The expression of toll-like receptors in peripheral blood mononuclear cells is altered in schizophrenia

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ABSTRACT

Increasing evidence suggests that in addition to neurochemical abnormalities, various immunological alterations are related to the pathogenesis of schizophrenia. Toll-like receptors (TLRs) actively mediate immune/inflammatory processes and play a pivotal role in damage/danger recognizing. Therefore, the aim of this study was to compare the expression of TLRs in peripheral blood mononuclear cells (PBMCs) in schizophrenic patients with those of healthy subjects. It also measures the metabolic status of the study subjects. Twenty-seven adult European Caucasian patients with paranoid schizophrenia and twenty-nine healthy volunteers were included in this prospective study. qRT-PCR assessed TLR mRNA expression levels. Body composition was measured using two methods: bioimpedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA). The TLR1, TLR2, TLR4, TLR6, and TLR9 expression were down-regulated, in opposite to TLR3 and TLR7 which manifested higher expression in patients with schizophrenia. TLR5 and TLR8 mRNAs did not differ between groups. TLR mRNA expression was highly correlated. Decreased TLR expression may protect against excessive cell stimulation *via* exogenous and/or endogenous ligands, and may be recognized as a counterbalancing mechanism limiting the excessive development of inflammation.

1. Introduction

Schizophrenia is a severe mental disorder characterized by positive, negative, cognitive, affective and behavioral symptoms. It is known to affect approximately 1% of the global population. Nowadays, increasing evidence suggests that, apart from neurochemical abnormalities (Plitman et al., 2014), various immunological alterations are related to the pathogenesis of schizophrenia. In particular, the inflammatory response and the dysregulation of innate immune mechanisms are believed to be involved in the pathomechanism of schizophrenia (Khandaker et al., 2015).

It has been demonstrated that patients with schizophrenia have elevated numbers of natural killer (NK) cells (Steiner et al., 2010, 2012). Moreover, complement system activity (Mayilyan et al., 2006) and C3 and C4 complement component plasma levels (Maes et al., 1997) are increased. However, Spivak et al. (1993) reported decreased complement activity in schizophrenia patients. There are also observations that some pro-inflammatory molecules are elevated in patients with schizophrenia: for example, C-reactive protein level (CRP) is

significantly higher in individuals with schizophrenia compared with healthy subjects (Frydecka et al., 2015; Joseph et al., 2015). It has also been reported that serum levels of selected pro-inflammatory cytokines, including IL-1β, IL-6, tumor necrosis factor (TNF) and interferon (IFN)-γ, and the chemokines CCL2, CCL4, CXCL8 and CXCL10 are elevated in the course of schizophrenia (Al-Hakeim et al., 2015; Beumer et al., 2012; Frydecka et al., 2015; Gariup et al., 2015; Kim et al., 2004; Zhang et al., 2016). In addition, the levels of anti-inflammatory cytokine IL-10 (Xiu et al., 2014) and IL-1 receptor antagonist (IL-1RA - the natural inhibitor of the pro-inflammatory effect of IL-1β) (Maes et al., 2000; Sirota et al., 2005) have been found to be reduced in schizophrenia patients.

Toll-like receptors (TLRs) are a family of cellular receptors that play a vital role in the initiation of innate immunity and inflammatory mechanisms. In human, the group comprise ten members (TLR1-10), expressed by various subsets of immune and non-immune cell types, including monocytes, macrophages, dendritic cells, neutrophils, B and T cells, mast cells, cardiomyocytes, fibroblasts, endothelial and epithelial cells (Vidya et al., 2018). Notably, TLRs are also expressed in

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certain cell types in the central nervous system (CNS), such as microglia, astrocytes, and neurons (Olson and Miller, 2004; Bowman et al., 2003; Tang et al., 2007). TLRs identify a wide range of molecules connected with pathogens (pathogen-associated molecular patterns, or PAMPs), such as bacterial lipopolysaccharides (LPSs), endotoxins, flagellin, lipoteichoic acids (LTAs), peptidoglycan (PGN), viral nucleic acids, zymosan and other (Paredes-Juarez et al., 2013). Significantly, TLRs also recognize different host-derived biomolecules that are generated following tissue injury or are released from stressed or dying cells, i.e., damage- (or danger-) associated molecular patterns (DAMPs). These molecules include heat shock proteins (HSPs), high mobility group box one protein (HMGB1), human cardiac myosin, S100 proteins, hyaluronan fragments, β-defensins, and mammalian genomic DNA (Franklin et al., 2017).

Given the fact that TLRs actively mediate immune/inflammatory processes and play a pivotal role in the recognition of damage or danger, the expression of these molecules in the course of mental disorders clearly merits further research. With this in mind, the present study investigates the expression of TLRs in peripheral blood mononuclear cells (PBMCs) in schizophrenic patients compared to healthy subjects. As TLRs appear to contribute to the chronic inflammatory state of obesity and metabolic syndrome (Jialal et al., 2014), which are frequently found in the course of schizophrenia treatment, the study subjects were matched for metabolic parameters (including anthropometric, laboratory and body composition).

2. Materials and methods

2.1. Subjects

Twenty-seven (27) adult (age 18–60 years) European Caucasian patients with paranoid schizophrenia (F20.0 according to ICD-10) were included into this prospective study. Patients were recruited from psychiatric outpatient clinics. All patients underwent a structured interview according to ICD-10 and DSM-IV criteria of schizophrenia. Twenty-nine (29) healthy volunteers were also randomly selected as a control group. The healthy volunteers were interviewed with the use of a standard, semi-structured medical form routinely used in our hospital. Any participant with self-reported personal or familial psychiatric history, or any previous psychiatric treatment, was excluded from the study. All study subjects were physically, neurologically and endocrinologically healthy with normal laboratory test results, including complete blood count, white blood cell (WBC) count, C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, urea, creatinine, and electrolytes. The exclusion criteria for both participants with schizophrenia and healthy controls were as follows: current active systemic infection with fever (temperature > 38 °C), long-term untreated chronic infections, acute and chronic inflammatory conditions (e.g., rheumatoid arthritis), immunological disorders (e.g., allergy, asthma, AIDS), pregnancy, and other conditions whose pathology and treatments (e.g., corticoid or immune suppressive treatments) may alter their immune status. All participants enrolled in the study had been informed about the aims and methods of the study and had expressed their written informed consent for participation in the study. The study protocol was approved by the Bioethics Commission of the Medical University of Lodz (RNN/122/16/KE). the investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

2.2. Clinical assessments

The clinical symptoms of schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS) and its sub-scores (positive, negative and general symptoms), while the severity of depressive symptoms was measured using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990). All assessments for all scales were performed by one trained rater for each patient.

2.3. Blood collection and isolation of PBMCs

Blood samples were collected between 8 am and 9 am, after at least an eight-hour overnight fast. Serum glucose and lipid levels were measured using a Dirui CS-400 analyzer (Dirui, China). CRP serum levels were determined in fresh blood using the latex-enhanced immunoturbidimetry method. PBMCs were isolated from whole blood by density gradient centrifugation using Histopaque-1077 (Sigma-Aldrich, Germany). After centrifugation at 400 g for 30 min at room temperature, the buffy coat was aspirated, transferred into a clean conical centrifuge tube, and washed three times in 1x phosphate buffered saline (PBS) (Sigma-Aldrich). The number of PBMCs was counted using a Bürker chamber.

2.4. Quantitative RT-PCR (qRT-PCR)

Total RNA was isolated from 5×10^6 PBMCs using TRI Reagent® (Sigma-Aldrich). The RNA concentration ($A$260) and the purity ($A$260/$A$280) were measured using a NanoDrop 2000 spectrophotometer (Thermo Scientific, USA). RNA samples were immediately frozen at −80 °C and stored until laboratory analysis. cDNA synthesis was performed using a High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, USA), according to the manufacturer's protocol. The primers were created in Primer3 and then confirmed by BLAST. The sequences of the used primers are given in Table 1. qRT-PCR was performed in duplicates using an Eco Real-Time PCR System (Illumina,

Table 1
Sequences of the primers used in this study.

Gene	Locus	Forward primer	Reverse primer
TLR1	NM003263	GGGTCAGCTGGACTTCAGAG	AAAATCCAAATGCAGGAACG
TLR2	NM003264	CATCGAAAAGAGCCACAAAACTG	GGTAGGTCTTGGTGTTCATTATCTTG
TLR3	NM003265	AGCCTTCAACGACTGATGCT	TTTCCAGAGCCGTGCTAAGT
TLR4	NM003266	GCATCATCTTCATTGTCCTTGAGA	CTCCCACTCGAGGTAGGTGTTT
TLR5	NM003268	GGAACCAGCTCCTAGCTCCT	AAGAGGGAAACCCCAGAGAA
TLR6	NM006068	CCCTTTAGGATAGCCACTGC	CTCACAATAGGATGGCAGGA
TLR7	NM016562	CCTTGAGGCCAACAACATCT	GTAGGGACGGCTGTGACATT
TLR8	NM016610	AACATCAGCAAGACCCAT	GACTCCTTCATTCTCCCT
TLR9	NM107442	CCCGCTACTGGTGCTATCC	CCTTCCTCTTTCCACTCCC
ACTB		CTGGGACGACATGGAGAAAA	AAGGAAGGCTGGAAGAGTGC

USA). 0.2 nM of forward and reverse primers, cDNA template, and TaqMan® Fast Universal PCR Master Mix (Applied Biosystems) were mixed to a final volume of 10 μL. All reactions were performed at 96 °C for 2 min, followed by 40 cycles of 96 °C for 5 s and 60 °C for 30 s. The expression of receptor mRNAs was corrected by normalization based on the transcript level of the housekeeping gene *ACTB*.

2.5. Anthropometry

Height was measured with a wall-mounted height measure to the nearest 0.5 cm. Weight was measured with a spring balance that was kept on a firm horizontal surface. Subjects wore light clothing, stood upright without shoes and weight was recorded to the nearest 0.5 kg. Body mass index (BMI) was calculated as body weight [kg]/height [m]^2. Waist and hip circumference was measured using a non-stretchable fiber measuring tape. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference.

2.6. Body composition

Body composition was measured using two methods: bioimpedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA). For BIA Maltron BIOSCAN 920-2-S Body Fat Analyzer (Maltron, UK), multifrequency (5 kHz, 50 kHz, 100 kHz, 200 kHz) bioelectrical impedance analyzer was used. DXA was performed using a Lunar iDXA scanner (GE Healthcare, UK) with version 15 of the CoreScan software. Standard operating conditions (including preparation of the participants, electrodes placement, and measurement procedures) were monitored by a trained operator. The DXA and BIA measurements was performed immediately before anthropometry measurements with participants lying supine and resting. Briefly, BIA determines the electrical impedance, or opposition to the flow of an electric current through body tissues which can then be used to calculate an estimate of total body water, which can be used to estimate fat-free body mass, and by calculating the difference from total body weight, thus determine body fat content. In DXA, two X-ray beams, with different energy levels, were aimed at the patient's body and different tissue types (bone, muscle, fat) can be determined from the absorption of each beam by tissues. The following body composition parameters were measured using the DXA method: total body fat (TBF), lean body mass (LBM), visceral adipose tissue (VAT) mass, VAT volume. TBF and LBM are expressed both in kilograms and as a percentage of total body mass. Subcutaneous adipose tissue (SAT) and VAT areas were measured at the level of the umbilicus, using data input from Maltron BIA analyzer, with a special electrode placement, and Maltron software, which converts raw data (impedance and phase angle). Fat mass index (FMI) was calculated as total body fat in kilogram (measured using DXA method) divided by the height in meter squared (kg/m^2).

2.7. Statistical analysis

Statistical procedures were performed with STATA 15.1 (StataCorp, USA). Simple descriptive statistics (means and standard deviations or standard mean error) were generated for all continuous variables. For discrete variables, the number of patients and percentages are given. The normality of distribution was tested with the Shapiro-Wilk test. TLR mRNA expression values were highly skewed and were transformed for normal distribution; for each TLR mRNA expression, the method of transformation was chosen empirically for best normality. Correlations were tested using the Pearson coefficient. Analysis of covariance was performed to examine the effect of clinical,

anthropometric parameters and body composition on TLR mRNA expression. The level of significance was set at $p < 0.05$ (two-sided).

3. Results

3.1. Baseline characteristics

Demographic and cardio-metabolic parameters of the study subjects are detailed in Table 2. Both study groups were highly comparable regarding demographic, clinical, laboratory, anthropometric and metabolic parameters.

3.2. Clinical data

All patients in the schizophrenic group were chronically ill (duration of treatment: 16.1 ± 10.8 years, number of hospitalizations: 10.3 ± 11.9, number of acute psychotic episodes: 6.1 ± 4.2, time from the last hospitalization: 4.0 ± 7.1 months). Treatment in the schizophrenia group was heterogeneous and included both first- (used by 9, 33.3% of patients) and second-generation (used by 27, 100% of patients) antipsychotics, with the majority (20, 74.1% of patients) being on antipsychotic polytherapy. Antipsychotics were administered in standard or above-standard doses, with the mean sum of DDDs (defined daily doses) for individual antipsychotics being 2.5 ± 1.3, which is an equivalent of 756.8 ± 381.9 mg/day of chlorpromazine. Six (22.2%) patients were also taking antidepressants, while 13 (48.1%) were taking mood stabilizers. A detailed description of the pharmacological treatment received by all study patients is presented in Appendix 2. Clinically, all study patients demonstrated medium severity of schizophrenia symptoms (total PANSS score 65.4 ± 14.6, P sub-score 15.3 ± 5.1, N sub-score 18.0 ± 4.5, G sub-score 32.1 ± 7.3) and low severity of depressive symptoms (CDSS score 1.9 ± 1.9).

3.3. Expression of TLR mRNAs

The TLR1-9 were detectable and quantifiable by qRT-PCR in PBMCs of all subjects. The highest mRNA copy numbers were observed for TLR5 and the lowest for TLR7 (Table 3). Five of the nine tested genes demonstrated alterations in mRNA expression between schizophrenic patients and control group (Fig. 1). TLR1, TLR2, TLR4, TLR6 and TLR9 expression was down-regulated in patients with schizophrenia, while TLR3 and TLR7 were upregulated. The most marked changes were detected for TLR4 and TLR2 with a 13.9 and 11.7-fold decrease in schizophrenic patients, respectively. In turn, TLR3 and TLR7 mRNAs tend to be higher in the schizophrenic group as compared to matched control. TLR5 and TLR8 mRNAs did not differ between groups (Table 3). TLR mRNA expression was highly correlated. Interestingly, there were more correlations in the control group, particularly for TLR1 and TLR2 (Appendix 1).

3.4. Associations between TLR mRNA expression and clinical features of schizophrenia

Symptoms of schizophrenia were moderately associated with elevated mRNA expression of individual TLR: TLR2 mRNA and total PANSS score ($R = -0.39$, $p = 0.04$) and N sub-score ($R = -0.40$, $p = 0.037$); TLR8 mRNA and total PANSS score ($R = 0.46$, $p = 0.015$) and PANSS G sub-score ($R = 0.44$, $p = 0.02$). There were no correlations with the severity of positive symptoms mRNA expression of TLR3 and TLR5 were positively correlated with the number of psychotic episodes ($R = 0.43$, $p = 0.025$ and $R = 0.39$, $p = 0.045$, respectively).

Table 2
Demographic and cardio-metabolic parameters of the study subjects.

	Schizophrenia (n = 27)	Control (n = 29)	p
Men	18 (66.7%)	20 (69.0%)	1.00
Age [years]	38.6 ± 9.3	37.9 ± 10.6	0.68
Smoking	19 (70.4%)	4 (13.8%)	< 0.001
Smoking [pack-years]	10.9 ± 10.8	2.8 ± 6.8	< 0.001
Comorbidities			
Hypertension	5 (18.5%)	7 (24.1%)	0.75
Diabetes	2 (7.4%)	0	0.23
Dyslipidemia	8 (29.6%)	6 (20.7%)	0.54
Anthropometric parameters			
Weight [kg]	79.8 ± 14.4	82.6 ± 18.4	0.53
Body mass index [kg/m^2]	27.3 ± 4.0	26.4 ± 5.5	0.48
Waist circumference [cm]	99.0 ± 10.6	91.2 ± 16.1	0.04
Hip circumference [cm]	103.0 ± 8.0	102.3 ± 10.4	0.80
Waist to hip ratio	0.96 ± 0.07	0.89 ± 0.09	< 0.001
Systolic blood pressure [mm Hg]	122.5 ± 14.5	132.5 ± 17.9	0.02
Diastolic blood pressure [mm Hg]	78.9 ± 11.1	83.8 ± 11.1	0.11
Laboratory tests			
CRP [mg/dL]	2.55 ± 3.27	4.12 ± 8.56	0.54
Glucose [mg/dL]	88.6 ± 19.7	88.3 ± 15.2	0.47
Triglycerides [mg/dL]	133.9 ± 53.3	170.8 ± 96.0	0.26
Total cholesterol [mg/dL]	197.2 ± 33.4	209.8 ± 44.1	0.24
HDL cholesterol [mg/dL]	53.3 ± 13.9	52.1 ± 12.8	0.81
LDL cholesterol [mg/dL]	114.5 ± 32.8	120.4 ± 36.1	0.52
Body composition			
SAT area [cm^2]	169.7 ± 70.1	150.4 ± 70.1	0.33
VAT area [cm^2]	142.4 ± 69.4	110.0 ± 69.5	0.08
VAT mass [g]	1309.1 ± 713.4	1087.5 ± 1025.3	0.15
VAT mass [% of body mass]	1.57 ± 0.72	1.16 ± 0.94	0.09
VAT volume [cm^3]	1387.7 ± 756.3	1152.8 ± 1086.9	0.15
TBF [g]	27,146.2 ± 8371.1	25,385.3 ± 12,278.4	0.26
TBF [% of body mass]	33.4 ± 6.7	30.0 ± 9.2	0.13
LBM [g]	51,684.6 ± 9480.6	52,966.5 ± 10,210.7	0.63
LBM [% of body mass]	64.9 ± 8.7	66.1 ± 8.8	0.62
Fat mass index [kg/m^2]	9.2 ± 2.8	8.2 ± 4.2	0.09

Data given as: *n* (%) or mean ± standard deviation. SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue; TBF = total body fat; LBM = lean body mass.

Table 3
mRNA expression of TLRs in the study groups. The expression of receptor mRNAs was corrected by normalization based on the transcript level of the housekeeping gene human ACTB. Results are the mean ± standard deviation.

	Control (n = 29)	Schizophrenia (n = 27)	p
TLR1	12.01 ± 9.40	3.72 ± 2.58	< 0.001
TLR2	189.45 ± 184.59	16.19 ± 10.31	< 0.001
TLR3	48.14 ± 38.52	92.06 ± 56.44	< 0.001
TLR4	262.36 ± 290.05	18.90 ± 11.71	< 0.001
TLR5	3355.03 ± 2493.41	3120.34 ± 1860.78	0.96
TLR6	724.62 ± 566.31	142.37 ± 93.43	< 0.001
TLR7	6.83 ± 4.54	23.37 ± 10.39	< 0.001
TLR8	31.33 ± 28.12	29.28 ± 27.29	0.83
TLR9	277.48 ± 381.29	54.07 ± 54.07	0.004

There were nor correlations between TLR mRNA expression and CDSS score. Also, no other correlations with clinical features of schizophrenia (i.e., illness duration, number of recurrences, daily dose (expressed as DDD or chlorpromazine equivalent) and number of antipsychotics) were found. Treatment was heterogeneous, so precise analysis of interaction with individual antipsychotics was not possible.

3.5. Potential confounders

A series of control analyses were performed to test possible correlations between the mRNA expression of TLRs and all other study variables (i.e., age, laboratory tests, anthropometric parameters and body composition). We have found only few significant correlations. In the total study group age was correlated with TLR9 ($R = -0.28$, $p < 0.05$), WHR with TLR1 ($R = -0.28$, $p < 0.05$), TLR6 ($R = -0.37$, $p < 0.01$), TLR7 ($R = 0.27$, $p < 0.05$), TLR9 ($R = 0.33$, $p < 0.05$); fasting glucose with TLR8 ($R = -0.36$, $p < 0.05$); triglycerides with TLR3 ($R = 0.23$, $p < 0.05$), TLR7 ($R = -0.29$, $p < 0.05$); total cholesterol with TLR7 ($R = -0.27$, $p < 0.05$). In the schizophrenia group lean body mass was correlated with TLR1 ($R = -0.45$, $p < 0.05$), TLR9 ($R = 0.38$, $p < 0.05$); VAT area with TLR1 ($R = -0.42$, $p < 0.05$); fasting glucose with TLR8 ($R = -0.56$, $p < 0.01$); triglycerides with TLR6 ($R = -0.40$, $p < 0.05$); HDL cholesterol with TLR1 ($R = 0.42$, $p < 0.05$). In the control group there were only two correlations: age with TLR9 ($R = -0.39$, $p < 0.05$); HDL cholesterol with TLR9 ($R = 0.39$, $p < 0.05$). Analysis of covariance revealed that all intergroup comparisons provided same results when the confounders were included as co-variates - see Appendix 3 for details.
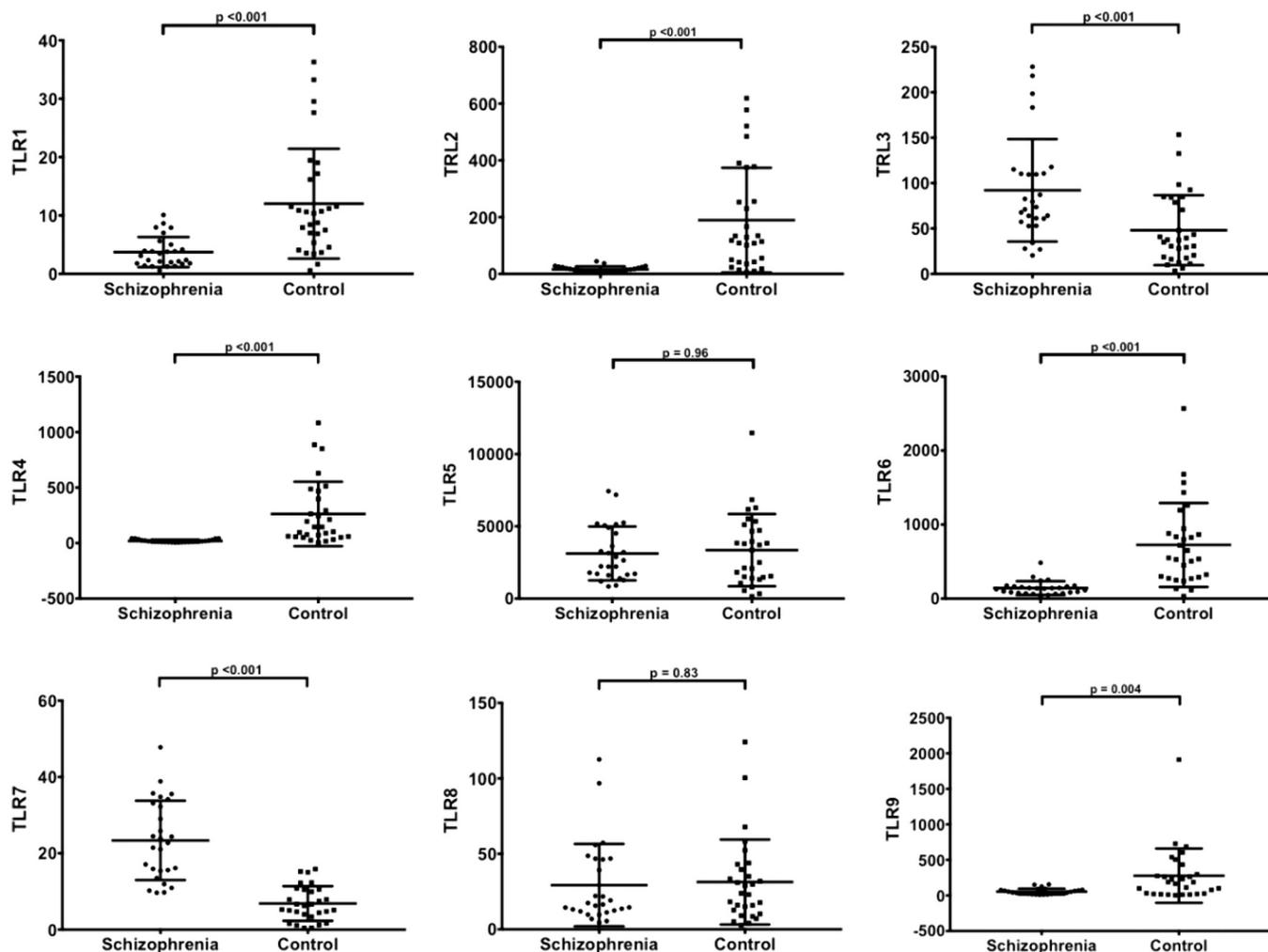
Fig. 1. mRNA expression of TLRs in schizophrenic patients and healthy controls. RNA was extracted from PBMCs, and TLR mRNAs were quantified by qRT-PCR and normalized to the level of ACTB.

4. Discussion

Our key finding is that patients with schizophrenia exhibited a significantly different TLR expression to healthy individuals. The expression profiles of TLR1, TLR2, TLR4, TLR6, and TLR9 were down-regulated in patients with schizophrenia, whereas those of TLR3 and TLR7 were elevated. No differences in TLR5 and TLR8 expression were observed between patients and controls.

So far, only a handful of studies have evaluated the expression of TLRs in schizophrenia patients. Müller et al. (2012) reported that individuals with schizophrenia have a significantly higher expression of TLR3 and TLR4 on monocytes compared with healthy volunteers. In turn, Chang et al. (2011) observed down-regulation in TLR3 and TLR5 and no changes in TLR1, TLR2, TLR4, TLR6, TLR9 expression in monocytes from schizophrenia patients. Kéri et al. (2017) indicated that treatment-naïve patients with schizophrenia displayed an increased percentage of TLR4 + and TLR5 + monocytes and TLR5 + Treg/Tact cells as compared to healthy controls. García-Bueno et al. (2016) reported that TLR4 expression was higher in postmortem prefrontal cortex samples from schizophrenia patients than matched controls. Interestingly, patients with schizophrenia had higher myeloid differentiation primary response 88 (MyD88) protein expression in post-mortem prefrontal cortex samples, and more top nuclear factor (NF)-ƙr expression in nuclear extracts. The above observations seem to indicate the activation of the TLR4 pro-inflammatory pathway in schizophrenia patients.

Despite the observation that TLR expression levels in patients with schizophrenia can be altered, understanding the biological importance of these changes in the pathomechanism of schizophrenia is unclear. The possible mechanism that explains the findings is the "leaky gut" hypothesis. Under normal circumstances, the physiological intestinal microbiota is separated from the gut-associated lymphoid tissue (GALT) by two layers of mucus, intestinal epithelial cells (IEC), and tight junctions between them. If the epithelial barrier is damaged and gut permeability is increased, intestinal microorganisms and their products translocate to lymphatic tissues and systemic circulation. This bacterial translocation may lead to subsequent immune cell activation *via* the TLR pathway, resulting in pro-inflammatory cytokine production, and,

in turn, to the development of inflammation. Some data suggests that increased gut permeability, and translocation of commensal microbiota across the gastrointestinal barrier, play a role in the development of schizophrenia. Elevated serum levels of soluble CD14, a marker of intestinal bacterial translocation (Severance et al., 2013), and of IgG antibodies to *Saccharomyces cerevisiae*, a marker of intestinal inflammation (Severance et al., 2012a), have been noted in cases of schizophrenia.

Many factors could induce increased gut permeability in schizophrenia. One significant reason is stress, which results in the activation of the HPA axis/sympathetic nervous system (Corcoran et al., 2003; Gispen-de Wied, 2000; Walker et al., 2008). Secondly, a link has been postulated between schizophrenia and food antigen sensitivity, especially hypersensitivity to wheat-derived glutens and bovine milk caseins and gastrointestinal inflammation (Samaroo et al., 2010; Severance et al., 2012a,b). Thirdly, there may be an association between *Toxoplasma gondii*-generated intestinal inflammation and schizophrenia (Severance et al., 2012a).

The "leaky gut" has also been hypothesized to play a role in the pathogenesis of major depressive disorder (MDD). The levels of the well-conserved 16S ribosomal RNA (rRNA) subunit of intestinal microbiota, an accepted marker of bacterial translocation, has been found to be significantly elevated in the plasma of MDD patients (Kéri et al., 2014). It should be stressed that in MDD TLR levels can change. Hung et al. (2014, 2016) indicated substantially higher expression of TLR3, TLR4, TLR5, TLR7, TLR8, and TLR9 but lower expression of TLR1 and TLR6 mRNAs in peripheral blood and PBMCs of MDD patients compared to healthy controls. Kéri et al. (2014) documented elevated TLR4 mRNA and protein expression in PBMCs in cases of MDD relative to healthy volunteers.

Another potential explanation is related to the neurodegenerative processes that are present in the course of schizophrenia, both at the onset and during exacerbations (Rund, 2009). In this hypothesis, the immunological alteration is less specific to schizophrenia itself, but contribute to or result from damage to the glia and neuronal cells. Glutamate is the largest excitatory neurotransmitter in the brain. The glutamatergic system, comprising approximately 50% of all brain neurons, is responsible for the transmission and modulation of the majority of brain signals (Carlsson et al., 2000), but is also one of the major factors mediating schizophrenia-induced neurotoxicity, and glutamate-mediated excitotoxicity may account for certain structural changes present in schizophrenia (Plitman et al., 2014). Also, glutamate may regulate the activation of various DAMP molecules (e.g., S100B, HMGB1) (Tramontina et al., 2006; Faraco et al., 2007), which ultimately activate TLRs. Zhu et al. (2015) documented significantly higher serum level of HMGB1 in schizophrenic patients relative to healthy subjects. It has also been found that schizophrenia patients present higher serum S100B levels than healthy controls (Lara et al., 2001; Zhang et al., 2010). Kim et al., (2001) found the levels of antibodies to both HSP90 and HSP70 to be significantly higher in the patients with schizophrenia than in normal controls, suggesting that the profile of TLRs activation may serve as an indirect biomarker of mental disorders, including schizophrenia.

In conclusion, our findings clearly demonstrate that patients with schizophrenia demonstrate different PBMC expression levels of most studied TLRs to controls. It seems very interesting that TLR1, TLR2, TLR4, TLR6, and TLR9 expression was decreased but the most significant reduction in expression was observed for TLR4 and TLR2. All these receptors play a crucial role in recognition pathogen-derived

molecules, i.e., PAMPs, as well as in identifying the molecules associated with cell/tissue damage, i.e., DAMPs. It is worth pointing out that TLR4 recognizes and binds LPS, the main cell wall component of Gram-negative bacteria and a strong bacterial antigen, and TLR2 is a receptor for different Gram-positive bacteria cell-wall components, including PGN and LTAs. TLR6 interacts with TLR2 to mediate the cellular response to bacterial lipoproteins, TLR1 recognizes bacterial lipopeptides, and TLR9 preferentially binds unmethylated CpG sequences in bacterial and viral DNA. In addition, TLR2 and TLR4 also recognize surface antigens of *T. gondii*, TLR4 binds S100 proteins, and TLR2, TLR4, and TLR9 recognize HMGB1 and various HSP molecules.

The recognition of pathogen- and/or damage-associated molecules *via* TLRs results in cell activation and, in consequence, the initiation of immune and inflammatory processes. It appears that TLR level clearly influences the intensity of immune/inflammatory responses, indicating that decreased TLR expression protects against excessive cell stimulation *via* exogenous and/or endogenous ligands, and is a counterbalancing mechanism limiting the excessive development of inflammation. However, further studies to clarify these changes are needed. Importantly, such studies should focus on clearly defined, homogenous subject groups in terms of dominating schizophrenia symptoms, as various clinical presentations (e.g., deficit subtype) may differ in terms of inflammatory and immunological alterations (Kanchanatawan et al., 2018). This may also potentially explain differences between our results and previously published studies.

The major limitation of this study results from its cross-sectional design and the fact that all study subjects were on medications, while treatment in the schizophrenia group was highly heterogeneous. It cannot be excluded that antipsychotics may have an effect on TLR expression, and some studies suggest that antipsychotics (Kéri et al., 2017) and antidepressants (Hung et al., 2014) may influence TLR expression. It is, however, uncertain whether these effects are related to medications or rather reflect symptomatic improvements and clinical recovery due to treatment; further longitudinal studies with more homogeneous antipsychotic treatment groups with regard to schizophrenia patients are required. One of the major strengths of the study is that it includes many co-variables that are usually not taken into consideration in studies on immunological alterations in mental disorders, i.e., body composition. Antipsychotics, mood stabilizers and antidepressants usually increase the amount of body fat, and developing obesity may significantly trigger chronic inflammatory response, including TLR activation (Jialal et al., 2014). Therefore, by controlling for metabolic status it is possible to eliminate one of the potential mechanisms by which antipsychotics could modify the TLR expression pattern.

Appendix 1

Correlations between TLR mRNA expression.

Total study group	TLR1	TLR2	TLR3	TLR4	TLR5	TLR6	TLR7	TLR8
TLR1								
TLR2	0.59***							
TLR3								
TLR4	−0.46***	−0.82***						
TLR5	0.47***		0.61***					
TLR6	0.78***	0.68***		−0.52***	0.54***			
TLR7		−0.39**	0.76***	0.36**	0.41**			
TLR8	0.45***		0.51***		0.58***	0.47***	0.47***	
TLR9	0.29*	0.62***		−0.62***		0.33*		

Schizophrenia	TLR1	TLR2	TLR3	TLR4	TLR5	TLR6	TLR7	TLR8
TLR1								
TLR2								
TLR3								
TLR4		−0.71***	−0.38*					
TLR5			0.66***					
TLR6			0.53***		0.56**			
TLR7	0.38*		0.67***		0.67***	0.84***		
TLR8			0.56***		0.53**	0.55**	0.70***	
TLR9		0.50**	0.62***	−0.69***	0.40*	0.45*	0.66***	0.53**

Control	TLR1	TLR2	TLR3	TLR4	TLR5	TLR6	TLR7	TLR8
TLR1								
TLR2	0.40*							
TLR3	0.70***	0.48**						
TLR4		−0.67***						
TLR5	0.69***	0.36*	0.74***					
TLR6	0.81***	0.52**	0.75***		0.83***			
TLR7	0.84***	0.45*	0.77***		0.61***	0.77***		
TLR8	0.71***		0.61***		0.61***	0.69***	0.80***	
TLR9		0.56**		−0.50**				

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Appendix 2

Detailed pharmacological treatment of the study subjects.

Subject id	DDD of all APs	AP 1	AP 1 dose	AP 2	AP 2 dose	AP 3	AP 3 dose	AD	AD dose	MS	MS dose
1	3.25	ziprasidone	80	amisulpride	800					lamotrigine	25
2	4	olanzapine	20	aripiprazole	30						
3	3.75	aripiprazole	30	quetiapine	700					lamotrigine	125
4	1.3	sulpiride	500	clozapine	200			fluoxetine	10		
5	5.25	quetiapine	500	aripiprazole	15	olanzapine	15			valproate	1200
6	3	aripiprazole	15	olanzapine	15					valproate	1500
7	1.7	clozapine	50	quetiapine	600			sertraline	50	lamotrigine	50
8	2	ziprasidone	160					sertraline	50		
9	2	aripiprazole	30								
10	5	olanzapine	20	aripiprazole	30					valproate	1200
11	1.6	clozapine	300	risperidone	3					valproate	1000
12	3	quetiapine	550	perazine	500			sertraline	25	lithium	375
13	2.7	perazine	100	olanzapine	20	risperidone	2				
14	4.75	clozapine	375	aripiprazole	15	amisulpride	600			valproate	600
15	2.75	amisulpride	600	quetiapine	500					valproate	500
16	1.25	perazine	500	quetiapine	500						
17	.56	olanzapine	5	quetiapine	25			sertraline	50		
18	1.83	clozapine	550								
19	1.33	aripiprazole	5	clozapine	150	amisulpride	200				
20	2.3	clozapine	400	flupenthixol	6						

21	1.67	amisulpride	400	clozapine	200						
22	1.67	clozapine	200	flupenthixol	6						
23	.75	clozapine	225							lithium	625
24	2.5	clozapine	200	flupenthixol	6			amitriptyline	25		
25	1.5	olanzapine	15								
26	2.7	haloperidol	6	clozapine	350	olanzapine	7.5			valproate	1750
27	4	aripiprazole	30	perazine	600					carbamazepine	450

Appendix 3

Inter-group comparison of TLR means adjusted for covariates.

TLR	Covariates	Adjusted mean ± SD [95%CI] Schizophrenia	Control	F(1, 53)	p
TLR1	Age [years]	3.73 ± 1.36 [1.06–6.39]	12.01 ± 1.31 [9.43–14.58]	19.17	< 0.001
	BMI [kg/m^2]	3.71 ± 1.36 [1.04–6.39]	12.02 ± 1.31 [9.44–14.60]	19.14	< 0.001
	WHR	4.00 ± 1.43 [1.20–6.81]	11.75 ± 1.37 [9.05–14.45]	13.83	0.0005
	SBP [mm Hg]	3.58 ± 1.39 [0.85–6.31]	12.15 ± 1.34 [9.52–14.77]	18.79	< 0.0001
	DBP [mm Hg]	3.65 ± 1.37 [0.95–6.35]	12.08 ± 1.32 [9.48–14.68]	19.00	< 0.0001
	TBF [g]	3.71 ± 1.36 [1.04–6.38]	12.82 ± 1.33 [10.20–15.43]	22.71	< 0.0001
	TBF [%]	3.58 ± 1.37 [0.90–6.27]	12.94 ± 1.34 [10.30–15.57]	23.25	<0.0001
	LBM [g]	3.76 ± 1.36 [1.08–6.44]	12.77 ± 1.34 [10.20–15.43]	22.05	< 0.0001
	LBM [%]	3.70 ± 1.35 [1.05–6.36]	12.82 ± 1.32 [10.22–15.43]	23.00	< 0.0001
	SAT area [cm^2]	3.74 ± 1.36 [1.07–6.42]	11.99 ± 1.31 [9.41–14.58]	18.71	< 0.0001
	VAT area [cm^2]	3.64 ± 1.37 [0.93–6.34]	12.09 ± 1.32 [9.49–14.70]	18.98	< 0.0001
	VAT mass [g]	3.83 ± 1.41 [1.06–6.59]	12.71 ± 1.35 [10.05–15.37]	20.41	< 0.0001
	VAT mass [%]	3.88 ± 1.42 [1.08–6.67]	12.66 ± 1.37 [9.97–15.35]	19.13	< 0.0001
	VAT volume [cm^3]	3.83 ± 1.41 [1.06–6.59]	12.71 ± 1.35 [10.05–15.37]	20.41	< 0.0001
	FMI [kg/m^2]	3.63 ± 1.36 [0.96–6.30]	12.89 ± 1.33 [10.27–15.51]	23.27	< 0.0001
	GLU [mg/dL]	3.72 ± 1.35 [1.06–6.39]	12.01 ± 1.31 [9.44–14.58]	19.25	< 0.0001
	TGA [mg/dL]	3.65 ± 1.38 [0.93–6.36]	12.08 ± 1.33 [9.47–14.70]	18.58	< 0.0001
	CHOL [mg/dL]	3.47 ± 1.33 [0.85–6.09]	12.25 ± 1.29 [9.72–14.78]	22.02	< 0.0001
	HDL [mg/dL]	3.67 ± 1.29 [1.03–6.31]	12.06 ± 1.29 [9.51–14.61]	20.09	< 0.0001
	LDL [mg/dL]	3.56 ± 1.31 [0.98–6.13]	12.17 ± 1.26 [9.68–14.65]	22.13	< 0.0001
TLR2	Age [years]	17.20 ± 25.28 [−32.36–66.76]	188.52 ± 24.39 [140.70–236.34]	23.76	< 0.0001
	BMI [kg/m^2]	16.04 ± 25.91 [−34.75–66.84]	189.59 ± 25.00 [140.58–238.60]	23.12	< 0.0001
	WHR	17.54 ± 27.30 [−35.96–71.05]	188.19 ± 26.24 [136.75–239.64]	18.46	< 0.0001
	SBP [mm Hg]	12.35 ± 23.39 [−39.37–64.08]	193.03 ± 25.42 [143.19–242.86]	23.22	< 0.0001
	DBP [mm Hg]	12.81 ± 26.02 [−38.19–63.82]	192.60 ± 25.08 [143.42–241.77]	24.15	< 0.0001
	TBF [g]	14.26 ± 25.94 [−36.58–65.11]	203.34 ± 25.45 [153.44–253.24]	26.96	< 0.0001
	TBF [%]	13.72 ± 26.49 [−38.21–65.65]	203.87 ± 25.99 [152.92–254.81]	25.68	< 0.0001
	LBM [g]	16.89 ± 26.26 [−34.59–68.37]	200.81 ± 25.77 [150.29–251.33]	24.92	< 0.0001
	LBM [%]	15.58 ± 26.27 [−35.90–67.07]	202.07 ± 25.77 [151.55–252.60]	25.61	< 0.0001
	SAT area [cm^2]	15.68 ± 25.96 [−35.20–66.58]	189.92 ± 25.04 [140.83–239.02]	23.11	< 0.0001
	VAT area [cm^2]	14.68 ± 26.20 [−36.67–66.04]	190.86 ± 25.25 [141.35–240.36]	22.81	< 0.0001
	VAT mass [g]	13.38 ± 26.79 [−39.12–65.90]	204.23 ± 25.77 [153.71–254.75]	26.14	< 0.0001
	VAT mass [%]	12.67 ± 27.35 [−40.93–66.28]	204.89 ± 26.28 [153.37–256.42]	24.94	< 0.0001
	VAT volume [cm^3]	13.38 ± 26.79 [−39.13–65.90]	204.23 ± 25.77 [153.72–254.75]	26.14	< 0.0001
	FMI [kg/m^2]	14.10 ± 26.30 [−37.44–65.66]	203.49 ± 25.80 [152.92–254.07]	26.13	< 0.0001
	GLU [mg/dL]	16.07 ± 25.74 [−34.39–66.54]	189.56 ± 24.84 [140.87–238.26]	23.51	< 0.0001
	TGA [mg/dL]	20.68 ± 26.14 [−30.55–71.93]	185.27 ± 25.19 [135.89–234.65]	19.84	< 0.0001
	CHOL [mg/dL]	18.95 ± 25.83 [−31.67–69.58]	186.89 ± 24.91 [138.06–235.72]	21.61	< 0.0001
	HDL [mg/dL]	15.86 ± 25.83 [−34.77–66.51]	189.76 ± 24.93 [140.89–238.62]	23.43	< 0.0001
	LDL [mg/dL]	16.80 ± 25.87 [−33.90–67.51]	188.89 ± 24.96 [139.96–237.81]	22.82	< 0.0001
TLR3	Age [years]	91.83 ± 9.24 [73.71–109.95]	48.35 ± 8.92 [30.86–65.83]	11.45	0.0014
	BMI [kg/m^2]	91.69 ± 9.31 [73.43–109.95]	48.48 ± 8.98 [30.86–66.10]	11.09	0.0016
	WHR	89.98 ± 9.80 [70.76–109.21]	50.07 ± 9.42 [31.59–68.55]	7.83	0.0072
	SBP [mm Hg]	92.97 ± 9.53 [74.27–111.66]	47.29 ± 9.18 [29.28–65.30]	11.36	0.0014
	DBP [mm Hg]	92.42 ± 9.43 [73.93–110.92]	47.80 ± 9.09 [29.97–65.63]	11.31	0.0014
	TBF [g]	86.79 ± 8.91 [69.31–104.26]	51.57 ± 8.75 [34.42–68.72]	7.92	0.0070
	TBF [%]	86.27 ± 9.01 [68.61–103.94]	52.06 ± 8.84 [34.74–69.39]	7.18	0.0099
	LBM [g]	87.40 ± 8.94 [69.87–104.94]	50.98 ± 8.77 [33.77–68.18]	8.43	0.0055
	LBM [%]	87.01 ± 8.94 [69.47–104.55]	51.36 ± 8.78 [34.15–68.56]	8.07	0.0065
	SAT area [cm^2]	91.65 ± 9.34 [73.33–109.98]	48.52 ± 9.01 [30.84–66.19]	10.39	0.0017
	VAT area [cm^2]	92.02 ± 9.45 [73.48–110.56]	48.18 ± 9.11 [30.31–66.05]	10.84	0.0018
	VAT mass [g]	89.38 ± 9.13 [71.49–107.28]	51.12 ± 8.78 [33.90–68.33]	9.05	0.0041
	VAT mass [%]	89.94 ± 9.22 [71.87–108.01]	50.60 ± 8.86 [33.23–67.97]	9.19	0.0039
	VAT volume [cm^3]	89.38 ± 9.13 [71.49–107.28]	51.12 ± 8.78 [33.90–68.33]	9.05	0.0041
	FMI [kg/m^2]	86.47 ± 8.95 [68.93–104.02]	51.87 ± 8.78 [34.66–69.09]	7.53	0.0084
	GLU [mg/dL]	92.05 ± 9.32 [73.78–110.32]	48.15 ± 8.99 [30.52–65.77]	11.49	0.0013
	TGA [mg/dL]	89.29 ± 9.28 [71.09–107.50]	50.72 ± 8.95 [33.17–68.26]	8.64	0.0049
	CHOL [mg/dL]	90.56 ± 9.21 [72.49–108.63]	49.54 ± 8.89 [32.11–66.96]	10.12	0.0024
	HDL [mg/dL]	91.82 ± 9.27 [73.63–110.00]	48.36 ± 8.95 [30.82–65.91]	11.35	0.0014
	LDL [mg/dL]	91.68 ± 9.30 [73.44–109.91]	48.49 ± 8.97 [30.90–66.09]	11.11	0.0016

TLR4	Age [years]	20.43 ± 39.76 [−57.51–98.37]	206.93 ± 38.37 [185.73–336.14]	18.93	< 0.0001
	BMI [kg/m^2]	20.63 ± 40.55 [−58.85–100.12]	260.75 ± 39.12 [184.06–337.44]	18.07	< 0.0001
	WHR	8.55 ± 42.65 [−75.04–92.16]	271.99 ± 41.00 [191.61–352.37]	18.02	< 0.0001
	SBP [mm Hg]	15.89 ± 41.57 [−65.58–97.38]	265.15 ± 40.05 [186.66–343.65]	17.82	< 0.0001
	DBP [mm Hg]	16.39 ± 41.06 [−64.09–96.88]	264.69 ± 39.59 [187.09–342.29]	18.50	< 0.0001
	TBF [g]	19.25 ± 42.02 [−63.11–101.62]	275.09 ± 41.23 [194.27–355.91]	18.81	< 0.0001
	TBF [%]	24.51 ± 42.11 [−58.03–107.05]	270.03 ± 41.31 [189.06–351.00]	16.95	0.0001
	LBM [g]	22.04 ± 41.04 [−58.41–102.49]	272.40 ± 40.28 [193.46–351.35]	18.91	< 0.0001
	LBM [%]	20.70 ± 41.74 [−61.12–102.53]	273.69 ± 40.96 [193.40–353.99]	18.66	< 0.0001
	SAT area [cm^2]	21.36 ± 40.64 [−58.29–101.02]	260.06 ± 39.20 [183.22–338.90]	17.71	< 0.0001
	VAT area [cm^2]	18.74 ± 41.19 [−61.98–99.47]	262.50 ± 39.70 [184.68–340.33]	17.67	0.0001
	VAT mass [g]	16.32 ± 43.12 [−68.19–100.84]	278.12 ± 41.48 [196.82–359.42]	18.99	< 0.0001
	VAT mass [%]	16.44 ± 43.82 [−69.44–102.32]	278.01 ± 42.11 [195.46–360.57]	17.99	< 0.0001
	VAT volume [cm^3]	16.32 ± 43.12 [−68.19–100.84]	278.12 ± 41.48 [196.81–359.42]	18.99	< 0.0001
	FMI [kg/m^2]	21.86 ± 42.02 [−60.50–104.23]	272.57 ± 41.23 [191.76–353.38]	17.93	< 0.0001
	GLU [mg/dL]	18.68 ± 40.36 [−60.43–97.80]	262.56 ± 38.95 [186.22–338.90]	18.90	< 0.0001
	TGA [mg/dL]	19.82 ± 41.36 [−61.24–100.90]	261.49 ± 39.86 [183.37–339.62]	17.10	0.0001
	CHOL [mg/dL]	18.23 ± 40.87 [−61.88–98.34]	262.98 ± 39.42 [185.71–340.25]	18.33	< 0.0001
	HDL [mg/dL]	19.55 ± 40.54 [−59.90–99.02]	261.75 ± 39.11 [185.08–338.42]	18.46	< 0.0001
	LDL [mg/dL]	18.78 ± 40.68 [−60.95–98.51]	262.47 ± 39.25 [185.54–339.40]	18.51	< 0.0001
TLR5	Age [years]	3114.90 ± 428.73 [2274.6–3955.21]	3360.09 ± 413.67 [2549.29–4170.89]	0.17	0.6824
	BMI [kg/m^2]	3148.53 ± 427.00 [2311.63–3985.44]	3328.78 ± 411.94 [2521.38–4136.18]	0.09	0.7630
	WHR	3229.14 ± 451.32 [2344.57–4113.71]	3253.73 ± 433.92 [2403.26–4104.21]	0.00	0.9703
	SBP [mm Hg]	3066.66 ± 439.05 [2206.13–3927.18]	3405.01 ± 422.93 [2576.06–4233.95]	0.29	0.5897
	DBP [mm Hg]	3042.58 ± 429.86 [2200.07–3885.09]	3427.42 ± 414.41 [2615.19–4239.66]	0.41	0.5270
	TBF [g]	2984.21 ± 420.22 [2160.59–3807.84]	3529.74 ± 412.34 [2721.57–4337.91]	0.86	0.3594
	TBF [%]	3014.08 ± 424.24 [2182.58–3845.58]	3500.98 ± 416.13 [2685.36–4316.59]	0.66	0.4215
	LBM [g]	2960.97 ± 422.40 [2133.07–3788.87]	3552.12 ± 414.49 [2739.73–4364.51]	1.00	0.3232
	LBM [%]	2980.23 ± 420.11 [2156.83–3803.64]	3533.57 ± 412.23 [2725.60–4341.55]	0.88	0.3523
	SAT area [cm^2]	3177.21 ± 423.95 [2346.28–4008.14]	3302.08 ± 408.94 [2500.57–4103.59]	0.04	0.8337
	VAT area [cm^2]	3176.59 ± 433.39 [2327.14–4026.03]	3302.66 ± 417.77 [2483.83–4121.49]	0.04	0.8371
	VAT mass [g]	3089.40 ± 424.99 [2256.42–3922.38]	3498.61 ± 408.82 [2697.32–4299.9]	0.48	0.4927
	VAT mass [%]	3141.75 ± 429.63 [2299.69–3983.81]	3450.14 ± 412.94 [2640.78–4259.5]	0.26	0.6123
	VAT volume [cm^3]	3089.36 ± 425.01 [2256.36–3922.37]	3498.64 ± 48.84 [2697.32–4299.96]	0.48	0.4927
	FMI [kg/m^2]	2998.77 ± 421.94 [2171.77–3825.77]	3516.73 ± 413.97 [2704.36–4327.09]	0.76	0.3886
	GLU [mg/dL]	3121.66 ± 428.79 [2281.24–3962.09]	3353.08 ± 413.74 [2542.87–4163.28]	0.15	0.6984
	TGA [mg/dL]	2956.02 ± 421.49 [2129.91–3782.12]	3508.02 ± 406.18 [2711.92–4304.12]	0.86	0.3582
	CHOL [mg/dL]	3051.80 ± 424.95 [2218.90–3884.69]	3418.84 ± 409.84 [2615.56–4222.13]	0.38	0.5394
	HDL [mg/dL]	3096.04 ± 418.6 [2275.60–3916.48]	3377.65 ± 403.89 [2586.04–4169.27]	0.23	0.6305
	LDL [mg/dL]	3107.09 ± 429.52 [2265.54–3949.23]	3367.09 ± 414.38 [2554.90–4179.27]	0.19	0.6658
TLR6	Age [years]	142.69 ± 80.21 [−14.53–299.91]	724.33 ± 77.40 [572.63–876.04]	27.21	< 0.0001
	BMI [kg/m^2]	146.94 ± 79.89 [−9.64–303.53]	720.37 ± 77.07 [569.31–871.44]	26.56	< 0.0001
	WHR	177.20 ± 83.39 [13.75–340.65]	692.20 ± 80.18 [535.05–849.35]	18.01	< 0.0001
	SBP [mm Hg]	133.66 ± 82.03 [−27.11–294.45]	732.73 ± 79.02 [577.85–887.61]	26.43	< 0.0001
	DBP [mm Hg]	127.57 ± 80.21 [−29.65–284.79]	738.41 ± 77.33 [586.83–889.99]	29.34	< 0.0001
	TBF [g]	142.43 ± 80.13 [−14.63–299.50]	772.00 ± 78.63 [617.87–926.12]	31.33	< 0.0001
	TBF [%]	143.16 ± 80.89 [−15.39–301.75]	771.29 ± 79.35 [615.76–926.82]	30.06	< 0.0001
	LBM [g]	142.60 ± 80.07 [−14.33–299.55]	771.83 ± 78.57 [617.82–925.83]	31.39	< 0.0001
	LBM [%]	142.10 ± 80.08 [−14.87–299.07]	772.32 ± 78.58 [618.28–926.35]	31.47	< 0.0001
	SAT area [cm^2]	148.33 ± 80.13 [−8.73–305.40]	719.08 ± 77.30 [567.57–870.58]	26.04	< 0.0001
	VAT area [cm^2]	147.78 ± 81.25 [−11.46–307.03]	719.59 ± 78.32 [566.07–873.10]	24.99	< 0.0001
	VAT mass [g]	148.80 ± 82.61 [−13.12–310.73]	770.13 ± 79.47 [614.37–925.90]	29.14	< 0.0001
	VAT mass [%]	152.71 ± 83.48 [−10.90–316.33]	766.51 ± 80.23 [609.25–923.77]	27.30	< 0.0001
	VAT volume [cm^3]	148.79 ± 82.61 [−13.12–310.72]	770.14 ± 79.45 [614.37–925.90]	29.14	< 0.0001
	FMI [kg/m^2]	143.97 ± 80.41 [−13.64–301.58]	770.52 ± 78.89 [615.88–925.15]	30.59	< 0.0001
	GLU [mg/dL]	142.62 ± 80.05 [−14.29–299.53]	724.39 ± 77.24 [572.99–875.80]	27.34	< 0.0001
	TGA [mg/dL]	119.55 ± 80.06 [−37.36–276.47]	745.87 ± 77.15 [594.65–897.09]	30.65	< 0.0001
	CHOL [mg/dL]	133.35 ± 80.06 [−23.56–290.26]	733.02 ± 77.21 [581.69–884.36]	28.69	< 0.0001
	HDL [mg/dL]	139.95 ± 79.66 [−16.18–296.09]	726.88 ± 76.86 [576.22–877.53]	28.08	< 0.0001
	LDL [mg/dL]	139.70 ± 80.15 [−17.40–296.80]	727.11 ± 77.33 [575.54–878.68]	27.71	< 0.0001
TLR7	Age [years]	23.36 ± 1.53 [20.35–36.38]	6.83 ± 1.48 [3.92–9.74]	59.72	< 0.0001
	BMI [kg/m^2]	23.37 ± 1.54 [20.35–26.39]	6.82 ± 1.48 [3.91–9.74]	59.39	< 0.0001
	WHR	23.60 ± 1.62 [20.42–26.78]	6.61 ± 1.55 [3.55–9.66]	51.89	< 0.0001
	SBP [mm Hg]	23.39 ± 1.57 [20.30–26.48]	6.81 ± 1.51 [3.83–9.78]	54.85	< 0.0001
	DBP [mm Hg]	23.45 ± 1.55 [20.40–26.50]	6.75 ± 1.50 [3.81–9.69]	58.22	< 0.0001
	TBF [g]	22.86 ± 1.55 [19.80–25.91]	7.29 ± 1.52 [4.29–10.29]	50.62	< 0.0001
	TBF [%]	22.67 ± 1.56 [19.61–25.74]	7.47 ± 1.53 [4.47–10.47]	47.23	< 0.0001
	LBM [g]	22.80 ± 1.53 [19.79–25.81]	7.35 ± 1.50 [4.39–10.30]	51.43	< 0.0001
	LBM [%]	22.79 ± 1.53 [19.78–25.80]	7.36 ± 1.50 [4.40–10.31]	51.38	< 0.0001
	SAT area [cm^2]	23.35 ± 1.54 [20.32–26.38]	6.84 ± 1.40 [3.92–9.76]	58.59	< 0.0001
	VAT area [cm^2]	23.33 ± 1.56 [20.28–26.39]	6.86 ± 1.50 [3.91–9.81]	56.25	< 0.0001
	VAT mass [g]	23.45 ± 1.56 [20.39–26.52]	7.23 ± 1.50 [4.28–10.18]	55.47	< 0.0001
	VAT mass [%]	23.47 ± 1.58 [20.37–26.58]	7.21 ± 1.52 [4.23–10.19]	53.39	< 0.0001
	VAT volume [cm^3]	23.45 ± 1.56 [20.39–26.52]	7.23 ± 1.50 [4.28–10.18]	55.47	< 0.0001
	FMI [kg/m^2]	22.79 ± 1.56 [19.73–25.84]	7.36 ± 1.53 [4.36–10.36]	49.22	< 0.0001
	GLU [mg/dL]	23.38 ± 1.50 [20.44–26.33]	6.81 ± 1.45 [3.97–9.66]	62.93	< 0.0001
	TGA [mg/dL]	23.01 ± 1.54 [19.98–26.04]	7.16 ± 1.49 [4.24–10.08]	52.59	< 0.0001
	CHOL [mg/dL]	23.05 ± 1.50 [20.10–26.00]	7.12 ± 1.45 [4.28–9.97]	57.35	< 0.0001
	HDL [mg/dL]	23.29 ± 1.50 [20.33–26.24]	6.90 ± 1.45 [4.05–9.75]	61.12	< 0.0001
	LDL [mg/dL]	23.21 ± 1.50 [20.26–26.16]	6.97 ± 1.45 [4.13–9.82]	60.14	< 0.0001

TLR8	Age [years]	29.31 ± 5.38 [18.75–39.86]	31.30 ± 5.19 [21.12–41.48]	0.07	0.7911
	BMI [kg/m^2]	29.24 ± 5.39 [18.66–39.82]	31.36 ± 5.20 [21.15–41.57]	0.08	0.7790
	WHR	31.08 ± 5.63 [20.03–42.12]	29.65 ± 5.41 [19.03–40.27]	0.03	0.8630
	SBP [mm Hg]	28.39 ± 5.49 [17.62–39.15]	32.16 ± 5.29 [21.79–42.53]	0.23	0.6309
	DBP [mm Hg]	28.39 ± 5.49 [17.62–39.15]	31.50 ± 5.25 [21.20–41.81]	0.23	0.6309
	TBF [g]	29.09 ± 5.45 [18.40–39.78]	31.50 ± 5.25 [21.20–41.81]	0.10	0.7542
	TBF [%]	28.34 ± 5.59 [17.37–39.30]	33.43 ± 5.48 [22.68–44.19]	0.41	0.5226
	LBM [g]	28.48 ± 5.52 [17.64–39.32]	33.29 ± 5.42 [22.66–43.93]	0.38	0.5380
	LBM [%]	28.48 ± 5.53 [17.64–39.32]	33.30 ± 5.42 [22.66–43.93]	0.39	0.5375
	SAT area [cm^2]	29.09 ± 5.40 [18.50–39.69]	31.50 ± 5.21 [21.28–41.72]	0.10	0.7507
	VAT area [cm^2]	29.18 ± 5.46 [18.47–39.89]	31.42 ± 5.26 [21.09–41.74]	0.08	0.7725
	VAT mass [g]	28.88 ± 5.72 [17.66–40.10]	33.17 ± 5.50 [22.38–43.96]	0.29	0.5928
	VAT mass [%]	28.89 ± 5.78 [17.54–40.23]	33.17 ± 5.56 [22.26–44.07]	0.28	0.6017
	VAT volume [cm^3]	28.88 ± 5.72 [17.66–40.10]	33.17 ± 5.50 [22.38–43.96]	0.29	0.5927
	FMI [kg/m^2]	28.39 ± 5.55 [17.49–39.28]	33.38 ± 5.45 [22.69–44.07]	0.41	0.5265
	GLU [mg/dL]	29.37 ± 5.01 [19.54–39.21]	31.24 ± 4.84 [21.75–40.73]	0.07	0.7902
	TGA [mg/dL]	28.14 ± 5.42 [17.50–38.77]	32.39 ± 5.22 [22.14–42.64]	0.31	0.5816
	CHOL [mg/dL]	28.66 ± 5.37 [18.13–39.19]	31.90 ± 5.18 [21.74–42.06]	0.19	0.6680
	HDL [mg/dL]	29.04 ± 5.30 [18.64–39.44]	31.55 ± 5.11 [21.52–41.58]	0.12	0.7350
	LDL [mg/dL]	28.87 ± 5.32 [18.44–39.31]	31.70 ± 5.13 [21.64–41.77]	0.15	0.7042
TLR9	Age [years]	57.04 ± 51.18 [−43.27–157.36]	274.72 ± 49.38 [177.92–371.52]	9.36	0.0035
	BMI [kg/m^2]	60.08 ± 52.41 [−42.64–162.82]	271.89 ± 50.56 [172.78–371.00]	8.42	0.0054
	WHR	82.15 ± 55.34 [−26.32–190.62]	251.34 ± 53.21 [147.05–355.64]	4.41	0.0404
	SBP [mm Hg]	39.09 ± 54.15 [−67.04–145.23]	291.43 ± 52.16 [189.18–393.68]	10.76	0.0018
	DBP [mm Hg]	46.91 ± 53.95 [−58.82–152.66]	284.15 ± 52.01 [182.20–386.09]	9.78	0.0029
	TBF [g]	54.50 ± 54.86 [−53.03–162.04]	283.83 ± 53.83 [178.32–389.04]	8.87	0.0045
	TBF [%]	59.98 ± 55.54 [−48.88–168.85]	278.56 ± 54.48 [171.77–385.34]	7.72	0.0077
	LBM [g]	47.10 ± 54.96 [−60.61–154.82]	290.96 ± 53.93 [185.26–396.66]	10.01	0.0027
	LBM [%]	52.81 ± 55.25 [−55.47–161.10]	285.46 ± 54.21 [179.20–391.73]	9.01	0.0042
	SAT area [cm^2]	60.02 ± 53.20 [−44.24–164.30]	271.94 ± 51.31 [176.04–372.52]	8.15	0.0061
	VAT area [cm^2]	66.00 ± 53.52 [−38.89–170.89]	266.38 ± 51.59 [165.26–367.50]	7.07	0.0103
	VAT mass [g]	57.34 ± 56.72 [−53.83–168.52]	282.11 ± 54.56 [175.16–389.07]	8.09	0.0065
	VAT mass [%]	64.74 ± 57.15 [−47.27–176.75]	275.26 ± 54.93 [167.60–382.93]	6.85	0.0117
	VAT volume [cm^3]	57.34 ± 56.72 [−53.83–168.53]	282.11 ± 54.56 [175.16–389.06]	8.09	0.0065
	FMI [kg/m^2]	57.12 ± 55.23 [−51.12–165.37]	281.32 ± 54.18 [175.11–387.52]	8.30	0.0058
	GLU [mg/dL]	54.15 ± 53.60 [−50.90–159.21]	277.41 ± 51.72 [176.04–378.78]	8.98	0.0041
	TGA [mg/dL]	42.89 ± 54.03 [−63.02–148.80]	287.90 ± 52.07 [185.83–389.96]	10.30	0.0023
	CHOL [mg/dL]	50.92 ± 53.86 [−54.64–156.49]	280.42 ± 51.94 [178.60–382.23]	9.28	0.0036
	HDL [mg/dL]	50.40 ± 51.57 [−50.68–151.48]	280.90 ± 49.76 [183.37–378.44]	10.33	0.0022
	LDL [mg/dL]	51.53 ± 53.43 [−53.20–156.27]	279.85 ± 51.55 [178.80–380.90]	9.42	0.0034

BMI = body mass index; WHR = waist to hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; TBF = total body fat; LBM = lean body mass; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue; FMI = fat mass index; GLU = glucose; TGA = triglycerides; CHOL = total cholesterol; HDL = HDL cholesterol; LDL = LDL cholesterol.

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