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Original Article

Association between IL-6 and related risk factors of metabolic syndrome and cardiovascular disease in young rats

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Abstract: Objective: Metabolic syndrome (MS) is conceived as the pathogenic basis of an increased cardiovascular burden. We investigate the correlation between interleukin-6 (IL-6) and the risk factors of MS and cardiovascular disease (CVD) in diet-induced model of MS and determined whether IL-6 was associated with the prevalence of MS and cardiovascular disease. Methods: A total of 40 Spague-Dawley (SD) rats were randomly divided into high-fat and high salt (FSC) group, high-fat (FC) group and normal control (NC) group. After feeding for 7 weeks, fasting blood glucose (FBG) and fasting insulin (FIN) were measured at the 60 min, 120 min and 180 min after the glucose administration. Blood pressure, body weight, height, waist circumference (WC), liver weight, visceral fat weight as well as blood lipid profile were determined at the end of 7-week. Furthermore, IL-6 levels from adipose tissues were analyzed using ELISA, and the correlation between IL-6 and the risk factors of MS and cardiovascular disease was investigated. Results: After treatment with different diets, significant difference was noted in the WC, body mass index (BMI), visceral fat weight and liver weight of FSC group compared with those of NC group ($P<0.05$). The levels of systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triacylglycerol (TG) and low density lipoprotein (LDL) were markedly elevated in FSC group compared with those in NC group, while the level of high density lipoprotein (HDL) was remarkable lower in FSC group ($P<0.05$). After glucose administration, the concentrations of blood glucose and insulin were significant higher in FSC group than those in NC group at different time points ($P<0.05$). Moreover, high-fat and high salt diet brought about significant elevation of IL-6 compared with that with normal or high-fat diet in SD rats. Furthermore, IL-6 was significantly associated with FIN, HOMA-IR, LDL, TC, TG, HDL, visceral fat mass and body weight in FSC group, while IL-6 was markedly correlated with TC, LDL, TG, visceral fat mass and body weight ($P<0.05$). Conclusion: A characteristic rat model of MS may be induced by the high-fat and high-salt diet. IL-6 may be considered as an early and representative marker in the pathogenesis of MS and related cardiovascular burden.

Keywords: IL-6, metabolic syndrome, cardiovascular disease, animal model, obesity

Introduction

Metabolic syndrome (MS) is a complex disorder with the co-occurrence of three or more metabolic abnormalities, including obesity, insulin resistance, hypertension, hyperglycemia, and dyslipidemia [1]. The prevalence of MS is increasing rapidly with affecting 20~25% of the adult population worldwide probably as a result of prolonged life expectancy and obesity, population aging and deficient nutrition [2, 3]. Currently, it has been acknowledged that patients with MS showed increased risks of cardiovascular disease (CVD) [4], type 2 diabetes [5], and renal damage [6]. Thus, it is reasonable to speculate that the prediction of MS may play a vital role in the early prevention and interference of the related diseases.

To our knowledge, MS-associated metabolic abnormalities are generally prone to be initiated from juvenile stage especially those with overweight and obesity. Therefore, it is urgent to establish an animal model to understand the pathogenesis, physiological changes and diagnosis of MS. To date, animal model of individual disease has been well established involving obesity, hypertension and diabetes mellitus [7, 8]. However, the study of MS with such models is not satisfactory due to the unilateral involve-

ment. The introduction of diet-induced MS model with high-fat and high-salt has attracted increasing concern for the better comprehension of MS.

Adipose tissues are considered to involve in the release of several inflammatory and immune mediators. The onset of MS and CVD is thought to be partly mediated by aberrant expression of adipokines, especially IL-6 [9]. As a pleiotropic cytokine, IL-6 plays an important role in various metabolic processes as an autocrine and/or paracrine actions of adipocyte function [10]. At present, accumulating evidences have demonstrated that IL-6 is closely linked to metabolic disorders such as MS and type 2 diabetes. Meanwhile, elevation of IL-6 have been documented in adipose tissues of patients with diabetes mellitus or obesity, particularly in those with features of MS [11]. Eckel et al believed that the increase of IL-6 in MS appeared to act on several key factors, which contributed to insulin resistance, elevated glucose production in liver, together with inhibition of the insulin mediated glucose uptake in skeletal muscle and the facilitation of hypertension [12]. Furthermore, IL-6 gene polymorphism is regarded as an aggravating factor in the development and progression of cardiovascular events [13]. Taken together, IL-6 may be considered as a significant prognostic indicator of risk of MS and cardiovascular dysfunction.

In this study, an infant rat model of MS was established through feeding with high fat and salt diet. The related metabolic parameters of MS were examined, including the levels of blood lipid profile, fasting blood glucose and insulin. The expression of IL-6 in visceral adipose tissues was determined, and the correlation of IL-6 and the risk factors of MS and CVD was further analyzed, based on which to investigate the role of IL-6 in the pathogenesis of MS and CVD, as well as early intervention of clinical therapy.

Materials and methods

Experimental design

A total of 40 weaned rats at 21 days of age were enrolled in this study. All rats were randomly divided into three groups after stratifying by weight. The rats were subjected to feed with high-fat and high salt diet (FSC group, n=14), high-fat diet (FC group, n=14), and normal diet (NC group, n=12) for 7 weeks, respectively. All rats were kept in cages under controlled condition of stable humidity (50%), temperature (23-26°C) with a 12/12 h light and dark cycle. All animals were free access to food and water. The study protocols were approved by the Ethical Committee of Tianjin Medical University.

Detection of physical index

Fasting blood glucose (FBG) was measured using a blood glucose minotir (YSI Inc, Yellow Springs, Ohio, USA). Fasting insulin (FIN) was determined using commercial ELISA kit (R&D Systems Inc., Minneapolis, Minnesota, USA). In brief, oral glucose tolerance test (OGTT) was conducted at week 7 after food deprivation. Afterwards, glucose (2 g/kg body weight) was given by gastric probe using a 50% glucose solution. The glucose and insulin concentration was measured followed by blood taken from tail vein at 60 min, 120 min and 180 min after glucose administration. Insulin resistance index (HOMA-IR) was calculated as follows: HOMA-IR = FIN × FBG/22.5. Meanwhile, blood pressure was measured from tail artery using blood pressure monitor (Chengdu Tai Meng Science and Technology Co., Ltd., Chengdu, China) at week 7. Measurement of blood lipid profile was performed at the end of 7-week after 12 h fasting, including total cholesterol (TC), triacylglycerol (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL). In addition, body weight, height, waist circumference (WC), liver weight and visceral fat weight (perirenal fat and epididymal fat) were measured. Afterwards, visceral adipose tissues were stored in -80°C for further study.

ELISA assay

IL-6 levels from adipose tissues were analyzed using quantitative ELISA kits purchased from R&D Systems Inc (Minneapolis, Minnesota, USA). ELISA was performed strictly according to the manufacturer's instructions. The absorbance was measured at 450 nm using a microplate reader (Wellscan MK3, Labsystems Dragon, Finland). Each sample was tested in duplicate and the coefficient of intra-assay variation among the duplicates was <10%. The cytokine concentrations were calculated from the standard curves by using linear regression analysis.

Table 1. Obesity related index for all rats

Group	N	WC	BMI	Visceral fat weight	Liver weight
FSC	14	7.33±0.62*,Δ	0.60±0.03*	2.53±0.09*,Δ	9.06±0.58*,Δ
FC	14	16.79±0.73	0.61±0.03*	1.99±0.09*	7.62±0.33*
NC	12	16.01±0.53	0.57±0.03	1.47±0.16	6.96±1.20

Compared with NC group, *P<0.05; Compared with FC group, ΔP<0.05.

Statistical analysis

Data analysis was performed with SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviations (SD). Student-Newman-Keuls test and one way analysis of variance (ANOVA) were carried out for the paired and multiple comparison, respectively. Pearson and Spearman correlation coefficients were calculated to determine the correlation degree between IL-6 and risk factors of MS. P<0.05 was considered as statistical difference.

Results

Obesity related index

Table 1 summarized obesity related index in three groups. Significant difference was noted in WC, BMI, visceral fat weight and liver weight of FSC group compared with those of NC group (P<0.05). The items of BMI, visceral fat weight and liver weight were markedly higher in FC group than those of NC group (P<0.05). Compared with FC group, significant difference was identified in WC, visceral fat weight and liver weight of FSC group (P<0.05). Furthermore, the appearance of liver was compared between FSC group and NC group. Remarkable color loss was noted in liver of FSC group in comparison with that of NC group (**Figure 1**).

Comparison of blood pressure

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly increased in FSC group compared with those in FC group and NC group (P<0.05). However, no statistical difference was identified in the SBP and DBP between the FC group and NC group (**Figure 2**).

Blood lipid biochemistry

Table 2 showed blood lipid related index for all rats. The levels of TC, TG and LDL were markedly elevated in FSC group than those in NC group. The level of HDL was significant lower in FSC group compared with the NC group and FC group (P< 0.05, **Table 2**). Compared with NC group, significant increase was noted in TC, TG and LDL of FC group (P<0.05). Moreover, the level of LDL was remarkable higher in FSC group than that in FC group (P<0.05).

Assessment of insulin resistance

Significant increase was noted in FBG in FSC group compared with that in NC group at different time points (P<0.05). After glucose administration, the concentration of blood glucose was significantly higher in FC group than that in normal group at 60 min (P<0.05), while significant elevation was noted in FSC group compared with that in FC group at 120 min (P<0.05, **Table 3**). Moreover, the levels of insulin were compared when treated with different diets (**Table 4**). The results indicated that insulin concentrations were significantly increased in FSC group in comparison with those in NC group (P<0.05). Compared with FC group, significant increase was identified in the levels of insulin in FSC group at the time of 60 min, 120 min and 180 min, respectively (P<0.05).

Expression of IL-6 in adipose tissue

Table 5 showed the level of IL-6 after treatment with different diets. After comparison of IL-6 level in visceral adipose tissue, significant elevation was revealed in the IL-6 level of FSC group and FC group compared with that in NC group (P<0.05). Furthermore, IL-6 level was remarkable higher (P<0.05) in FSC group than that in FC group.

Correlation of IL-6 and risk factors in MS and cardiovascular

Tables 6 and **7** presented the correlation of IL-6 and various risk factors of MS in FSC group and FC group, respectively. Significant positive correlation was identified between IL-6 and FIN, HOMA-IR, LDL, TC, TG, visceral fat mass and body weight, while IL-6 was negatively related to HDL in FSC group (P<0.05). However, no significant correlation was noted between IL-6 and blood pressure, UA and FBG. For the FC group,

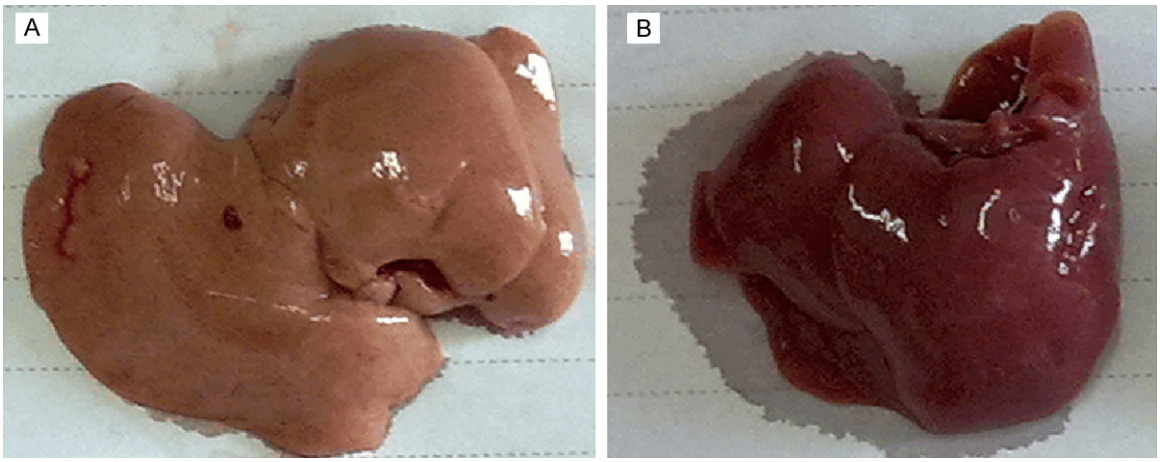

Figure 1. Comparison of liver size in FSC group (A) and NC group (B).

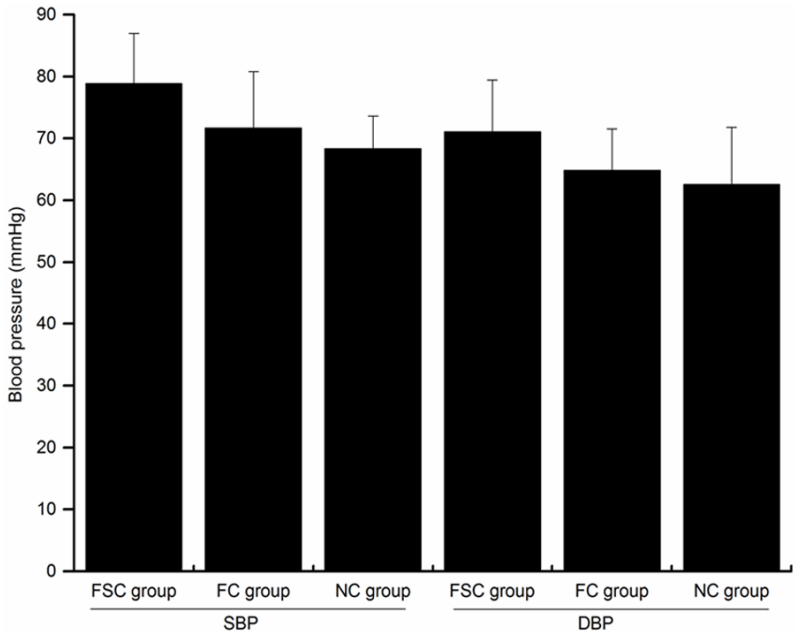

Figure 2. Blood pressure in three groups. SBP, systolic blood pressure; DBP, diastolic blood pressure.

IL-6 was positively associated with TC, LDL, TG, visceral fat mass and body weight ($P<0.05$).

Discussion

MS has been recognized as important risk factors for the morbidity and mortality of diabetes and cardiovascular diseases. The prevalence of MS varies depending on the criteria used in different definitions. However, the incidence of MS is high and increasing worldwide as a consequence of obesity epidemic [14, 15]. MS is more likely to develop in Asians than the counterparts in Europe and America [16]. Chinese population based studies showed a high prevalence of MS which has reached up to 21.3% as given in the China Health and Nutrition Survey [17]. To date, the occurrence of MS in children and adolescents is increased markedly with the increased obesity incidence and altered lifestyle [18]. With the high prevalence of MS in overweight adolescents, coupled health threat should attract our attention and precaution [19]. Although the specific mechanism of MS remains unclear, strong evidences have been presented for hormone regulation and molecular etiology in its pathophysiology [20].

Animal model is an essential and indispensable prerequisite for the experimental study of MS. Currently, transgenic mice and diet-induced mice are frequently served as animal models for the research of MS and correlated diseases [21]. In this study, the establishment of model was based on the onset period of childhood obesity and integration various characteristics of metabolic disorders. An infant rat model of MS was successfully established through feeding high fat and high salt diet. After treatment with high fat and high salt diet for 7 weeks, remarkable elevation was noted in the WC, BMI, visceral fat weight and liver weight in

Table 2. Blood lipid related index in three groups

Group	N	TC	TG	LDL	HDL
FSC	14	4.01±0.40*	1.02±0.05*	2.11±0.12*,Δ	0.73±0.04*
FC	14	3.82±0.29*	0.97±0.04*	1.99±0.28*	0.98±0.08
NC	12	3.22±0.08	0.81±0.03	0.94±0.04	1.11±0.06

Compared with NC group, $^{*}P<0.05$; Compared with FC group, $^{\Delta}P<0.05$.

Table 3. Blood glucose concentration at different time points in three groups

Group	N	Blood glucose (mmol/L)			
		0 min	60 min	120 min	180 min
FSC	14	4.30±0.48*	7.59±0.06*	8.63±0.05*,Δ	5.97±0.08*
FC	14	4.17±0.04	7.77±0.06*	7.95±0.57	5.74±0.06
NC	12	3.96±0.11	7.12±0.05	8.21±0.09	5.68±0.9

Compared with NC group, $^{*}P<0.05$; Compared with FC group, $^{\Delta}P<0.05$.

Table 4. Insulin concentration at different time points in three groups

Group	N	Insulin (μIU/mL)			
		0 min	60 min	120 min	180 min
FSC	14	52.23±0.68*	61.7±0.88*,Δ	79.53±2.72*,Δ	44.38±1.10*,Δ
FC	14	44.59±0.69	57.43±0.48	62.63±1.21	38.26±1.15
NC	12	42.73±6.58	54.42±0.75	61.21±1.1	37.37±5.62

Compared with NC group, $^{*}P<0.05$; Compared with FC group, $^{\Delta}P<0.05$.

Table 5. IL-6 level in adipose tissue of three groups

Group	N	Mean ± SD	F value	P
FSC	14	0.23±0.04*,Δ	24.13	0.000
FC	14	0.18±0.02*		
NC	12	0.15±0.04		

Compared with NC group, $^{*}P<0.05$; Compared with FC group, $^{\Delta}P<0.05$.

these rats compared with those with normal diet. The levels of blood pressure (i.e. SBP and DBP), and TC, TG and LDL were markedly raised in FSC group compared with those in NC group, while the level of HDL was significant decreased when treated with high fat and high salt diet in SD rats. Furthermore, the concentrations of blood glucose and insulin were apparently higher in FSC group than those in NC group at 60 min, 120 min and 180 min. On this basis, the diet with high fat and high salt provided an alternative option for the successful induction of MS model in infant rats.

IL-6, a circulating multifunctional cytokine, is one of most common effectors in response to different types of inflammatory insults [22]. It is considered to be a key mediator in both low-grade inflammatory process and the onset of inflammatory crisis. Large epidemiologic studies have demonstrated that increased levels of IL-6 are associated with several diseases such as hypertension, malnutrition, cardiovascular events and atherosclerosis [23, 24]. It was reported that chronic elevation of IL-6 in the systemic circulation was consistently linked with an increased risk of cardiovascular morbidity and mortality in the independent of other factors of systemic inflammation [25].

To date, great concerns have been raised about the role of IL-6 in MS and CVD since IL-6 appears to be involved in the occurrence and development of all components in MS such as hypertension, insulin resistance, obesity and lipid dysmetabolism. Meanwhile, interaction of IL-6 and each constituent may bring about vicious spiral with a concomitant of disease deterioration.

High blood pressure is a frequent component of MS and generally associated with central obesity and insulin resistance [26]. Over 85% patients with MS exhibit high blood pressure or systemic arterial hypertension. The prevalence of MS appeared to be 6 times in hypertension population, with 14 times increased risk of MS in hypertensive patients as compared to those non-hypertensive individuals [27]. Previous data showed that the increase of IL-6 played a crucial role in the pathogenesis of hypertension in response to the reductions in uterine perfusion pressure [28]. Another report indicated that IL-6 was significantly elevated in adult patients with hypertension and the increase was more marked in those with obesity [29]. In this study, no correlation was noted in the IL-6 and blood pressure in FSC group, which may be induced by the simple sample data and artifi-

Table 6. Correlation of IL-6 and various risk factors of MS and cardiovascular in FSC group

Variable	r_s	*P* value
SBP	0.211	>0.05
DBP	0.154	>0.05
TC	0.896	<0.05
TG	0.887	<0.05
HDL	-0.912	<0.01
LDL	0.866	<0.01
FIN	0.732	<0.05
FBG	0.183	>0.05
HOMA-IR	0.712	>0.05
Body weight	0.862	<0.05
Visceral fat mass	0.935	<0.01
UA	0.208	>0.05

Table 7. Correlation of IL-6 and various risk factors of MS and cardiovascular in FC group

Variable	r_s	*P* value
SBP	0.119	>0.05
DBP	0.440	>0.05
TC	0.862	<0.05
TG	0.975	<0.05
HDL	0.642	>0.05
LDL	0.974	<0.05
FIN	0.331	>0.05
FBG	0.059	>0.05
HOMA-IR	0.233	>0.05
Body weight	0.946	<0.05
Visceral fat mass	0.924	<0.05
UA	0.532	>0.05

cial measurement errors. Repeated tests with large sample are essential for the further verification.

Insulin resistance is a determining factor and early feature in the development of MS. It is frequently linked to a range of comorbidities such as obesity, type 2 diabetes and atherosclerotic diseases [30]. Low-grade inflammation has been proposed to be associated with insulin resistance [31]. Currently, extensive studies have been focused on the physiological and pathological effects of IL-6 on insulin resistance since IL-6 is one of the major cytokines in low-grade inflammation. Elevated circulating level of IL-6 was closely related to insulin resistance and type 2 diabetes [32, 33]. In addition, chronic IL-6 treatment resulted in insulin resistance with the increase of blood glucose and impairment of insulin tolerance [34]. Moreover, IL-6 administration promoted energy expenditure and systemic insulin sensitivity in a diet-induced obesity mouse model [35]. In the present study, we found that IL-6 in adipose tissue was positively associated with fasting insulin, raising the possibility that the role of IL-6 on insulin resistance may serve as blasting fuse in the development of MS.

Obesity, particularly visceral fat, is an important link among the components of MS as visceral fat is highly active involving in metabolic aspect. Under normal conditions, metabolic activation of adipose tissue contributes to the secretion of biological cytokines capable of regulating immunological responses and autocrine and paracrine signaling [36]. Increased and sustained production of IL-6 was presented in obese patients and experimental animals [37]. Roytblat et al suggested that IL-6 levels were elevated in obese in comparison with those in non-obese individuals [38]. Furthermore, previous reports demonstrated that IL-6 levels were positively associated with BMI and percent fat mass [36, 39]. In this study, significant correlation was noted between IL-6 and body weight and adipose tissue mass in FSC group and FC group. Moreover, IL-6 appeared to be more relevant to adipose tissue, which was consistent with previous study [40]. All these results suggested that the level of IL-6 was closely related to obesity, particularly with the visceral fat deposition in the development of early MS or simple obesity.

Dyslipidaemia is one of components in MS and CVD, and is a well acknowledged risk factor for the progression of atherosclerosis [41]. Decreased HDL and raised TG were accompanied by the increased levels of IL-6, cortisol and C-reaction protein [42]. Clinical trials indicated that blocking IL-6 resulted in the elevation of cholesterol in patients with rheumatoid arthritis, suggesting that functional lack of IL-6 may lead to an atherogenic lipid profile [43]. In our study, we found that IL-6 in adipose tissue was positively associated with TC, TG and LDL in FSC group and FC group. Moreover, a negative correlation was identified between IL-6 and HDL in SD rats with high fat and high salt diet, indicating the intimate connection of IL-6 and blood lipid profile in the stage of early MS and simple lipid disorder.

In conclusion, animal model of MS is successfully established after treatment with high fat and high salt diet. IL-6 in adipose tissue is strongly associated with fasting insulin, blood lipid profile, body weight and visceral fat mass in SD rats of MS, based on which suggests that IL-6 may be served as an early and typical marker in the pathogenesis and development of MS and cardiovascular events.

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Disclosure of conflict of interest

None.

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