The Abundance of Bifidobacterium in relation to visceral obesity and Serum uric acid

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Article

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Abstract

Many studies have found that people with obesity have significant gut microbiota dysbiosis. Most of these studies on obesity were based on the BMI classification criteria, which doesn't distinguish Visceral adipose tissue (VAT) from subcutaneous adipose tissue (SAT). However, research showed that VAT has a higher risk of inducing metabolic diseases than SAT. This study focused on the visceral obesity defined by increased visceral fat area. It assessed the association of visceral obesity with gut predominant microbiota and metabolic status.

This study included 388 individuals from medical examination center in our hospital. Quantitative polymerase chain reaction (q-PCR) technique was used to detect ten kinds of gut predominant bacteria in fresh feces. visceral fat area (VFA)was measured by bioelectrical impedance analysis. According to the VFA results, the individuals were divided into two groups: Visceral obesity group (VFA $\geq$ 100cm^2) and lean control group (VFA < 100cm^2). The results showed that the abundance of Bifidobacterium significantly decreased in the Visceral obesity group and combined with metabolic indicators such as Serum uric acid, triglycerides, low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C) and fasting blood sugar (FBS), serum uric acid was an independent influencing factor for bifidobacterial. serum uric acid was negatively correlated with Bifidobacterium. serum uric acid was positively correlated with visceral fat area. The results suggested that serum uric acid was probably a mediator to the link between decreased Bifidobacterium and increased visceral adipose tissue.

Introduction

Obesity is a problem that seriously affects human health in the world. Obesity increases the risk of hypertension□diabetes, and cardiovascular disease[1].BMI is the main criteria for obesity currently. It reflects the characteristics of body weight and total fat mass, but it cannot reflect distribution characteristics of adipose tissue. Body adipose tissue is divided into subcutaneous adipose tissue (SAT) and Visceral adipose tissue (VAT). VAT refers to the fat surrounding the heart, liver, stomach and other organs. Several researches have confirmed that the relationship between obesity and cardiovascular diseases, metabolic diseases depended on the distribution of adipose tissue rather than its total amount[2,3]. Visceral adipose tissue has been shown to have higher inflammatory activity than subcutaneous adipose tissue[4]. Accumulation of visceral white adipose tissue is closely associated with the progression of insulin resistance, However, subcutaneous white adipose tissue has no adverse effects on metabolic health [5,6].

Gut microbiome is a very important ecosystem in the human body. Most studies show there are significant gut microbiota abnormalities in obese individuals[7]. Compared with lean people, the abundance of Firmicutes was increased and the abundance of Bacteroidetes was decreased in the obesity people[8]. At the genus and species level, obesity individuals had higher count of Fusobacterium[9],

Enterococcus[10], Prevotella[11], and lower counts of Faecalibacterium[9], Bifidobacterial than lean people[12,13]. Different Lactobacillus species are associated both with a lean and an obese status[14].

At present, most studies on obesity and gut microbiota are based on BMI classification. there are relatively few studies on visceral obesity and gut microbiota. Studying the link between visceral obesity and gut microbiota will help us to remove the influence of subcutaneous fat. We can specifically understand the mechanism by which obesity increases the risk of metabolic disease.

Based on the results of previous studies[9–13], we used quantitative polymerase chain reaction (q-PCR) to detect ten kinds of predominant gut microbiota, including probiotics: Lactobacillus, Bifidobacterium; Butyric acid producing bacteria: Faecalibacterium prausnitzii, Clostridium butyricum, Clostridium leptum, Eubacterium rectale; opportunistic pathogenic bacteria: Enterococcus, Enterobacteriaceae, Atopobium cluster;and Bacteroides. We used bioelectrical impedance analysis to measure visceral fat area, Investigate the link between these ten gut dominant microbiota and visceral fat obesity, identify meaningful gut bacteria, then study their relationship with metabolic markers: Serum uric acid, triglycerides, low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C) and fasting blood sugar (FBS). To explore the relationship between gut microbiota, serum metabolic markers, and visceral adipose tissue.

Materials And Methods

Study design

In this study, A total of 388 individuals were all from the health checkup people in the medical examination center department of our hospital. We used q-PCR to detect the ten predominant gut microbes in their fresh stool. We used Body Composition Tester (INBODY720, Korea) to measure the visceral fat area (VFA). According to the VFA measurement results, all the individuals were divided into two groups: Visceral obesity group (VFA $\geq$ 100cm^2) and lean control group (VFA < 100cm^2)[15,16]. The two groups were matched for gender and age. All the clinical metabolic data were collected from physical examination results. They are listed in Table 1.

Inclusion criteria for all the people were: (1) No antibiotics and probiotics were used within 1 month before enrollment. (2) No acute disease or serious chronic disease in the past 3 months. Exclusion criteria: (1) Secondary obesity: hypothalamus, pituitary disease, hypothyroidism, etc. (2) having severe heart, brain, liver and kidney disease, combined with tumors, immune or blood system diseases (3) Pregnancy or lactation women. The study was approved by the ethics committee of the Shulan (Hangzhou) Hospital and informed consent was obtained from all participants. All research was performed in accordance with relevant guidelines/regulations and the study was conducted in accordance with the Declaration of Helsinki.

Table 1
Personal and laboratory results in visceral obesity and lean group

Variable	Visceral obesity(n = 104)	lean group(n = 268)	P
Sex(male, proportion)	67 (64.4%)	167 (62.3%)	0.705
age(year)	51.22±10.60	49.39±9.93	0.119
FBG (mmol/L)	5.34±0.95	4.93±0.89	0.000***
HDL-C(mmol/L)	1.16±0.31	1.27±0.35	0.005**
LDL-C(mmol/L)	3.01±0.86	2.85±0.72	0.007**
TG (mmol/L)	2.39±1.74	1.81±1.36	0.003**
SUA (μmol/L)	364.43±103.25	331.99±89.79	0.003**

*:P < 0.05,**:P < 0.01,***:P < 0.001 FBG: fasting blood glucose, HDL-C: high density lipoprotein, LDL: Low-density lipoprotein, TG: Triglycerides, SUA: Serum uric acid

Use Q-pcr To Detect Predominant Gut Microbiota

The information of PCR primers was shown in Table 2. All oligonucleotide primers were synthesized by Gen Script (China). The ABI7500 real-time fluorescent PCR system (Applied Biosystems, USA) was used for the q-PCR amplification reaction. The amplification reaction contained 10uL of SYBRTM q-PCR master mix (Tong Chuang, China), 8μL primers (0.2–0.6μM),2μL template DNA, or 2μL water (negative control), for a final volume of 20μL. Each reaction was performed in triplicate, and the cycling threshold (ΔCt) < 0.5 between repetitions was required. Amplification was performed with the following temperature profiles: one cycle at pre-denaturation at 95 ℃ for 3 min, denaturation at 95 ℃ for 15 s, annealing and extension at 60 ℃ for 30 s, collection of fluorescence signals, a total of 40 cycles. The annealing and plate-reading temperatures for each primer pair are shown in Table 2. The copy number of ribosomal DNA (rDNA) operons of targeted bacteria in crude DNA templates was determined by comparison with serially diluted plasmid DNA standards run on the same plate. Plasmid DNA standards were made from known concentrations of plasmid DNA that contained the respective amplicon for each set of primers. Bacterial count results were normalized to fecal bacteria count per gram(copies/g).

Table 2
Primers used in this study

Target group	Sequence (5'→3')	Annealing temperature(°C)
Lactobacillus	F: GAGGCAGCAGTAGGGAATCTTC	60.48
	R:GGCCAGTTACTACCTCTATCCTTCTTC	62.09
Bifidobacterium	F: CTCCTGGAAACGGGTGG	56.76
	R:GGTGTTCTTCCCGATATCTACA	57.07
F. prausnitzii	F: GGAGGAAGAAGGTCTTCGG	57.89
	R:AATTCCGCCTACCTCTGCACT	61.52
C. butyricum	F: ATGCAAGTCGAGCGAKG	60.00
	R:TATGCGGTATTAATCTYCCTTT	60.00
C. leptum	F: GCACAAGCAGTGGAGT	53.81
	R:CTTCCTCCGTTTTGTCAA	52.40
E. rectale	F: CGGTACCTGACTAAGAAGC	54.75
	R:AGTTTCATTCTTGCGAACG	54.38
Bacteroides	F: GAGAGGAAGGTCCCCCAC	66.67
	R:CGCTACTTGGCTGGTTCAG	57.89
Enterococcus	F: CGTGCGAACATGACCGATAT	58.51
	R:CGAAACGGCCATTAACCAAC	58.03
Enterobacteriaceae	F: GGTAGAGCACTGTTTTGGCA	58.40
	R:TGTCTCCCGTGATAACTTTCTC	57.55
Atopobium	F: GGGTTGAGAGACCGACC	56.11
	R:CGGRGCTTCTTCTGCAGG	57.80

Statistical analysis

SPSS software version 23.0 was used for statistical analysis. Normally distributed data were expressed as means and standard deviations. The t-test was used for comparison between groups, and the chi-square test was used for comparison of rates between groups. non-normally distributed data were presented as median and interquartile range (IQR). Comparisons between groups were performed using the Mann-Whitney rank-sum test. Use Pearson correlation analysis to evaluate the correlation between gut microbiome and blood lipids, blood sugar and serum uric acid. Multiple linear regression was used to

analyze the influencing factors of gut microbiome and blood lipids, blood glucose and uric acid after adjusting for confounding factors. $P < 0.05$ was considered statistically significant.

Results

Demographic and clinical metabolic characteristics

A total of 388 individuals were divided into two groups according to visceral fat area measurements results: Visceral obesity group (VFA $\geq$ 100cm^2), Containing 104 people, 67 of them are male; lean control group (VFA < 100cm^2), Containing 268 people, 167 of them are male. There was no significant difference in gender and age between the two groups ($P > 0.05$). Visceral obesity group had significantly higher levels of Serum uric acid, triglycerides, low-density lipoprotein, fasting blood sugar and lower high-density lipoprotein ($P < 0.05$). (Table 1)

Changes In The Composition Of The Gut Microbiome

Among the 10 gut bacteria, Bacteroides has the highest counts, and Enterococcus has the lowest counts in both two groups. Except that the count of Eubacterium rectale and Clostridium butyricum in visceral obesity group was higher than lean group. The other eight bacteria in visceral obesity group were all lower than lean group. (Fig. 1). The count of Bifidobacterium in the visceral obesity was significantly decreased, with a median of $6.08*10^4$ copies/g, the median of Bifidobacterium in lean group was $2.30*10^5$ copies/g. The difference between the two groups was statistically significant ($P < 0.05$). (Fig. 2). Meanwhile, Bifidobacterium was negatively correlated with visceral fat area($R=-0.144, P < 0.01$).

Correlation Analysis Between Bifidobacterium, Laboratory Metabolic Indicators And Visceral Fat Area

Pearson correlation analysis was performed to analyze the correlation between Bifidobacterium and laboratory metabolic indicators: Serum uric acid, TG, LDL-C, HDL-C and FBS. Bifidobacterium was negatively correlated with serum uric acid ($R=-0.176$ $P < 0.01$). (Fig. 3a). Bifidobacterium was positively correlated with HDL ($R = 0.123$, $P < 0.05$). Adjusting the age factor, incorporate serum uric acid and HDL into the multiple linear regression model, the result showed that serum uric acid was an independent influencing factor for Bifidobacterial ($\beta=-0.151, P = 0.004$)(Table 3). Pearson correlation analysis showed that serum uric acid was positively correlated with visceral fat area($R = 0.195$, $P = 0.000$. (Fig. 3b)

Table 3
Pearson correlation and multiple linear regression

variables	correlation analysis		Linear Regression Analysis	
	R	P	β	P
SUA(μmol/L)	-0.176	0.000**	-0.151	0.004**
HDL-C(mmol/L)	0.123	0.015*	0.095	0.074

*:P < 0.05,**:P < 0.01,***:P < 0.001

SUA: serum uric acid. HDL-C: high density lipoprotein.

Discussion

This study showed that the people with visceral obesity had lower level of Bifidobacterium, and there was a negative correlation between Bifidobacterium and visceral fat area. Serum uric acid was an independent influencing factor for Bifidobacterial. Serum uric acid was negatively correlated with Bifidobacterium and serum uric acid was positively correlated with visceral fat area.

Most studies have showed that there was gut microbiota dysbiosis in obese individuals. Special gut microbiome leaded to fat deposits. Transplant gut microbiota from mice with diet induced obesity to lean germ-free mice, The germ-free mice developed more fat deposits[17]. The vast majority of gut microbiota belong to four main families (phyla): Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria[18]. At the genus and species level, obesity individuals had higher count of Fusobacterium、Enterococcus, Prevotella, and lower counts of Faecalibacterium, Bifidobacterial than lean people[9–13]. In this study, the counts of Faecalibacterium prausnitzii were also decreased in visceral obesity, but the difference was not significant. The counts of Bifidobacterium significantly decreased in visceral obesity, that was the same as previous studies based on BMI criteria for obesity[12,13]. This result emphasized the role of Bifidobacterium as probiotics in obesity.

The gut microbiota is an important micro-ecosystem. Gut microbes contribute to the pathogenesis of obesity by fermenting indigestible dietary polysaccharides, producing short-chain fatty acids, and regulating energy homeostasis[19]. Supplementation of Bifidobacterium breve to high-fat diet-induced obese mice, significantly dose-dependently suppressed the accumulation of body weight and epididymal fat, and improved the serum levels of total cholesterol, fasting glucose and insulin[20]. Epididymal fat in this study was visceral fat. This study did not detect serum uric acid level. In another study, Supplementation of probiotic yogurt with Bifidobacterium lactis Bb12 decreased the level of serum uric acid[21]. In our study, we found that serum uric acid was an independent influencing factor for Bifidobacterium, Combining the factors of TG、LDL-C、HDL-C,FBG and age. Serum uric acid was negatively correlated with Bifidobacterium. Meanwhile, serum uric acid was positively correlated with visceral fat

area. So serum uric acid is probably to be the mediator of the link between decreased Bifidobacterium and increased visceral adipose tissue.

Serum uric acid is a product of purine nucleotide metabolism, mainly derived from exogenous diet and endogenous nucleic acids. A certain level of serum uric acid is considered to be a beneficial antioxidant, but excess uric acid is associated with various diseases, such as hypertension[22], diabetes[23], cardiovascular disease[24]. Multiple epidemiological studies have shown a positive correlation between visceral fat and serum uric acid levels[25,26]. High levels of serum uric acid can increase insulin secretion, thereby promote fat synthesis[27]. Uric acid can also directly promote fat synthesis in hepatocytes via ER stress-induced activation of SREBP-1c[28]. This suggests that controlling serum uric acid levels may reduce the accumulation of visceral fat.

except for exogenous diet, the gut microbiota also plays an important role in serum uric acid levels. About one-third of uric acid is excreted through the gut[29]. The gut microbiota has gradually become a new target to study the pathogenesis of hyperuricemia. Transplant fecal microbiota of diet induced hyperuricemia rats into recipient rats, Serum uric acid levels were significantly increased in recipient rats[30]. The abundance of gut Faecalibacterium prausnitzii, Clostridium butyrate-producing bacterium, Bifidobacterium decreased in the gout people[31]. As a member of probiotics, Lactobacillus can reduce serum uric acid levels by synthesizing uric acid degrading enzymes[32].The mechanism of Bifidobacterium lowering serum uric acid remains unclear. Several studies have found that Bifidobacterium can reduce endotoxin levels, reduce intestinal mucosal permeability, and have a protective effect on the intestinal mucosal barrier[33,34].Normal intestinal mucosal barrier helps to prevent the translocation of intestinal bacteria or bacterial lipopolysaccharide(LPS) into the blood. Elevated LPS levels in the blood increased the risk of hyperuricemia[35].

Currently the main and widely used medications for lowering serum uric acid are xanthine oxidase inhibitors such as allopurinol. Some people cannot tolerate these medications because of its side effects. Bifidobacterium is a kind of probiotic that has been widely used. Its clinical safety has been proven, almost no side effects. In addition to direct supplementation with Bifidobacterium, supplementation with specific prebiotics, such as chicory, could also help to reduce serum uric acid levels[36]. Our study found that serum uric acid was probably a mediator to the link between decreased Bifidobacterium and increased visceral adipose tissue. By lowering serum uric acid levels, we can lower the accumulation of visceral adipose tissue, further reduce the risk of metabolic diseases caused by visceral obesity.

Our study also has some insufficiency. First, we only detected ten gut bacteria. There is an interaction between the vast gut microbiota. It's easy to miss other meaningful gut microbiota. We need to further use 16S rRNA gene amplicon sequencing to detect gut microbiota in people with visceral obesity. Assess the species composition of the gut microbiota and its relative abundance information in visceral obesity. Then use q-PCR to analyze the role of specific gut bacteria. Second, We just found a correlation between

Bifidobacterium, serum uric acid, and visceral adiposity. The specific cause and effect relationship need more research to confirm.

Conclusions

This is a new perspective to study obesity and gut microbiota. Studying visceral obesity independently is beneficial to precisely prevent obesity-induced metabolic disease risk. The counts of Bifidobacterium significantly decreased in visceral obesity. Serum uric acid was an independent influencing factor for Bifidobacterial. Serum uric acid was negatively correlated with Bifidobacterium and serum uric acid was positively correlated with visceral fat area. Serum uric acid was probably a mediator to the link between Bifidobacterium and visceral obesity.

Declarations

Author Contributions

Hualan Gong and Hainv Gao contributed to conception and design of the study. Hualan Gong, Qingye Ren and Jia He contributed to the acquisition and analysis of the data. Hualan Gong drafted the manuscript and prepared the tables 1-2, figures 1-3. All authors contributed to manuscript revision, read, and approved the submitted version.

Availability of Data and Materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Figures

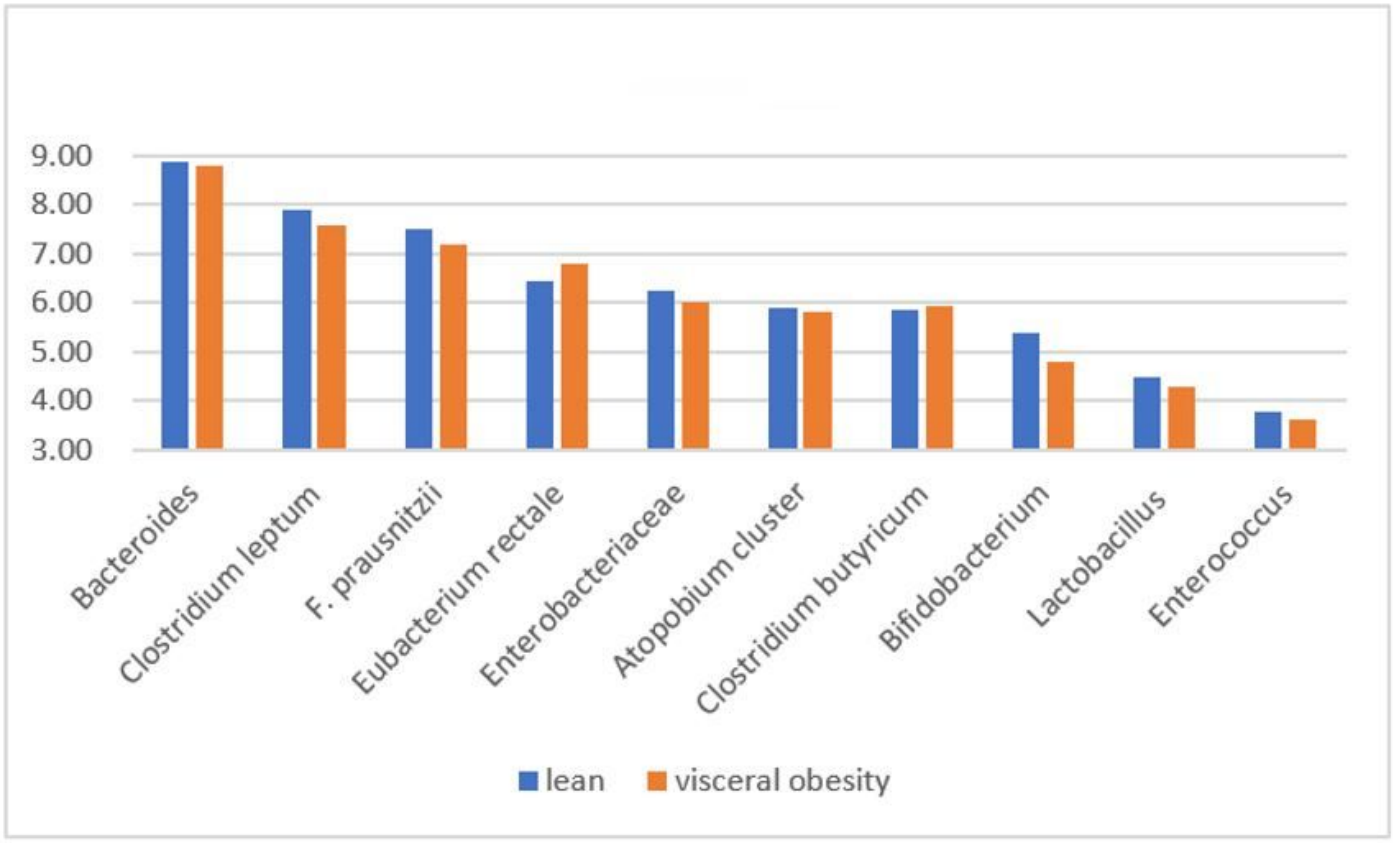

Figure 1

Counts of ten bacteria in visceral obesity and lean groups. Common logarithm (lg) is used to convert bacterial counts.

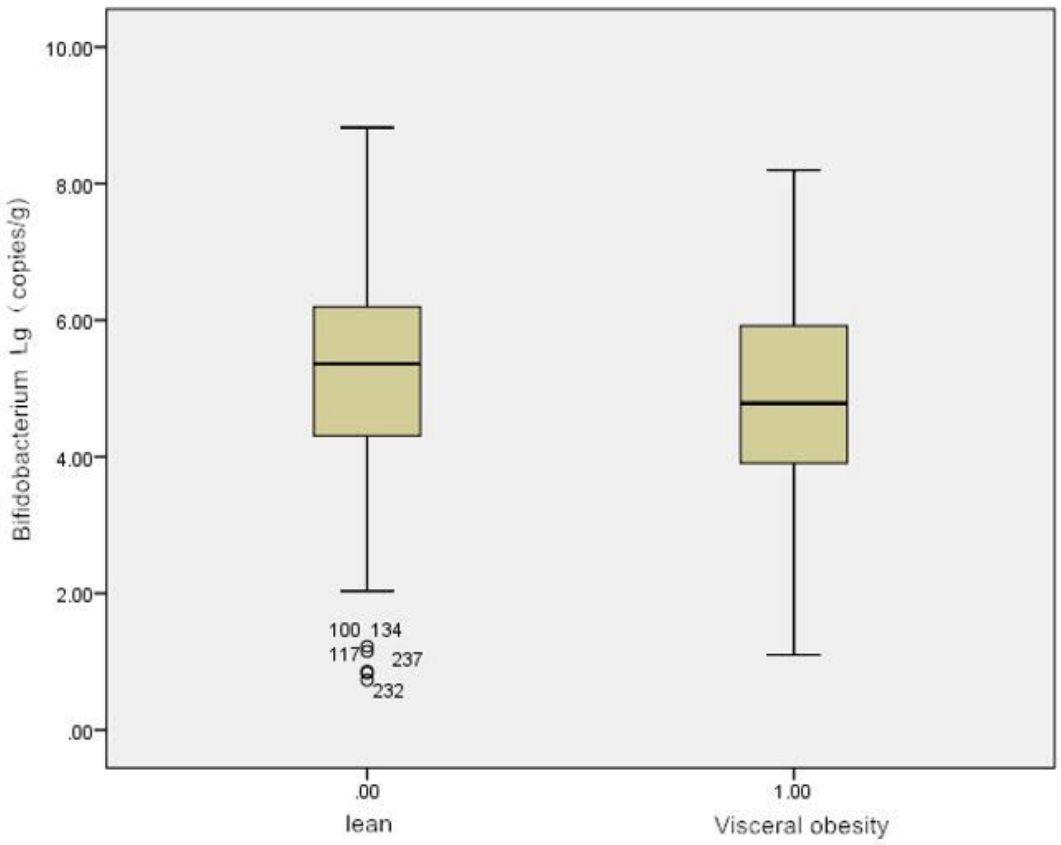

Figure 2

Counts of Bifidobacterium in visceral obesity and lean groups . The median of visceral obesity was 6.08*104 copies/g, The median of lean group was $2.30*10^5$ copies/g. The difference was statistically significant (P <0.05).

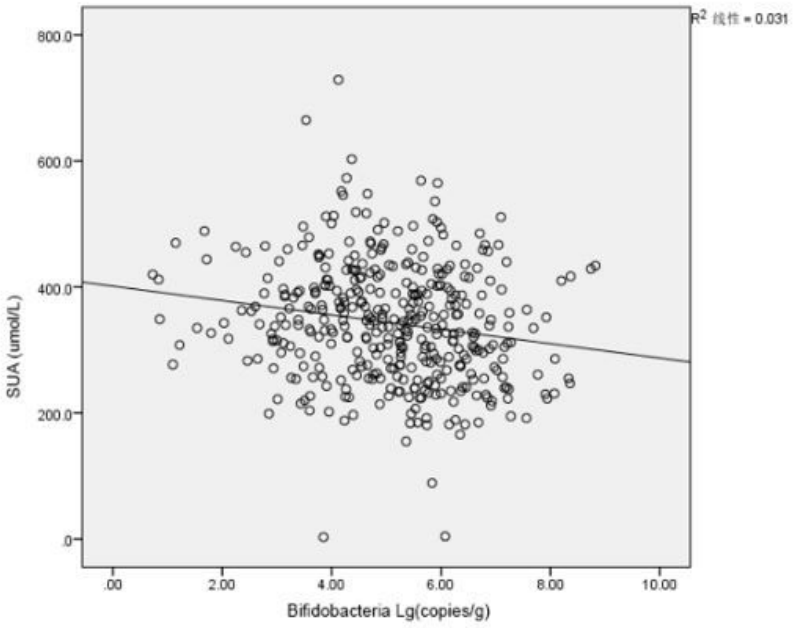

Fig. 3a

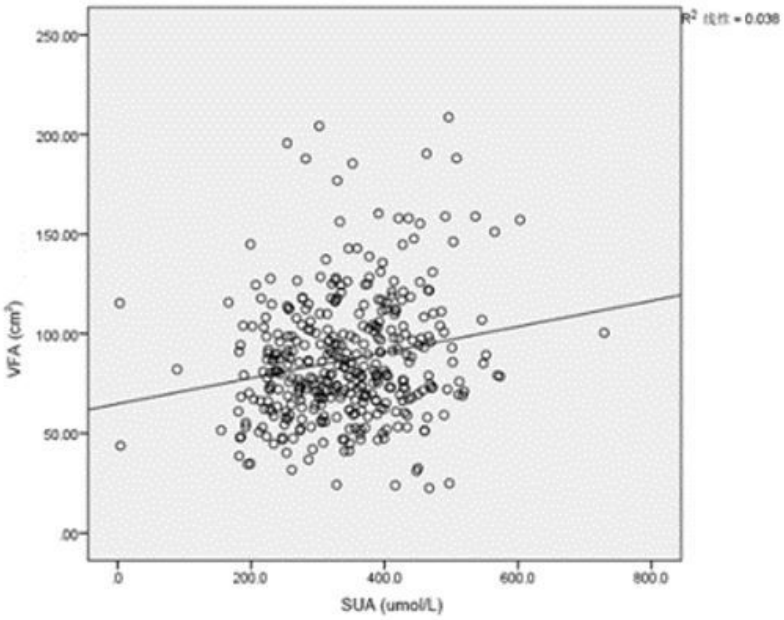

Fig. 3b

Figure 3

3a Correlation between Bifidobacterium and SUA. SUA: serum uric acid

3b Correlation between SUA and VFA. SUA: serum uric acid. VFA: visceral fat area.