Scientific Research Publishing

Yangtze Medicine, 2023, 7, 1-10
https://www.scirp.org/journal/ym
ISSN Online: 2475-7349
ISSN Print: 2475-7330

NLRP3 Inflammasome in Relation to Glucose and Lipid Metabolism, and Insulin Resistance in Diabetes and Pre-Diabetes

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How to cite this paper: Hu, S.J., Liu, D., Zhang, Y.Q., Ding, Y.T., Li, B.Q. and Wang, X.W. (2023) NLRP3 Inflammasome in Relation to Glucose and Lipid Metabolism, and Insulin Resistance in Diabetes and Pre-Diabetes. *Yangtze Medicine*, **7**, 1-10.
https://doi.org/10.4236/ym.2023.71001

Received: January 4, 2023
Accepted: March 6, 2023
Published: March 9, 2023

Abstract

Aims: To investigate the relationship among NLRP3 inflammasome, glucose and lipid metabolism, and insulin resistance (IR) in the serum of patients with diabetes and pre-diabetes. **Methods:** A total of 100 patients with abnormal blood glucose divided into the pre-diabetes mellitus (PDM) group (N = 46) and the type 2 diabetes mellitus (T2DM) group (N = 54). 20 normoglycemic subjects (NG, N = 20) were selected as a control group. The serum levels of glucose and lipid metabolism, IR, and the expression of NLRP3, ASC and Caspase-1 were measured. Besides, the correlations of NLRP3 inflammasome with glucose and lipid metabolism, and IR were analyzed. **Results:** Compared with the NG group, the levels of NLRP3, ASC, Caspase-1, FBG, HbA_1C, TG, LDL-C, FINs, and HOMA-IR were higher ($P < 0.05$), while the contents of HDL-C and HOMA-β were lower ($P < 0.05$) in the serum of both PDM and T2DM groups. Elevated levels of NLRP3, ASC, Caspase-1, FBG, HbA_1C, FINs, and HOMA-IR were detected ($P < 0.05$), while decreased contents of HDL-C and HOMA-β were seen ($P < 0.05$) in T2DM group when compared with those in the PDM group. Correlation analysis found that activation of NLRP3 inflammasome was positively correlated with the concentrations of HbA_1C, FINs, and HOMA-IR ($P < 0.05$), but negatively correlated with HDL-C and HOMA-β. Regression analysis further showed that blood glucose related indexes, FINs, and NLRP3 have made a decisive contribution to IR. **Conclusions:** Collectively, this evidence suggested that NLRP3 is

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closely related to glucose and lipid metabolism, and IR, and activated in PDM and T2DM.

Keywords

Type 2 Diabetes Mellitus, Pre-Diabetes Mellitus, NLRP3, Glucose and Lipid Metabolism, Insulin Resistance

1. Introduction

According to the diabetes map released by the International Diabetes Federation in 2019, there are nearly 500 million diabetes patients in the world, and it is estimated that there will be 629 million diabetes patients in 2045 [1], more than 90% of them are type 2 diabetes mellitus (T2DM). Pre-diabetes mellitus (PDM) is a state in which blood glucose concentrations are between normal and diabetic hyperglycemia [2]. The prevalence of PDM in adults is 35.7%, and it is increasing year by year [2]. Due to the complex pathogenesis of diabetes, it is characterized that chronic inflammation and insulin resistance (IR) are pivotal factors for the occurrence and development of diabetes [3]. The roles of inflammasome and its related factors in diabetes and IR have attracted much attention, and have become important targets for the prevention and treatment of metabolic diseases [4] [5].

Nod-like receptor protein 3 (NLRP3) inflammasome is a multi-protein complex composed of the core member (NLRP3), apoptosis-associated spot-like protein (ASC), and Caspase-1 [6] [7]. Chronic inflammatory responses mediated by NLRP3 inflammasome and related factors play an important role in the progression of diabetes [5]. It was found that the levels of NLRP3 and Caspase-1 in the serum of diabetic patients were significantly increased, and correlated with the progression of diabetes [8] [9]. However, the activation of NLRP3 inflammasome in PDM patients, and the correlation among NLRP3 inflammasome, glucose and lipid metabolism, and IR remain unexplored. The aim of this study was to address the activation of NLRP3 inflammasome in both T2DM and PDM patients, and to analyze the relationship among NLRP3 inflammasome, glucose and lipid metabolism, and IR, thereby providing an important clue for the clinical prevention and alleviation of metabolic related diseases.

2. Materials and Methods

2.1. General Information

A total of 100 patients with abnormal blood glucose in the Second School of Clinical Medicine and Jingzhou Central Hospital of Yangtze University from April to August 2022 were selected. According to the Guidelines for the Diagnosis and Treatment of Diabetes issued by the American Diabetes Association (ADA) in 2019 [10], the patients were divided into the PDM group (N = 46) and

the T2DM group (N = 54). There were 16 males and 38 females in the PDM group with an age of (60.63 ± 6.44) years. There were 26 males and 20 females in the T2DM group with an age of (60.22 ± 6.07) years, and the disease duration was (7.09 ± 2.98) years. At the same time, 20 normoglycemic subjects (NG group) in the outpatient department of the hospital were selected as a control group. There were 10 males and 10 females in the NG group with an age of (58.50 ± 5.41) years. There was no significant difference in age among the groups ($P > 0.05$). The study was approved by the ethics committee of the Health Science Center of Yangtze University (approval number: YZLL2022-006).

2.2. Inclusion and Exclusion Criteria

Inclusion criteria: T2DM patients (N = 54), 1) Subjects with fasting blood glucose (FBG) > 125 mg/dL or plasma glucose after 2 hours (2 hPG) > 199 mg/dL. 2) Blood glucose ≥ 199 mg/dL at any time. 3) Age: 50 - 70 years old. PDM patients (N = 46), a) Subjects with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), defined as FBG 100 - 125 mg/dL or 2 hPG 140 - 199 mg/dL. b) Age: 50 - 70 years old. NG group (N = 20), i) Subjects with normal fasting glucose and normal glucose tolerance, defined as FBG < 100 mg/dL and 2 hPG < 140 mg/dL. ii) Age: 50 - 70 years old.

Exclusion criteria: Patients with type 1 diabetes mellitus, other special types of diabetes mellitus, abnormal liver and kidney function, tumor history and other serious diseases were excluded.

2.3. The Research Methods

Blood samples were collected from all subjects. Fasting for more than 8 hours was required. 5 ml of venous blood was extracted on an empty stomach in the next morning and centrifuged at 1000 r/min for 20 min with a radius of 12.8 cm, and 2 ml serum was collected. Serum levels of NLRP3, ASC and Caspase-1 were detected by an enzyme-linked immunosorbent assay (ELISA) kit (Sin-Troch, China). The operation was completed according to the kit instructions. The biochemical indexes including fasting insulin (FINs), total cholesterol (TC), triglyceride (TG), low-density cholesterol (LDL-C), high-density cholesterol (HDL-C) were measured with Hitachi 7600 automatic biochemical analyzer. FBG was measured by a Roche blood glucose meter. In addition, Hitachi 7170A automatic glycosylated hemoglobin analyzer was used to determine glycosylated hemoglobin (HbA_1C). To evaluate IR, the homeostatic model assessment for IR was calculated: HOMA-IR = (FBG × FINs)/22.5. To evaluate beta cell function, the homeostatic model assessment of beta cell function was calculated: HOMA-β = 20 × FINs/(FBG-3.5) [11].

2.4. Statistical Analysis

SPSS23.0 statistical software was used to process the measured data, and the experimental data were expressed as the mean ± standard deviation ($x \pm s$). Com-

parison among the three groups was performed by one-way ANOVA, and the LSD-T test was used for pairwise comparison between groups. Pearson method was used for correlation analysis, and linear regression was used for regression analysis. $P < 0.05$ or $P < 0.01$ means the difference is statistically significant.

3. Results

3.1. Clinical Data and Biochemical Indexes Analysis

One-way ANOVA was applied to analyze the related indexes of glucose and lipid metabolism, and IR in the NG, PDM and T2DM groups. As shown in Table 1, the results demonstrated that statistically significant differences in FBG, HbA_1C, TG, HDL-C, LDL-C, FINs, HOMA-IR, and HOMA-β ($P < 0.05$). Compared with the NG group, the levels of HbA_1C, TG, LDL-C, FINs, and HOMA-IR were higher ($P < 0.05$), HDL-C and HOMA-β were lower ($P < 0.05$) in the serum of either PDM or T2DM groups. Moreover, the contents of FBG, HbA_1C, FINs, and HOMA-IR were increased ($P < 0.05$), HDL-C and HOMA-β were decreased ($P < 0.05$) in the serum of the T2DM group when compared with those in the PDM group.

3.2. Activation of NLRP3 Inflammasome in the Patients with PDM and T2DM

To detect the expression of NLRP3 inflammasome in the serum of the NG, PDM and T2DM groups, ELISA assay was implemented. As shown in Table 2, the relative expression levels of NLRP3 in the NG, PDM and T2DM groups were (387.64 ± 34.87), (779.91 ± 124.63) and (841.04 ± 81.76), respectively. The expression levels of ASC were (327.21 ± 45.00), (651.64 ± 117.40) and (726.00 ± 79.95) in the NG, PDM and T2DM groups, separately. The Caspase-1 expression

Table 1. Clinical data and biochemical indexes.

Group	FBG (mmol/L)	HbA_1C (%)	TG (mmol/L)	TC (mmol/L)	HDL-C (mmol/L)
T2DM	9.64 ± 3.27[a,b]	8.70 ± 1.28[a,b]	2.68 ± 1.73[a]	5.09 ± 0.92	1.27 ± 0.26[a,b]
PDM	6.40 ± 0.28	6.17 ± 0.32[a]	2.20 ± 1.23[a]	5.18 ± 1.02[a]	1.80 ± 0.58[a]
NG	5.52 ± 0.34	5.59 ± 0.28	1.18 ± 0.27	4.66 ± 1.00	2.05 ± 0.39
P	0.000**	0.000**	0.000**	0.126	0.000**

Group	LDL-C (mmol/L)	FINs (μU/mL)	HOMA-IR	HOMA-β
T2DM	3.49 ± 0.73[a]	11.46 ± 2.23[a,b]	4.94 ± 2.11[a,b]	46.02 ± 20.93[a,b]
PDM	3.33 ± 0.67[a]	10.40 ± 2.28[a]	2.96 ± 0.68[a]	72.12 ± 16.04
NG	2.72 ± 0.68	7.15 ± 1.36	1.76 ± 0.37	73.27 ± 20.90
P	0.000**	0.000**	0.000**	0.000**

Note: **$P < 0.01$, *$P < 0.05$. [a]$P < 0.05$ vs. NG group; [b]$P < 0.05$ vs. PDM group.

were (37.39 ± 2.74), (67.32 ± 14.82) and (75.02 ± 8.12) in the NG, PDM and T2DM groups, respectively. Analysis of variance found that the differences were statistically significant among the NG, PDM and T2DM groups (P = 0.000). Compared with the NG group, the relative expression levels of NLRP3, ASC and Caspase-1 were higher in the PDM and T2DM groups (P < 0.01). The relative expression levels of NLRP3, ASC and Caspase-1 in the serum of the T2DM group were higher (P < 0.05) when compared with those the PDM group.

3.3. NLRP3 Inflammasome Is Closely Related to Glucose and Lipid Metabolism, IR

Correlation analysis is applied to address the relationship among the expression level of NLRP3 inflammasome, glucose and lipid metabolism, and IR. As shown in Table 3, the expression level of NLRP3 in the serum was positively correlated with ASC, Caspase-1, FBG, HbA_1C, FINs, and HOMA-IR (P < 0.01), and was negatively correlated with HDL-C and HOMA-β (P < 0.01). No significant correlation was detected between NLRP3 inflammasome with TC. The expression level of ASC was closely related to NLRP3, Caspase-1, FBG, HbA_1C, TG, LDL-C, FINs, and HOMA-IR (P < 0.01), especially positively correlated with NLRP3, Caspase-1, HbA_1C, FINs and HOMA-IR, and negatively correlated with HDL-C

Table 2. The expression levels of NLRP3 inflammasome in the serum of the NG, PDM and T2DM groups.

Group	NLRP3 (pm/ml)	ASC (pm/ml)	Caspase-1 (pm/ml)
T2DM	841.04 ± 81.76[a,b]	726.00 ± 79.95[a,b]	75.02 ± 8.12[a,b]
PDM	779.91 ± 124.6[a]	651.64 ± 117.40[a]	67.32 ± 14.82[a]
NG	387.64 ± 34.87	327.21 ± 45.00	37.39 ± 2.74
P	0.000**	0.000**	0.000**

Note: **P < 0.01, *P < 0.05. [a]P < 0.05 vs. NG group; [b]P < 0.05 vs. PDM group.

Table 3. Correlation among NLRP3 with inflammasome, glucose and lipid metabolism, and IR.

NLRP3	ASC	Caspase-1	FBG	HbA_1C	TC	TG	HDL-C	LDL-C	FINs	HOMA-IR	HOMA-β
r	0.701	0.700	0.337	0.473	0.107	0.222	−0.412	0.211	0.473	0.410	−0.266
P	0.000**	0.000**	0.000**	0.000**	0.245	0.015*	0.000**	0.021*	0.000**	0.000**	0.003**
ASC	**NLRP3**	**Caspase-1**	**FBG**	**HbA1C**	**TC**	**TG**	**HDL-C**	**LDL-C**	**FINs**	**HOMA-IR**	**HOMA-β**
r	0.701	0.609	0.380	0.511	0.264	0.288	−0.303	0.254	0.473	0.452	−0.266
P	0.000**	0.000**	0.000**	0.000**	0.004**	0.001**	0.001**	0.005**	0.000**	0.000**	0.003**
Caspase-1	**NLRP3**	**ASC**	**FBG**	**HbA1C**	**TC**	**TG**	**HDL-C**	**LDL-C**	**FINs**	**HOMA-IR**	**HOMA-β**
r	0.700	0.609	0.329	0.481	0.122	0.206	−0.503	0.246	0.484	0.415	−0.209
P	0.000**	0.000**	0.000**	0.000**	0.186	0.024*	0.000**	0.007**	0.000**	0.000**	0.022*

Note: **P < 0.01,*P < 0.05.

and HOMA-β ($P < 0.01$). The expression level of Caspase-1 was positively correlation with NLRP3, ASC, HbA_1C, FINs, and HOMA-IR ($0.4 < r < 0.7$), and negatively correlated with HDL-C and HOMA-β ($P < 0.05$). To sum up, NLRP3 inflammasome was positively correlated with HbA_1C, FINs, HOMA-IR, and negatively correlated with HDL-C and HOMA-β.

3.4. NLRP3 Act as an Important Affecting Factor for IR

To estimate the contribution of NLRP3 to IR, the linear regression analysis was applied. HOMA-IR and HOMA-β are commonly thought to be the representatives for IR [11]. As shown in Table 4, HOMA-IR was performed as the dependent variable, and FBG, HbA_1C, TG, HDL-C, LDL-C, FINs, HOMA-β, NLRP3, ASC, and Caspase-1 were used as the independent variables. The results indicated that FBG, FINs, and NLRP3 were important factors influencing HOMA-IR. Furtherly, linear regression analysis was performed with HOMA-β as the dependent variable, FBG, HbA_1C, TG, HDL-C, LDL-C, FINs, HOMA-IR, NLRP3, ASC, and Caspase-1 as the independent variables. We found that HbA_1C, FINs, and NLRP3 are crucial factors for HOMA-β (Table 5). Taken together, these results suggested that FBG, HbA_1C, FINs, and NLRP3 are vital factors for IR. Especially, NLRP3 is a key affecting factor for IR.

4. Discussion

IR and chronic inflammation are the main causes for the development of T2DM [12]. T2DM is closely related to abnormal glucose and lipid metabolism, IR, and islet function [13]. The results of this study confirmed that the contents of HbA_1C, TG, LDL-C, FINs, and HOMA-IR were enhanced, while HDL-C and HOMA-β were decreased in the serum of patients with PDM and T2DM, further suggesting that the abnormal levels of them is related to the occurrence of

Table 4. Regression analysis of HOMA-IR.

Factor	β	SE	t	P	95%CI
FBG	0.521	0.020	25.929	0.000**	0.481 - 0.561
HbA_1C	−0.029	0.025	−1.149	0.253	−0.079 - 0.021
TG	0.009	0.019	0.480	0.632	−0.028 - 0.046
HDL-C	0.017	0.055	0.309	0.758	−0.092 - 0.126
LDL-C	−0.003	0.035	−0.077	0.939	−0.071 - 0.066
FINs	0.350	0.018	19.446	0.000**	0.314 - 0.385
HOMA-β	−0.003	0.002	−1.129	0.262	−0.008 - 0.002
NLRP3	0.000	0.000	−2.068	0.041*	−0.001 - 0.000
ASC	0.000	0.000	−1.028	0.306	−0.001 - 0.000
Caspase-1	−0.002	0.002	−1.090	0.278	−0.007 - 0.002

Note: **$P < 0.01$,*$P < 0.05$.

Table 5. Regression analysis of HOMA-β.

Factor	β	SE	t	P	95%CI
FBG	−3.978	2.015	−1.975	0.051	−7.972 - 0.015
HbA_1C	−2.751	0.935	−2.943	0.004**	−4.604 - −0.898
TG	−0.049	0.706	−0.070	0.944	−1.449 - 1.350
HDL-C	−0.804	2.091	−0.384	0.701	−4.947 - 3.340
LDL-C	0.119	1.316	0.090	0.928	−2.489 - 2.726
FINs	7.017	1.283	5.468	0.000**	4.474 - 9.561
HOMA-IR	−4.095	3.628	−1.129	0.262	−11.286 - 3.096
NLRP3	−0.023	0.008	−2.930	0.004**	−0.039 - −0.007
ASC	−0.008	0.008	−0.984	0.327	−0.024 - 0.008
Caspase-1	−0.071	0.083	−0.862	0.390	−0.235 - 0.092

Note: **$P < 0.01$, *$P < 0.05$.

T2DM. In addition, FBG, HbA_1C, FINs, and HOMA-IR were increased, and HDL-C, HOMA-β were lower in the serum of the T2DM group when compared with those in the PDM group, indicating that the development of diabetes may be closely related to glucose and lipid metabolism, and IR.

The NLRP3 inflammasome is a multiprotein complex responsible for the activation of inflammatory responses and plays an important role in the development of innate immunity and inflammation-related diseases [5] [14]. Brown *et al.* found that the mRNA and protein levels of NLRP3, ASC, and Caspase-1 were elevated in diabetic rats from the 4^{th} or 8^{th} week of diabetes [15]. Luo *et al.* indicated that the expression levels of NLRP3, ASC, and Caspase-1 proteins were significantly increased in the serum and adipose tissue of the patients with T2DM [16]. Our data suggested that the expression levels of NLRP3, ASC, and Caspase-1 were upregulated not only in T2DM patients but also in PDM subjects. Moreover, the expression levels of NLRP3, ASC, and Caspase-1 were higher in the T2DM group when compared with those in the PDM group. Therefore, NLRP3 inflammasome complex is formed and activated in the patients with both T2DM and PDM.

The possible association with NLRP3 inflammasome and diabetes has been discussed previously [17]. Due to NLRP3 inflammasome could affect the blood glucose level and IR, which are related to the pathogenesis of diabetes [9] [17], and facilitating diabetes-induced systemic chronic inflammation and insulin signaling [18]. Ruscitti *et al.* demonstrated that hyperglycemia will lead to the upregulation of NLRP3 [19]. Rheinheimer *et al.* have been suggested that IR is associated with increased NLRP3 expression in adipose tissue [9]. In this study, we found that NLRP3 inflammasome is positively correlated with blood glucose and IR-related indicators, and negatively correlated with HDL-C and HOMA-β, suggesting that NLRP3 may involve in IR and the development of diabetes by regulating glucose and lipid metabolism. Moreover, the blood glucose related

indexes, FINs, and NLRP3 are crucial factors for IR. It is demonstrated that the increase of blood glucose level and activation of NLRP3 could lead to metabolic inflammation and IR. Therefore, the upregulation of NLRP3 in the serum of T2DM and PDM patients may contribute to the development of diabetes by regulating glucose and lipid metabolism, and IR. However, the sample size is small and the collection point is simple in this study.

Further studies are required to expand the sample size and collection range, and continue to explore the mechanism of NLRP3 inflammasome on glucose and lipid metabolism in the patients with T2DM and PDM. In addition, as the objects of study are T2DM and PDM, the expressions of inflammatory-related factors at different levels. It is suggested that it is more appropriate to study one kind of patients in the future. Finally, future studies need animal experiments to verify the relationship among NLRP3, glucolipid metabolism and IR.

5. Conclusion

NLRP3 inflammasome participates in systemic chronic inflammation and insulin signaling. This study found that NLRP3 inflammasome is activated in patients with both T2DM and PDM and closely related to glucose and lipid metabolism, and IR. In addition, studies revealing the contribution of NLRP3 in IR signaling. This may offer potential novel therapeutic perspectives in T2DM prevention and treatment.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Yangtze University Health Science Center (YZLL2022-006) and participants provided written informed consent.

Author Contributions

SJ and XW designed the study. SJ, Dang and XW drafted the manuscript. SJ, BQ and YT analyzed the data and filled the tables. XW and SJ revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The Teaching Research Project of Yangtze University (JY2020042, JY2020128), The Central Government guides local funds for scientific and Technological Development (XZ202201YD0024C), Key R & D Program of Hubei Province (2021BGD010), Hubei Province Scientific and Technological Research Project (D20201306), Hubei Medical Youth Tip-Top Talent (to XW Wang).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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