

Correlation study on gut microbiota and omentin-1 gene polymorphism in Uyghur newly diagnosed type 2 diabetes

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Research

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Abstract

Background: Type 2 diabetes (T2DM) is a top risk factor for health in China. Gut microbiota, genetic factors and lipids metabolism play important role in development of T2DM. In this study, we investigated the relationship between the gut microbiota and omentin-1 gene polymorphism to explore the interaction between host gene and gut microbiota in Uyghur T2DM.

Methods: A total of 98 newly diagnosed Uyghur T2DM patients and 99 healthy normal controls (NC) enrolled into this study according to inclusion criteria. The total DNAs was extracted from the fecal microbiota. Abundance of the *Lactobacillus* genus, *Bacteroides thetaiotaomicron* and *Clostridium* in the gut microbiota was determined with 16S rDNA gene Real-time fluorescence quantitative PCR amplification. PCR-PFLP was applied to determine the genotypes of Val109Asp variant (rs2274907) in the Omentin-1 gene. And the relationship between rs2274907 and gut microbiota was assessed.

Results: There were no significant differences of the Val109Asp variant (rs2274907) between T2DM and NC group. The abundance of *Lactobacillus* genus and *Clostridium* genus was lower in newly diagnosed T2DM group than in the NC group ($P<0.05$). Serum insulin, LDL-C, the abundances of *Lactobacillus* genus and *Clostridium* genus were the risk factors of T2DM. (OR=1.094 95%CI 1.014-1.180), (OR=3.868 95%CI 1.250-11.971), (OR=0.288 95%CI 0.145-0.571), (OR=0.044 95%CI 0.012-0.154).

Conclusions: The abundance of *Lactobacillus* and *Clostridium* genus may be related to the pathogenesis of new-onset T2DM in Uyghur population, the mechanism of which needs to be further studied. The interactive relationship between the gut microbiota and omentin-1 gene polymorphism in newly diagnosed T2DM was not observed in this study.

Background

Type 2 diabetes mellitus (T2DM) is a top risk factor for health in China [1], the crude prevalence of diabetes in Chinese Uyghur population is 12.2% [2]. While genetic variants contribute to the T2DM, non-genetic factors, such as the gut microbiota, also play key roles. Metabolic disease arises from complex interactions between host genetic and environmental factors. And interaction between the gut microbiota and the host gene may have an important role in development of T2DM. Dysbiosis of gut microbiota is related to T2DM [3]. Furthermore, recent studies have reported specific human genetic variants that were associated with gut microbiota [4-8]. But the relationship between gut microbiota and host genetics remains incompletely elucidated. Because of different ethnic people have different gut microbiota diversity and genetic variations.

Gut microbiota closely related to the obesity [9], and obesity is an important risk factor for T2DM [10]. Gut microbiota affects the development of obesity and T2DM mainly through the energy acquisition in the intestine, regulating fat storage and affecting adipocytes, and regulating the inflammation induced by metabolic endotoxemia [11]. Insulin and adipocytokines are in a disordered state in T2DM patients [12]. [Virtue AT](#) reported that the gut microbiota regulates white adipose tissue inflammation and obesity [13]. Related studies have shown that these adipokines are closely related to insulin resistance and diabetes, and have confirmed that body fat storage depends on different intestinal flora [14].

Omentin is a newly discovered adipokines. Its expression and secretion are uniquely different. It is mainly expressed and secreted by vascular stromal cells in visceral adipose tissue, but is rarely expressed in subcutaneous adipose tissue [15]. Based on current research reports, omentin-1 also involved in insulin resistance, inflammatory response, endothelial cell function regulation, vascular calcification, etc., which is closely related to the occurrence of cardiovascular disease, especially for revealing the mechanism of cardiovascular disease complications in obese and diabetic patients [16]. The expression and secretion of omentin-1 were significantly decreased in overweight and obese patients, and negatively correlated with BMI, waist circumference, leptin level and HOMA-IR index [17-18]. Therefore, regulation of intestinal flora and regulation of plasma omentin levels may become a new direction for the future treatment of diabetes.

We here study the interaction between the gut microbiota such as *Lactobacillus* genus, *Bacteroides thetaiotaomicron*, *Clostridium* and omentin-1 gene variation in Chinese Uyghur ethnic population who have a high prevalence of T2DM.

Methods

Subjects

A total of 197 Uyghur subjects participated in and contributed blood and fecal samples to this study, where 98 of their newly diagnosed with T2DM according to ADA criteria (2014) and 99 served as healthy controls. All subjects come from the Endocrinology department and physical examination center of the first affiliated hospital of Xinjiang medical university. Each participant gave written informed consent following a full description of the study, which was approved by the Ethics Committee of the first affiliated hospital of Xinjiang Medical University. The control group comprised 99 normal glucose tolerance subjects who were randomly selected and matched for age, gender to cases from the general population. We excluded those subjects who reported already having diabetes, receiving antidiabetic medicine (metformin, etc.), had antibiotic or drugs used to regulate intestinal flora (i.e. prebiotic, symbiotic, or probiotics) during the previous month, cardiovascular disease, kidney disease and cancer. Pregnant women, lactating women were not included in the study. Subjects who had pets at home were also excluded. People who had neurological impairments, and or severe mental illness were excluded.

Clinical measurements and laboratory study (anthropometrics)

Anthropometrics data of the subjects were collected using a designed questionnaire by professional staff, including general demographic data such as age, gender, occupation, education level, economic status, and chronic disease. Height, weight, waist circumference, hip circumference and blood pressure were measured, and body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. Blood glucose (FPG, 2hPG), blood lipids (TC, TG, HDLC, LDLC) level was measured using an automated analyzer. Plasma omentin-1 levels were determined by enzyme-linked immunosorbent assay (ELISA).

Genotyping study

Blood DNA was extracted by Tiangen genomic DNA extraction mini kit. Primers were designed by Shanghai Tianhao Genetic Analysis Co. The forward primer of rs2274907 was 5'-CCCTCACCCGAGTGGGTAAGAA-3', and the reverse primer was 5'-AGTCAGCAGGGCAGCAAAGC-3'. The PCR reactions were conducted using the following program: 2min of denaturation at 95°C, 11 cycles of 20s at 94°C, 40s for annealing at 65°C, and 30s for elongation at 72°C, 24 cycles of 20s at 94°C, 30s for annealing at 59°C, and 30s for elongation at 72°C and a final extension at 72°C for 2min. PCR reactions were performed in triplicate 20µL mixture containing 4µL of 1×GC Buffer (TAKARA), 2µL of 2.0mM dNTPs, 1µL of each primer (2µM), 0.4µL of HotStarTaq polymerase (Qiagen Inc.) and 1µL of template DNA. The resulted PCR products were extracted from a 2% agarose gel. PCR-RFLP was applied to determine the genotypes of Val109Asp variant (rs2274907) in the Omentin-1 gene. In the RFLP test 20µL mixtures containing 1µL restriction endonuclease, 10µL PCR products, 2µL 1×buffer and 7µL DNase free distilled water. One unit of restriction enzyme is required to digest 1µg of lambda DNA in 1h at 37°C for AccI. The digested product was diluted 10 times and applied to 3730 XL for capillary electrophoresis.

Real-time quantitative PCR (qPCR)

DNA was extracted from 200mg of stool samples using a QIAamp DNA Stool Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. Quantification of the bacterial species of interest in each original sample DNA were performed by qPCR using a (Bio-rad IQ5) Real-Time PCR System (Bio-rad, USA), and the primers and annealing temperatures are shown in **Table S1**. All the oligonucleotide primers were synthesized by Shenggong Co. (Shanghai, China). Amplification reactions contained 10 µL of SYBR Green PCR Master Mix (Applied Biosystems, Warrington, UK), 0.5µL each primer, and 0.5µL of the respective crude template DNA or water (negative control) in a final volume of 20 µL. Each reaction was performed in duplicate. Amplifications were performed under the following conditions: one cycle at 95°C for 3 min, 39 cycles of denaturation at 95°C for 30 s, annealing at different temperatures (**Table S1**) for 30 s, and extension at 72°C for 1 mins, followed by a final extension step at 72°C for 5 min. The copy number of rRNA gene operons of targeted bacteria in crude DNA templates was determined against serially diluted DNA standards. Bacterial quantity was expressed as log₁₀ copies per mg total microbial DNA.

Statistical analysis

All the analyses were performed by using SPSS version 21. Sample characteristics were presented as mean values and standard deviations for continuous variables, and percentages for categorical variables. Baseline characteristics were compared between three groups by using the analysis of chi-square test (categorical variables) and *t* test (continuous variables). Hardy-Weinberg equilibrium (HWE) for allele frequencies was examined by the chi-square test. Potential correlations between SNP and gut microbiota assessed using logistic regression models following adjustments for participant gender, BMI, and age. The risk for

T2DM was evaluated by calculating the 95% confidence intervals (95% CIs) and odds ratios (ORs) and their corresponding *P* values. Comparisons with *P*<0.05 were considered significantly significant.

Results

Participant characteristic

Table 1 presents the clinical characteristics of the two groups. Age, BMI, WHR, SBP of newly diagnosed T2DM individuals were significantly higher than that of NC individuals (*P*<0.01), and the FPG, TG levels of newly diagnosed T2DM were also significantly higher than those of the NCs (*P*<0.001). The LDL-C level of newly diagnosed T2DM was significantly higher than that of NCs (*P*<0.05), while HDL level was significantly lower in the newly diagnosed T2DM than in the NCs (*P*<0.05). Plasma insulin levels of newly diagnosed T2DM individuals were significantly higher than that of NC individuals (*P*<0.01), and Omentin-1 level was significantly lower in the newly diagnosed T2DM than in the NCs (*P*<0.001).

Table 1 Comparison of clinical characteristics between two groups

Clinical parameters	Newly T2DM [n=98]	NC [n=99]	<i>c</i> ² / <i>t</i>	<i>P</i>
Gender (male/female)	54/44	46/53	1.47	0.255
Age (years)	53.43±9.07	41.42±7.12	10.45	<0.001
BMI (kg/m ²)	28.90±3.35	27.26±4.64	2.84	0.005
WHR	0.96±0.10	0.90±0.07	5.61	<0.001
SBP (mmHg)	133.51±16.27	119.66±15.55	6.11	<0.001
DBP (mmHg)	81.25±8.98	76.91±15.81	2.36	0.019
FBG (mmol/L)	9.78±3.41	5.08±0.45	13.54	<0.001
TC (mmol/L)	4.86±1.47	4.00±0.84	5.04	<0.001
TG (mmol/L)	3.06±3.14	1.83±1.32	3.59	<0.001
LDL-C (mmol/L)	2.71±0.91	2.24±0.64	4.21	<0.001
HDL-C (mmol/L)	1.39±0.59	1.62±0.53	2.92	0.040
Insulin (pmol/L)	15.32±12.49	10.20±6.80	3.58	<0.001
Omentin-1 (ng/mL)	80.00±18.51	89.18±19.04	3.428	<0.001
Smoking status (yes/no)	17/81	28/71	3.34	0.089

Genotyping of Ometin-1 gene variation (rs2274907)

It was determined that the SNPs of interest, rs2274907 was in Hardy-Weinberg equilibrium in both T2DM and NC (*P*> 0.1) (MAF: 0.294). In addition, there were no significant differences of the genotypes allele were observed between T2DM and NC (Table 2).

Table 2 Comparison of distributions of *omentin-1* genotype and alleles [n (%)]

Group	Number	rs1169288 Genotype			rs1169288 allele	
		AT	TT	AA	A	T
T2DM	98	47 (47.96)	47(47.96)	4(4.08)	58 (29.00)	142(71.00)
NC	99	46 (46.46)	48(48.48)	5(5.05)	59 (29.80)	139 (70.20)
<i>P</i>		>0.05			>0.05	

Quantification of the bacterial species of interest among T2DM group and NC groups in the fecal microbiota by qPCR

To quantify the bacterial species of interest in all subjects, qPCR was used to analyze the original DNA samples using bacterial species-specific primers. The qPCR data were expressed as log¹⁰ copies per mg total microbial DNA as showed in Figure 1. The

abundance of *Lactobacillus* genus and *Clostridium* genus was lower in newly diagnosed T2DM group than in the NC group ($P < 0.05$). There was no significant difference in the abundance of *Bacteroides thetaiotaomicron* between two groups ($P > 0.05$).

Logistic regression

Variables with significant difference (BMI, SBP, DBP, LDL-C, LDL-C, TC, TG, Insulin, abundance of *Lactobacillus* genus, abundance of *Clostridium* genus and omentin-1) in the univariate analysis t-test, abundance of *Bacteroides thetaiotaomicron* and Omentin-1 gene genotype were included in the logistic regression model, and multivariate logistic regression analysis was performed using the stepwise advancement method. The results showed LDL-C (OR: 1.094 95% CI: 1.014~1.180), Insulin (OR: 3.868, 95% CI: 1.250 ~11.971), abundances of *Lactobacillus* genus (OR: 0.288, 95% CI: 0.145~0.571), abundances of *Clostridium* genus (OR: 0.044, 95%CI 0.012~0.154) was associated with newly diagnosed T2DM, and the difference was statistically significant ($P < 0.05$) (Table 3).

Table 3 Multivariate logistic regression analysis of T2DM influencing factors

Variable	β	Wald χ^2	P	OR	95%CI
LDL-C	1.353	5.506	0.019	3.868	1.250~11.971
Insulin	0.090	5.392	0.020	1.094	1.014~1.180
<i>Lactobacillus</i>	-1.244	12.703	0.01	0.288	0.145~0.571
<i>Clostridium</i>	-3.127	23.843	0.01	0.044	0.012~0.154

Discussion

Environment is dominant over the genome of impacting microbiome variability [19]. Depicting composition of gut microbiota in a population with varied ethnic origins but shared geography [19]. So we selected newly diagnosed T2DM without using antidiabetic drug and antibiotics. All Uyghur subjects are from Urumqi city that they have the same dietary habit.

Bioactive substances which produce from gut microbiota may have molecular crosstalk with host gene and cells and modulate metabolism. Microbiome associated disease with genetic components, for example colon cancer [20]. Mi Young Lim reported that the phylum *Actinobacteria*, to which *Bifidobacterium* belongs, had the highest heritability (45.7%) in metabolic syndrome, and reduced abundance of *Actinobacteria* and *Bifidobacterium* was significantly linked to the minor allele at the *APOA5* SNP rs651821. The study suggests that an altered gut microbiota composition mediated by a specific host genotype can contribute to the development of metabolic syndrome [21]. Bonder MJ had undergone the genome-wide analysis that for the association between common SNPs (minor allele frequency (MAF) > 0.05) and microbial taxonomy, and identified associations of 9 loci with microbial taxonomies and 33 Loci with microbial pathways [4]. Study in Iranian individuals reported the association of omentin rs2274907 gene polymorphisms with insulin resistance in with newly diagnosed type 2 diabetes [22]. But we didn't find the difference of omentin rs2274907 gene polymorphisms between Uyghur T2DM and healthy normal group. Our study revealed no association of Omentin-1 genetic variants with T2DM risk ($P > 0.05$). The result of our study suggests that gene polymorphism of omentin rs2274907 may have ethnic diversity.

Gut microbiota dysbiosis can contribute to the development of obesity and insulin resistance (IR), and dysregulation of the gut microbiota-miR-181 axis was required for the development of obesity, IR, and white adipose tissue inflammation in mice [13]. Omentin levels correlate inversely with markers of metabolic syndrome. Omentin expression varies throughout the body (heart, lungs, ovary and placenta) but its main tissue of production is now considered to be visceral adipose tissue [23]. Omentin 1 is an adipokine secreted by visceral adipose tissues and has been reported to have anti-inflammatory, cardioprotective, and enhances insulin sensitivity. Chandan K Jha et al, 2019 reported that in CAD Indian patients, there were lower omentin-1 levels in plasma and in pericardial adipose tissue compared to controls without CAD [24]. Moreover, it was suggested that reduced plasma omentin levels can be used as a biomarker for metabolic risk factors [25]. In our study, plasma omentin-1 levels were significantly decreased ($P < 0.001$) in Uyghur newly diagnosed T2DM group. Probiotic like *Bifidobacterium pseudocatenulatum* CECT 7765 could increase the omentin-1 level in children with obesity and insulin resistance [26]. We also did not discover the interaction between the omentin rs2274907 polymorphism and gut microbiota.

Microbiota plays causative roles for many diseases. *Clostridium* belongs to the *Firmicutes*, is a gram-positive large bacillus that can form spores and grow in an anaerobic environment. Most of them are saprophytic bacteria, with only a few pathogenic. The latest study reported that *Clostridium* abundance in the intestinal microbiota of Danish pre-diabetes is reduced and associated with low inflammation [27]. In order to rule out changes in dietary habits after diagnosis and the effect of hypoglycemic agents on intestinal

microbiota, the level of *Clostridium* was quantitatively analyzed by 16S rDNA gene qPCR in newly diagnosed T2DM in this study. It was found that the relative abundance of *Clostridium* in the T2DM group was significantly lower than that in the NC group, suggesting that *Clostridium* was changed in the intestinal microbiota of T2DM patients. In the clinical trial of Shimozato A et al., transglucosidase treatment use to improve the abundance of intestinal *Clostridium cluster IV* and *Clostridium subcluster XIVa* in order to alleviate intestinal peristalsis of T2DM [28]. It has also been reported that hypoglycemic drugs such as metformin regulate the balance of intestinal microbiota and achieve the purpose of treating diabetes [29]. It was discovered that the abundance of *Clostridium* in the intestine of diabetic rats was significantly reduced [10]. At the same time, Denmark's study of 134 pre-diabetes patients reported that the abundance of *Clostridium* was significantly reduced [27]. The results of this study are consistent with the above findings. The digestive system is an organ that communicates with the outside world. The gastrointestinal mucosa has the function of preventing foreign toxic substances and pathogenic microorganisms from invading the body. The damage of the intestinal barrier function leads to an increase in permeability and an increase in the level of inflammatory factors such as LPS in the blood circulation. Some studies have done HE staining on the ileal tissue of mice in the diabetic state, and observed severe destruction of the intestinal mucosa [30]. *Clostridium butyricum* can accelerate the growth of intestinal mucosal epithelial cells and promote intestinal peristalsis. Short-chain fatty acids such as butyric acid are produced by *Clostridium butyricum* that can play an important role in the occurrence and development of T2DM [31]. Another mechanism by which *Clostridium butyricum* regulates intestinal flora is its ability to produce antimicrobial substances such as antimicrobial peptides [32]. Therefore, the occurrence of T2DM may be related to the relative abundance of *Clostridium* and its protective effect on the intestinal mucosa.

Lactobacillus genus is Gram-positive bacteria and consumes glucose and produces lactic acid. *Lactobacillus* genus is often added to various foods as probiotics. Even though *Lactobacillus* is only a minor member of the human colonic microbiota, the proportions of those bacteria are frequently either positively or negatively correlated with T2DM [33]. Similarly, preliminary studies found increased levels of *Lactobacillus* in T2DM patients [34]. But consumption of yogurt and other dairy products fermented by *Lactobacillus* is also significantly associated with protection from T2DM [35]. In our study, we discovered decreased level of *Lactobacillus* genus in newly diagnosed T2DM. The genus *Lactobacillus* is a taxonomically complex and is composed of over 170 species that cannot be easily differentiated phenotypically. These results suggest that the research on the relationship between the bacteria and T2DM should be carried out at the species level.

Conclusions

The abundance of *Lactobacillus* and *Clostridium* genus may be related to the pathogenesis of new-onset T2DM in Uyghur population, the mechanism of which needs to be further studied. Gut microbiota biomarkers for metabolic disease also showed significant variations among location. Our study was taken in Chinese Uyghur population. The result provides a research basis for further analysis of the correlation between gut microbiota and omentin in T2DM population. One caveat of this study is that the sample size was small. Therefore, it is important that future work includes replicating this study in a larger population, as well as performing functional studies to delineate the mechanisms governing these effects.

Abbreviations

T2DM: Type 2 diabetes mellitus; BMI: Body mass index; CI: Confidence interval; SBP: systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; 2hPG: 2 hour plasma glucose; IR: Insulin resistance; HOMA-IR: Homeostasis model assessment-Insulin resistance; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride; WHR: waist-to-hip ratio; ELISA: enzyme-linked immunosorbent assay; MAF: minor allele frequency; SNP: single nucleotide polymorphism; qPCR: Real-time Quantitative PCR Detecting System.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University. All participants gave written informed consent following a full description of the study.

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Authors' contributions

RN and YG designed and supervised this investigation. RN and JS performed this investigation. JS and RL contributed to the data collection. All authors read and approved the final manuscript. RN and YG contributed writing-review and editing.

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Availability of data and materials

The data used to support the findings of this study are available from the first author and the corresponding author upon request.

Consent for publication

All the subjects have signed informed consent and all the authors of the article have consented to publish the manuscript.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Supplementary Information

Additional file 1: Table S1 Primers of bacterial genus

Figures

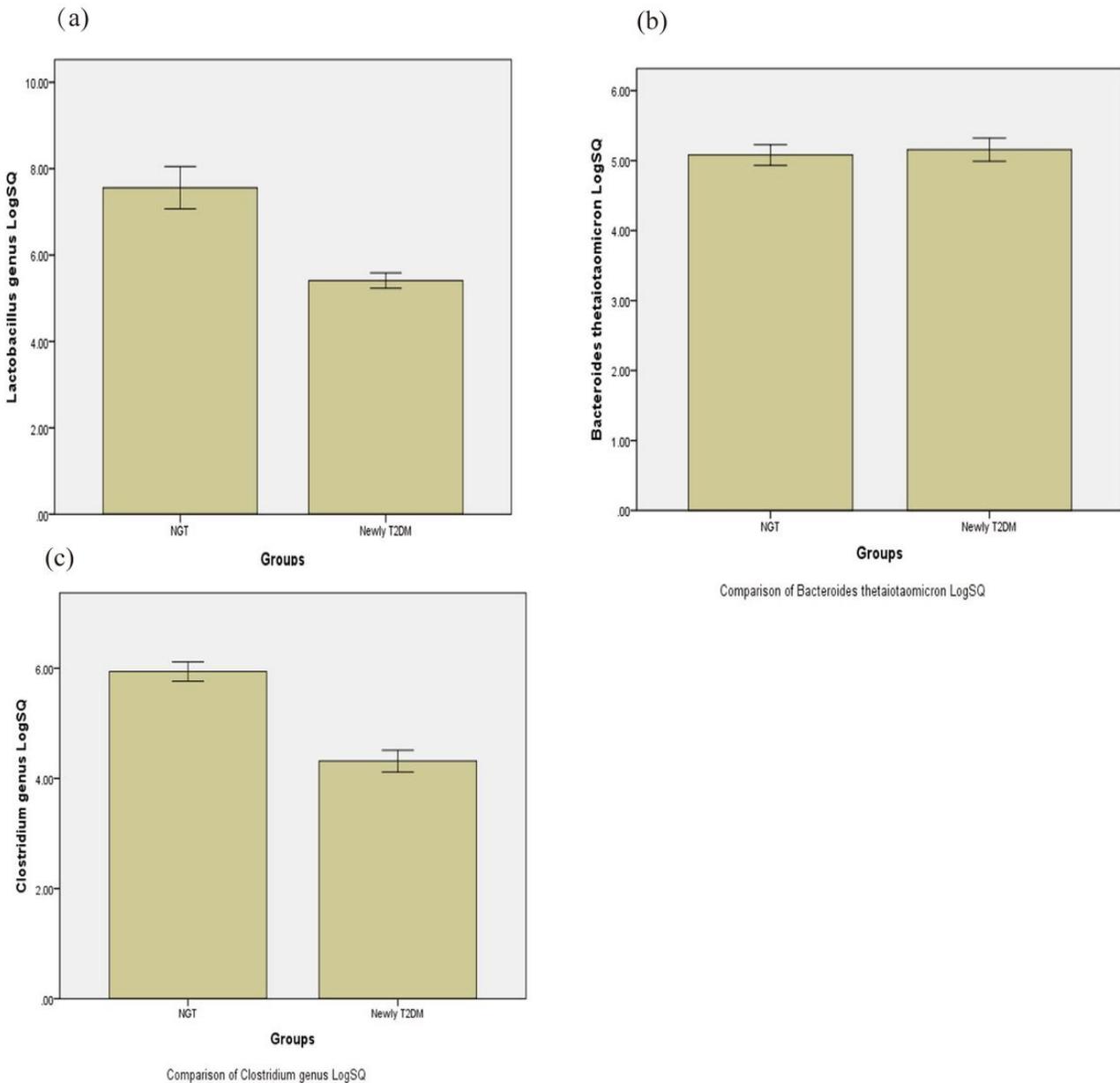


Figure 1

Bar chart of comparison of abundances bacterial genus between newly diagnosed T2DM and NC group. a: Comparison of abundances of Lactobacillus genus. b: Comparison of abundances of Bacteroides thetaiotaomicron. c: Comparison of abundances

of Clostridium genus.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarytable1.docx](#)