the liver was carried out in dorsal recumbence and left lateral position and in inspiration. The presence of steatosis was recognized as a marked increase in hepatic echogenicity, poor penetration of the posterior segment of the right lobe of the liver, and poor or no visualization of the hepatic vessels and diaphragm. The liver was assessed to be normal if the texture was homogeneous, exhibited fine-level echoes, or was minimally hyperechoic or isoechoic compared with normal renal cortex, and if there was no posterior attenuation of the ultrasound beam. Fatty liver may be diagnosed if liver echogenicity exceeds that of renal cortex and spleen and there is attenuation of the ultrasound wave, loss of definition of the diaphragm, and poor delineation of the intrahepatic architecture. Normal Liver had homogeneous texture and exhibited fine-level echoes, or was minimally hyperechoic or isoechoic compared with normal renal cortex and spleen, and if there was no posterior attenuation of the ultrasound beam. While fatty liver was diagnosed if liver echogenicity exceeds that of renal cortex and spleen and there was attenuation of the ultrasound wave, loss of definition of the diaphragm, and poor delineation of the intrahepatic architecture. Hepatomegaly was diagnosed if a liver size was above 155 mm, measured at a subcostal diameter in the mid-clavicular line [13]. The maximum subcutaneous fat thickness (SFT) and visceral fat thickness (VFT) were obtained 1 cm above umbilicus in the midline of the abdomen. Application of the transducer on the body surface was done without undue pressure that would alter the body layer contour and thickness. SFT was defined as the distance between the external face of the recto-abdominal muscle and the internal layer of the skin, while VFT was defined as the distance between the anterior wall of the aorta and the internal layer of the rectoabdominal muscle perpendicular to the aorta [14]

Laboratory Measurements

Blood samples

Five milliliters of blood was withdrawn from the anticubital vein after a fast of 12–14 h under aseptic conditions. Samples were labeled and left to clot at room temperature for 15 min then centrifuged, sera were collected and aliquated for evaluation of the following parameters and inflammatory markers:

- FBS & Lipid profile was assessed by an OLYMPUS AU 400 Chemistry Analyzer [15].
- Insulin and hsCRP levels were estimated by Enzyme immunoassay (ELISA).
- Insulin resistance was calculated by the homeostasis model (HOMA-IR) using the following formula: HOMA- IR = fasting insulin (mU/L) × fasting glucose (mmoL/L)/ 22.5.
- Serum IL-6 was assessed by Enzyme immunoassay (ELISA).
- Serum progranulin was performed using Enzyme immunoassay (ELISA)
- Lipopolysaccharide (LPS) was performed using Enzyme immunoassay (ELISA) Glory Science Co., tdTX78840, USA.

Bacteriology

Collection of human fecal samples

The fecal samples were collected from the obese and control human subjects as two gram from each subject mixed with 10 ml of phosphate buffer (pH 7) and stored at – 80ºC for analysis.

Bacterial strains and growth conditions

The bacterial strains used for standard curve in real time PCR analysis were obtained from the American Type Collection Culture (ATCC) and their culture media were obtained from (Oxoid, Basingstoke, UK). Their cultivation was as follow: Bifidobacterium longum subsp. infantis (ATCC 15697) was grown anaerobically in modified reinforced clostridial medium at 37℃, Lactobacillus gasseri (ATCC 33323) was grown anaerobically in DeMan Rogosa Sharpe MRS medium at 37℃, Enterobacter cloacae subsp. cloacae (ATCC 29005) was grown in nutrient medium at 30℃, and Bacteroides fragilis BAA (ATCC 2283) anaerobically in trypticase soy media supplemented with 5% defibrinated sheep blood. The anaerobic conditions were achieved by using the anaerobic jar with AnaeroGen (Oxoid, Basingstoke, UK). The colony forming unit (CFU) for each culture was determined by plating serial dilutions.

DNA extraction

Genomic DNA was extracted from fecal samples and bacterial cultures by using the Qiagen MiniPrep Stool DNA extraction kit (Qiagen, Hilden, Germany) and MiniPrepDNA extraction kit (Fermentas Life Sciences, Vilnius, Lithuania) respectively according to the manufacturer's instruction.

Primers and probes for quantification bacterial groups

TaqMan probe quantitative PCR was used to quantify Bifidobacterium species. Quantitative PCR using SYBR-Greens was performed for the Bacteroides/Prevotella group Enterococcus group, and for the Lactobacillus/Leuconostoc/Pediococcus group. Primers and probe used in this study [16, 17] were purchased from Sigma Scientific Services, Cairo, Egypt.

Standard curves and quantification

Pure overnight cultures of the strains: Bifidobacterium longum, Lactobacillus gasseri, Enterobacter cloacae, and Bacteroides fragilis were diluted individually to seven serial dilutions with defined cell numbers (ranging from 102 to 109 CFU/ml) and were used to extract genomic DNAs. These DNAs were then used as templates in real-time PCR to generate standard curves for quantification of the target groups: Bifidobacteria, Lactobacillus/Leuconostoc/Pediococcus, Enterococcus, and Bacteroides/Prevotella. Standard curves were generated by plotting threshold cycles (Cq) vs. bacterial quantity (CFU). The (CFU) of each bacterial group was interpolated from the averaged standard curves. When PCR was performed on unknown fecal samples, we used these standard curves to quantify each bacterial population.

Real-time PCR amplification

Real-time qPCR was performed using Thermo Scientific PikoReal real-time PCR machine 24-well block format. Each reaction was carried out in duplicate in a volume of 25 µl with 0.2 mM final concentration of each primer, 0.25 mM final concentration of each probe and 10 mL of appropriate dilutions of DNA samples. The detection was carried out using DyNAmo™ Flash Probe qPCR Kit or DyNAmo™ ColorFlash SYBR® Green qPCR 2X master mix (Thermo scientific). Amplifications were carried out using the following ramping profile: one cycle at 95 °C for 10 min, followed by 40 cycles of 95 °C for 30 s, and 60 °C for 1 min. SYBR-Greens reactions ended with melting step 60-98 °C. The Cq (cycle at which the signal crosses a threshold) values were plotted as a linear function of the base 10 logarithm of the number of respective bacterial cells in the culture as determined by plate counts. The standard curves were then used to quantify the fecal samples with unknown cell concentrations collected during the study [18].

Statistical Analysis

Each variable was assessed for a normal distribution. The standard computer program SPSS for Windows, release 12.0 (SPSS Inc., USA) was used for data entry and analysis. All numeric variables were expressed as mean ±SD. Comparison of different variables in various groups were carried out using the Student t-test and the Mann–Whitney U-test for normal and nonparametric variables, respectively. Pearson's and Spearman's correlation tests (r=correlation coefficient) were used for correlating normal and

nonparametric variables, respectively. For all tests, a probability (P) less than 0.05 (<0.05) is considered significant.

RESULTS

In this prospective cross-sectional study we included 25 obese and 25 normal weight adults (20 males and 30 females). The mean age was 41.3±21.0 years in non- obese adults, while in obese adults it was 45.15±15.11years with no statistical difference**.**

The Comparative Study between Obese and Normal Weight Adults

Table 1: Demographic characteristic of study groups

	1=non obese 2=obese	N	Mean	Std. Deviation	Sig. (2-tailed)
Age Years	1	25	41.30	21.05	NS
	2	25	45.15	15.11	
BMI	1	25	24.09	4.38	.000**
	2	25	40.52	3.84	
WHTR	1	25	0.73	0.18	.013*
	2	25	0.83	0.08	
WHR	1	25	0.65	0.15	NS
	2	25	0.67	0.09	
Body Fat %	1	25	31.69	12.29	.000**
	2	25	49.74	8.24	
Systolic BP	1	25	107.50	11.98	.000**
	2	25	125.66	18.35	
Diastolic BP [mm Hg]	1	25	65.75	7.30	.000**
	2	25	82.24	13.24	
Liver Size (cm)	1	25	14.80	1.57	.000**
	2	25	16.51	0.93	
SCF(cm)	1	25	1.44	0.73	.000**
	2	25	2.4689	0.70896	
Visceral Fat(cm)	1	25	4.39	1.32025	.000**
	2	25	6.1714	1.75201	

. ** P value is highly significant * P value is significant

Table1 shows the comparative study between obese adults and controls as regard the anthropometric and clinical characteristics. Obese adults had significantly different higher levels of BMI, WHTR and percentage body fat (P>.000, .013 and.000 respectively). Differences between systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in obese adults (P<.000). It was noticed that the liver size was significantly higher in obese group (P<.000). Fatty liver was detected in 30 (72%) obese adults and in 7(32%) of normal weight controls (P<.001). Comparison between controls and obese persons revealed that there were significant differences between them as regards subcutaneous fat thickness (SFT) and visceral fat thickness (VFT) (P<.000).

Comparison between biochemical results revealed that there were significant differences between them as regards all studied variables except high density lipoprotein (HDL). All data are shown in Table 2.

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. Table 2 Laboratory Data of obese adults and controls

	1=non obese 2=obese	N	Mean	Std. Deviation	Sig. (2-tailed)
HOMA-IR	1	25	5.43	4.07	.006**
	2	25	5.53	3.73	
hsCRP [mg/l]	1	25	10.92	5.73	.003**
	2	25	61.66	24.16	
PROGRANULIN [ng/mL]	1	25	86.22	37.48	.009**
	2	25	10.21	4.75	
LPS [ng/mL]	1	25	17.41	19.97	.047*
	2	25	9.81	8.62	
IL6 [ng/mL]	1	25	16.15	19.12	.034*
	2	25	114.58	47.95	
CHOLESTEROL [mg/l]	1	25	179.88	40.26	.000**
	2	25	68.33	24.28	
TRIGLYCERIDE [mg/l]	1	25	119.53	57.07	.000**
	2	25	82.83	47.54	
HDL [mg/l]	1	25	64.95	59.35	NS
	2	25	67.30	59.30	
LDL [mg/l]	1	25	119.31	34.40	.012*
	2	25	5.43	4.07	

** P value is highly significant * P value is significant

Table 3 shows the comparison between obese adults and controls regarding Gut microbiota. This work has shown that obesity in adults was associated with a significant reduction in fecal Bifidobacteria (P<.017). Our study showed a significant increase in fecal Enterobacteria in obese adults (P<.033). While no significant difference was observed in fecal Bacteroidetes and lactobacillus in both groups.

Table 3: Comparison between obese adults and controls regarding Gut microbiota

	1=non-obese 2=obese Adults	N	Mean	Std. Deviation	Sig. (2-tailed)
LACTOBACILLUS (log 10 CFU/ml)	1	25	3.44	2.18	NS
	2	25	3.89	1.35	
ENTEROBACTERIA (log 10 CFU/ml)	1	25	5.03	1.17	.033*
	2	25	5.82	1.40	
BACTEROID (log 10 CFU/ml)	1	25	4.85	2.10	NS
	2	25	5.19	2.17	
BIFIDOBACTERIA (log 10 CFU/ml)	1	25	2.70	2.71	.017*
	2	25	1.17	1.98	

* P value is significant

Table 4 shows a comparison between adults with fatty liver and without fatty liver. Our study showed a significant increase in inflammatory markers (progranulin, LPS, IL6 and hsCRP) in obese adults with fatty liver (P<.008, .016, .000 &.019 respectively). A significant increase in fecal Lactobacteria, Enterobacteria and Bifidobacteria in obese adults with fatty liver (P<.000, .041, .000 respectively). While no significant difference was observed in fecal Bacteroidetes between the two groups.

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Table 4: Comparison between adults with fatty liver and without fatty liver

	Fatty liver 1=Negative 2=Positive	N	Mean	Std. Deviation	Std. Error Mean
PROGRANULIN [ng/mL]	1	13	55.18	15.61	.008*
	2	37	78.51	35.25	
LPS [ng/mL]	1	13	7.70	4.07	.016*
	2	37	18.04	21.58	
IL6 [ng/mL]	1	13	4.73	3.60	.000**
	2	37	16.61	17.67	
hsCRP	1	13	4.78	4.00	.019*
	2	37	8.95	6.55	
LACTOBACTERIA (log 10 CFU/ml)	1	13	1.68	1.52	.000**
	2	37	4.42	1.39	
ENTEROBACTERIA (log 10 CFU/ml)	1	13	4.64	1.45	.041*
	2	37	5.68	1.17	
BACTEROID (log 10 CFU/ml)	1	13	4.68	2.58	NS
	2	37	5.15	2.02	
BIFIDOBACTERIA (log 10 CFU/ml)	1	13	4.79	2.13	.000**
	2	37	1.04	1.76	

** P value is highly significant * P value is significant

Results of correlation are shown in table 5. The relations between BMI and fecal microbiota are shown in fig 1. A significant negative correlation was detected between fatty liver and fecal Bifidobacterium r=.595 and P=.000 .We reported significant correlation between BMI and fecal Bifidobacteria r=-.422 and P=.001, A significant positive correlation was detected between insulin resistance and fecal Enterobacteria r=.261 and P=.046, while non-significant negative correlation was detected between insulin resistance and fecal Bifidobacterium r= -.205). Also, a negative correlation was detected between Bifidobacterium and inflammatory markers (hsCRP, progranulin, LPS and IL6) .No significant correlation was detected between different types of fecal bacteria and blood pressure.

Table 5: Correlation between fecal microbiota and some studied data

		Fatty liver			
BIFIDOBACTERIA	Spearman's rho Correlation	-.595(**)			
	Sig. (2-tailed)	.000			
	N	47			
		ENTEROBCTERIA	BIFIDOBACTERIA		
HOMA-IR	Pearson Correlation	.261(*)	-.205		
	Sig. (2-tailed)	.046	.123		
	N	59	58		
		HSCRP	PROGRANULIN	LPS	IL6
BIFIDOBACTRIA	Pearson Correlation	-.196	-.218	-.090	-.008
	Sig. (2-tailed)	.141	.128	.532	.951
	N	58	50	50	57

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

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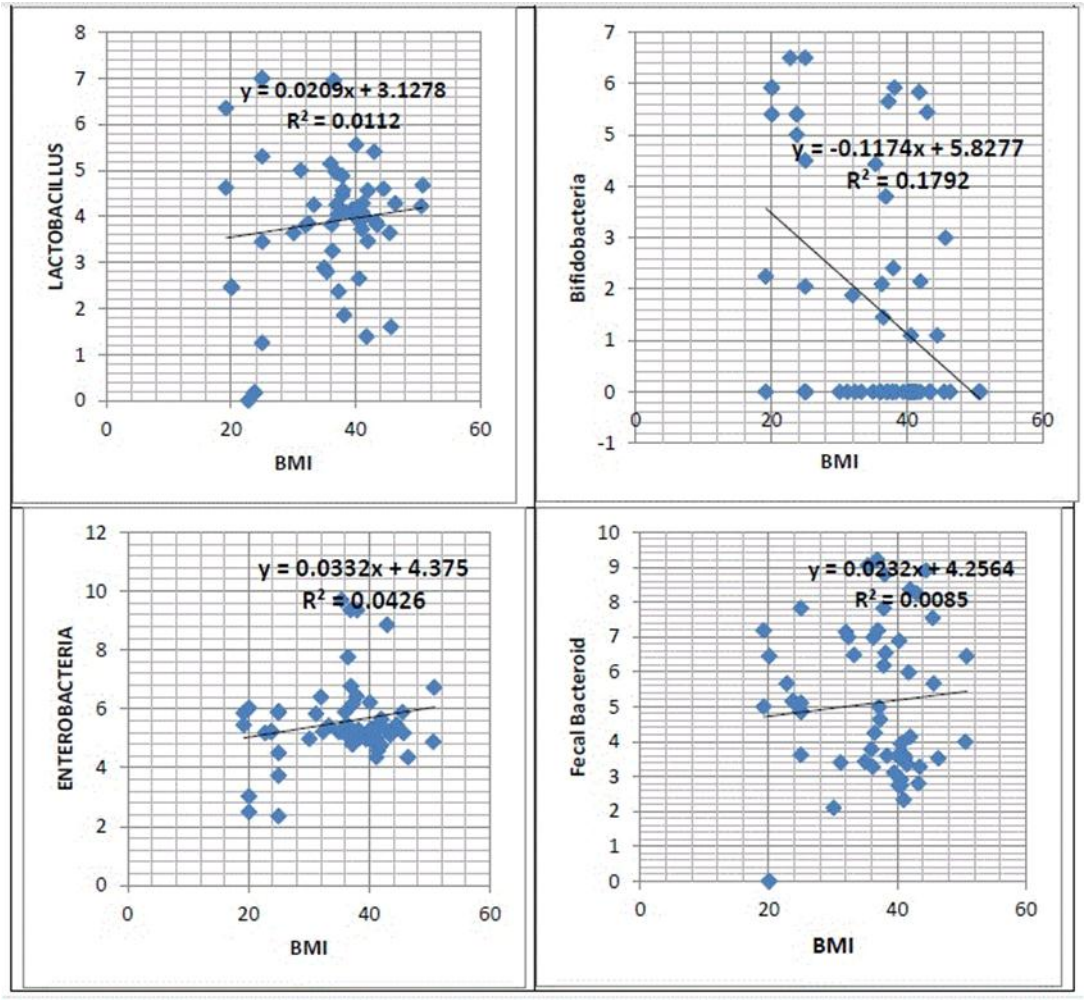

Figure 1: Relation between fecal microbiota (log 10 CFU/ml) and BMI

DISCUSSION

Endotoxemia, low-grade inflammation, insulin resistance in obesity are characterized by disordered cytokine production and activation of a network of inflammatory signal pathways [19]. Our study showed significant increase in inflammatory markers and insulin resistance in obese adults. Obesity is a predisposing factor for chronic diseases both in the adolescent years and into adulthood. Assessment and characterization of gut microbiota has become a major research area in human disease. It is now recognized that the gut microbiota plays an even more important role in maintaining human health than previously thought [20]. Consequently, the gastrointestinal tract (GIT) microbiota is gaining significant research interest in relation to obesity in an attempt to better understand the etiology of obesity and potentially new methods of treatment. Obesity in humans leads to changes in the composition of gut microbiota. Our results reveal a significant decrease in levels of fecal bifidobacteria in obese adults. In accordance with our results, this specific decrease in Bifidobacterium has recently been confirmed in another model of genetically obese and diabetic rodents (falfa rats) [21]. Among the human studies exploring a dysbiosis of the gut microbiota during obesity, Collado et al. observed significant differences in gut microbiota composition according to the body weight during pregnancy. The Bifidobacterium group was present in higher numbers in normal-weight than in overweight women and also in women with lower weight gain over pregnancy [22]. These studies support that the gut microbiota profile (in favor of a higher bifidobacteria) may provide protection against overweight and obesity development. Indeed, Bifidobacterium represent an important group of bacteria whose presence is often associated with beneficial health effects [23].

Our study showed a significant increase in fecal Enterobacteria in obese adults. This result is in agreement with those reported by Turnbaugh et al. They reported a marked difference in the abundance of n

obese group [24]. The lipopolysaccharides (LPS) which are highly inflammatogenic component of the cell wall of the Gram-negative bacteria were causally involved in the onset of the low-grade inflammation in response to a fat-enriched diet [18]. Bacterial fragments are recognized by Toll-like receptors (TLRs) that are a conserved family of integral membrane pattern-recognition receptors that have a crucial role in the innate immune system, which is the early host defense against invading pathogens but are also required for intestinal homeostasis [25]. Our study revealed a significant higher level of serum LPS in obese children and adults. Serum LPS concentration could also be considered as a risk factor since it was present in excess in the blood of apparently healthy patients feeding more fat than carbohydrate or proteins [26]. The increased serum LPS concentration could be acutely induced by a single absorption of lipid in human [27] and in mice [8] and seems to depend on an increased intestinal permeability through a GLP-2 dependent mechanism [28]. Other evidences showed that the TLR5 receptor was conversely protecting against metabolic syndrome since mice genetically deficient in TLR5 exhibited hyperphagia and developed hallmark features of metabolic syndrome [29]. LPS molecules are carried into the blood mostly by lipoproteins where in the liver they have been proposed to induce hepatitis [30]. Therefore, it has been suggested that LPS can be absorbed by the intestine during the synthesis of chylomicrons [31] then exchanged with other lipoproteins [32] that can be chronically transported toward target tissues such as liver [33] or blood vessels [34] and trigger inflammation. The increased levels of bifidobacteria in non- obese subjects may decrease intestinal permeability and lower the circulating levels of endotoxin [8]. Our results showed that serum LPS was a negative correlation with bifidobacteria count. The increased levels of bifidobacteria in normal weight controls decrease intestinal permeability and lower the circulating levels of endotoxin (LPS).

A significant negative correlation was detected between fatty liver and Bifidobacterium. This could be explained by Terpstra et al who reported that mammalian intestinal Bifidobacteria can synthesize from free linoleic acid bioactive isomers of conjugated linoleic acid, which have antidiabetic, anti- atherosclerotic, immunomodulatory, and anti-obesity properties [35]. Wall et al found that the supplementation of Bifidobacterium and linoleic acid to different mammalian species resulted in a two- to threefold higher intestinal, hepatic, and adipose tissue content of cis-9, trans-11 conjugated linoleic acid, eicosapentaenoic acid, and docosahexaenoic acid, concomitantly with a reduced proinflammatory cytokines TNF-, IL-6, and interferon-ex-pression, than the linoleic acid-alone supplemented diet [36].

Our study showed a significant increase in fecal Enterobacteria in obese adults. Obese with fatty liver had significantly higher fecal Enterobacteria than obese adults without fatty liver. Zhu et al [37] showed that Enterobacteria (is a well-known ethanol producer bacteria) exhibiting a significant difference between the patients with and without nonalcoholic-steatohepatitis microbiomes. Nair et al [38] demonstrated that obese women with nonalcoholic-steatohepatitis had higher breath ethanol concentrations than healthy controls detected by gas chromatography. Similar blood-ethanol concentrations were observed between healthy subjects and obese non- nonalcoholic-steatohepatitis patients; however, nonalcoholic-steatohepatitis patients exhibited significantly elevated blood ethanol levels [37]. Ethanol contributes to iNOS-mediated intestinal hyperpermeability, and therefore enhances the passage of endotoxins from the intestinal lumen into the portal system [39]. Gustot et al showed that enteral ethanol exposure induced steatosis and increased liver weight [40].

CONCLUSION

Obesity is associated with gut dyspiosis, and, the metabolic endotoxemia induced by LPS derived from the gut microbiota is associated with inflammation and insulin resistance. Subsequently these result in systemic metabolic dysregulation that indirectly impact the storage of fatty acids in the liver .Intestinal microbiota might play an important part in progression of nonalcoholic fatty liver in obese adults. Modulation of gut microbiota by diet modifications or by using probiotics and prebiotics as a treatment for obesity and fatty liver disease might be the issue for further investigations.

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REFERENCES

[1] Ley RE, Hamady M, Lozupone C, et al. Science 2008; 320: 1647–1651.
[2] Ley RE, Lozupone CA, Hamady M, et al., Nat Rev Microbiol 2008; 6 : 776–788.
[3] Backhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Science 2005; 307 : 1915–1920.
[4] Peterson DA, Frank DN, Pace NR, Gordon JI. Cell Host Microb 2008; 3 : 417–427.
[5] Alberti KG, Zimmet P, Shaw J. Lancet 2005; 366:1059-1062
[6] Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Proc Natl Acad Sci U S A 2005; 102:11070-11075.
[7] Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA: Science 2005; 308:1635-1638.
[8] Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C et al. Diabetes 2007; 56:1761-1772.
[9] Griffiths EA, Duffy LC, Schanbacher FL, Qiao H, Dryja D, Leavens A, et al. Dig Dis Sci Apr, 2004; 49(4):579–89.
[10] Wang Z, Xiao G, Yao Y, Guo S, Lu K, Sheng Z. J Trauma 2006; 61(3):650–7.
[11] Jawad A Al-Lawatia and Pekka Jousilahtia. Public Health Nutr 2008;1: 102-108.
[12] Deurenberg P, Weststrate JA, and Seidell JC. The British J Nutr 1991;65; 105-114.
[13] Wafaa MA, Ragab R, Ismail NA, Yasser, Elhosary A, et al. J Genetic Eng Biotechnol 2012; 10:221-227.
[14] Kim SK, Kim HJ, Hur KY, et al. American J Clin Nutr 2004, 79; 593-599.
[15] Friedewald WT, Levy RI, Fredrickson DS. Clin Chem 1972; 18: 499–502.
[16] Furet JP, Firmesse O, Gourmelon M, Bridonneau C, Tap J, Mondot S, Doré J, Corthier G. FEMS Microbiol Ecol 2009; 68 351–362.
[17] Rinttil¨a T, Kassinen A, Malinen E, Krogius L & Palva A. J Appl Microbiol.2004; 97: 1166–1177.
[18] Nagwa Abdallah Ismail , Nahla M. Mansour , Shadia Ragab ,Abeer M Nour Eldin Abd El Baky , Mona Hamed , and Dina F Ayoub. Res J Pharm Biol Chem Sci 2015;5(6): 646-653.
[19] Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Diabetes Res Clin Pract 2014; 105: 141-150
[20] Jia W, Li H, Zhao L, Nicholson JK. Nat Rev Drug Discov 2008;7:123-129.
[21] Waldram A, Holmes E, Wang Y ,et al. J Proteome Res 2009, 8:2361-2375.
[22] Collado MC, Isolauri E, Laitinen K, Salminen S. Am J Clin Nutr2008, 88:894-899.
[23] Boesten RJ, de Vos WM. J Clin Gastroenterol 2008, 42(Suppl 3, Pt 2):S163-S167.
[24] Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, et al. Nature 2006; 444: 1027–1131.
[25] Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Cell 2004; 118(2):229–241.
[26] Amar J, Burcelin R, Ruidavets J, Cani P, Fauvel J, Alessi M et al. Am J Clin Nutr 2008; 87:1219–1223.
[27] Laugerette F, Vors C, Geloen A, Chauvin MA, et al. J Nutr Biochem2010; 22(1):53–59.
[28] Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O et al. Gut 2009;t 58(8):1091–1103.
[29] Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Science2010; 328:228–231.
[30] Harris HW, Brady SE, Rapp JH. J Surg Res 2002; 106(1):188–195
[31] Ghoshal S, Witta J, Zhong J, de Villiers W, Eckhardt E. J Lipid Res2009; 50(1):90–97
[32] Rensen PC, Oosten M, Bilt E, Eck M, Kuiper J, Berkel TJ. J Clin Invest 1997; 99(10):2438–2445
[33] Kumwenda ZL, Wong CB, Johnson JA, Gosnell JE, Welch WJ, Harris HW. Shock 2002; 18(2):182–188
[34] Westerterp M, Berbee JF, Pires NM, et al. Circulation 2007; 116(19): 2173–2181
[35] Guerra RR, et al. Growth Factors 2007; 25: 280-285.
[36] Ueki K, Kondo T, and Kahn CR. Mol Cell Biol 2004; 24: 5434–5446.
[37] Zhu L, Baker SS, Gill C, Liu W, Alkhouri R, Baker RD, Gill SR. Hepatol 2013; 57: 601-609.
[38] Nair S, Cope K, Risby TH, Diehl AM. Am J Gastroenterol 2001; 96: 1200-1204.
[39] Forsyth CB, Tang Y, Shaikh M, Zhang L, Keshavarzian A. Alcohol Clin Exp Res 2011; 35: 1635-1643
[40] Gustot T, Lemmers A, Moreno C, et al. Hepatol 2006; 43: 989-1000.

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