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Plasma interleukin-22 levels are associated with prediabetes and type 2 diabetes in the Han Chinese population

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ABSTRACT

Aims/Introduction: The objective of the present study was to investigate the relationship between plasma interleukin-22 (IL-22) levels and prediabetes or type 2 diabetes, and search the relevance between plasma concentrations of IL-22 and selected diabetes risk factors in Chinese people.

Materials and Methods: The Han Chinese origin men and women participants were recruited in our study during a conventional medical checkup. Fasting plasma IL-22 levels were detected by enzyme-linked immunosorbent assay, and their relevance with selected diabetes risk factors was explored. Multiple logistic regression analysis was carried out to assess the odds ratio of impaired fasting glucose (IFG) and type 2 diabetes according to plasma IL-22 level.

Results: Compared with normal glucose participants (250 pg/mL [interquartile range 154–901]), the plasma IL-22 levels in IFG participants (185 pg/mL [interquartile range 145–414]) and type 2 diabetes participants (162 pg/mL [interquartile range 128–266]) were significantly lower ($P < 0.05$, $P < 0.001$, respectively). Correlation analysis showed that plasma concentrations of IL-22 were negatively associated with some diabetes risk factors, including body mass index, glucose, systolic blood pressure, diastolic blood pressure and triglyceride. Furthermore, the plasma concentrations of IL-22 showed a highly significant association with IFG and type 2 diabetes.

Conclusions: In Chinese subjects, the plasma concentration of IL-22 is profoundly associated with susceptibility to IFG and type 2 diabetes, and decreased plasma IL-22 level is a potential trigger of IFG and type 2 diabetes.

INTRODUCTION

Type 2 diabetes mellitus is a complex disease that is characterized by insulin resistance and a relative lack of compensatory pancreatic insulin secretion. During the past few decades, the prevalence of diabetes has increased dramatically in China[1,2]. Up to now, the underlying pathophysiology of type 2 diabetes mellitus remains unclear, but it has been closely linked to inflammation. Some recent studies have shown that chronic low-grade inflammation is a critical factor in the course of development of type 2 diabetes mellitus[3–5].

Interleukin-22 (IL-22) is a cytokine of the IL-10 family, and is predominantly expressed by innate lymphoid cells and activated CD4+ T helper subsets, such as T helper type 17 (TH17) and TH22 cells[6–9]. Although IL-22 has 22% homology with IL-10, IL-22 and IL-10 have certain differences in the role of inflammation. In contrast to the anti-inflammatory effects of IL-10, IL-22 has apparently contradictory roles in inflammation[10,11]. IL-22 can induce the expression of anti-inflammatory proteins, such as IL-11 and follistatin, which can protect against tissue damage, and regulate inflammation and autoimmunity. Meanwhile, IL-22 can also induce the expression of pro-inflammatory cytokines, such as IL-6 and chemokines, which might exacerbate the inflammatory disease process[12]. For example, IL-22 plays a beneficial role in wound healing and defense against infection in the skin, but it promotes inflammation in psoriasis[13,14].

Recently, some researchers have found a novel role for IL-22 in improving metabolic disorders. Hasnain *et al.*[15] showed that

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IL-22 suppressed endoplasmic reticulum stress and inflammation, and protected the insulin β-cells; promoted secretion of efficacious insulin; then fully restored glucose homeostasis in mice. Another recent study by Wang *et al.*[16] reported that IL-22 can preserve the integrity of the gut mucosal barrier, and improve the endotoxemia and chronic inflammation in obese mice. Further study found that intraperitoneal injection of IL-22 can significantly improve glucose and lipid metabolism, and insulin resistance in different animal models of diabetes. Furthermore, compared with control mice, IL-22 receptor-deficient mice are prone to developing glucose intolerance and insulin resistance feeding with high-fat diet[16].

In animal studies, IL-22 has a significant effect on glucose and lipid metabolism. However, in humans, whether IL-22 level also affects glucose and lipid metabolism remains unclear. Therefore, we carried out the present study to investigate plasma IL-22 levels among the different glucose metabolism disorder categories, and furthermore, to explore the relevance between plasma IL-22 levels and selected diabetes risk factors in Chinese people.

METHODS

Ethics statement

The study was an observational study, and did not influence the patients' diagnosis or treatment. Before participating in the study, all participants signed the informed consent form. The study protocol was in accordance with the Declaration of Helsinki, and approved by the ethics committee of Drum Tower Hospital Affiliated to Medical School of Nanjing University.

Study participants

From 2013 through 2014, Han Chinese men and women were recruited during a conventional medical checkup from the Physical Examination Center in Drum Tower Hospital Affiliated to Medical School of Nanjing University, Nanjing, Jiangsu, China. Impaired fasting gluose (IFG) and diabetes were diagnosed according to the American Diabetes Association diagnostic criteria (1997).[17] Fasting plasma glucose (FPG) of 6.1–7.0 mmol/L was defined as IFG, and FPG ≥7.0 mmol/L was diagnosed as diabetes. FPG concentration <6.1 mmol/L was defined as normal glucose (NG). Information for the participants' medical history, medication history and psychosocial factors was obtained through interviews using a questionnaire. The exclusion criteria for recruitment of participants were suffering from the following diseases or conditions: pregnancy, heart diseases, mental disorders, acute infectious disease, hepatitis virus, cirrhosis, cancer and received anti-inflammatory drugs in the most recent month. All recruited participants in the study were given a comprehensive physical examination, and underwent the blood and urine routine analysis.

Anthropometric and biochemical measurements

The height and weight of all participants were measured, and then the body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured in the sitting position following the standard operating procedures. After overnight fasting, venous blood samples were obtained from all participants. Then, some related blood biochemical indexes, including alanine aminotransferase, aspartate

Table 1 | Baseline characteristics among participants with normal glucose, impaired fasting glucose and type 2 diabetes mellitus

Characteristics	NG (106)	IFG (107)	Type 2 diabetes mellitus (105)
Male (%)	69.8	71.0	69.5
Age (years)	45.09 ± 13.15	57.68 ± 14.05***	57.09 ± 13.82***
BMI (kg/m^2)	23.91 ± 3.35	25.57 ± 3.09***	25.91 ± 3.27***
FPG (mmol/L)	5.03 ± 0.54	6.49 ± 0.25***	8.96 ± 2.31***,†††
TG (mmol/L)	1.58 ± 0.81	2.13 ± 1.48**	2.58 ± 2.89**
TC (mmol/L)	4.84 ± 0.84	4.79 ± 1.02	4.82 ± 0.99
HDL-C (mmol/L)	1.17 ± 0.31	1.13 ± 0.32	1.08 ± 0.29*
LDL-C (mmol/L)	2.69 ± 0.65	2.66 ± 0.76	2.63 ± 0.78
SBP (mmHg)	123.10 ± 18.27	137.97 ± 17.03***	138.40 ± 17.85***
DBP (mmHg)	77.83 ± 12.08	86.21 ± 9.93***	85.30 ± 10.50***
ALT (U/L)	27.17 ± 16.73	32.01 ± 22.33	32.57 ± 26.92
AST (U/L)	23.61 ± 10.13	25.50 ± 13.03	25.47 ± 17.06
GGT (U/L)	29.44 ± 21.91	46.13 ± 58.10*	37.15 ± 27.30*
IL-22 (pg/mL)	250 (154–901)	185 (145–414)*	162 (128–266)***

Data are mean ± standard deviation, medians (interquartile range) or percentages. Data were analyzed using the unpaired Student's *t*-test, χ^2-test and Mann–Whitney test as appropriate, and multiple testing was corrected using the Bonferroni correction. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ impaired fasting glucose (IFG) vs normal glucose (NG), †††$P < 0.001$ IFG vs type 2 diabetes mellitus. ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, glutamyltranspeptidase; HDL-C, high-density lipoprotein cholesterol; IL-22, interleukin-22; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 2 | Baseline characteristics of subjects according to quartile groups of plasma interleukin-22 levels

Characteristics	Quartiles of IL-22 levels				
	Quartile 1 (n = 80) (lowest)	Quartile 2 (n = 79)	Quartile 3 (n = 80)	Quartile 4 (n = 79) (highest)	P-value for trend*
Male (%)	73.8	68.4	66.3	72.2	0.759
Age (years)	51.19 ± 13.30	56.78 ± 15.78	54.90 ± 15.46	50.29 ± 14.04	0.640
BMI (kg/m^2)	25.66 ± 3.17	25.23 ± 3.00	25.16 ± 3.67	24.45 ± 3.46	0.016
FPG (mmol/L)	7.31 ± 2.18	6.97 ± 2.38	6.72 ± 1.89	6.26 ± 1.89	<0.001
TG (mmol/L)	2.73 ± 3.29	1.91 ± 0.98	1.91 ± 1.42	1.81 ± 1.09	0.025
TC (mmol/L)	4.82 ± 0.97	4.93 ± 0.90	4.78 ± 1.04	4.73 ± 0.90	0.393
HDL-C (mmol/L)	1.08 ± 0.34	1.17 ± 0.34	1.13 ± 0.27	1.14 ± 0.27	0.093
LDL-C (mmol/L)	2.60 ± 0.80	2.76 ± 0.66	2.67 ± 0.76	2.61 ± 0.70	0.945
SBP (mmHg)	134.33 ± 19.43	136.51 ± 18.81	132.94 ± 19.98	128.85 ± 17.50	0.036
DBP (mmHg)	84.69 ± 11.13	85.73 ± 12.06	81.04 ± 10.43	81.01 ± 11.69	0.011
ALT (U/L)	30.27 ± 15.63	29.50 ± 17.16	31.36 ± 30.38	31.20 ± 23.92	0.266
AST (U/L)	23.53 ± 6.85	24.08 ± 7.44	26.84 ± 21.27	24.97 ± 13.95	0.911
GGT (U/L)	38.97 ± 48.82	35.37 ± 29.12	40.31 ± 48.80	35.71 ± 27.74	0.420

Data are mean ± standard deviation, medians (interquartile range) or percentages. *P-value by ANOVA for continuous variables and χ^2-test for categorical variables. ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, glutamyltranspeptidase; HDL-C, high-density lipoprotein cholesterol; IL-22, interleukin-22; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

transaminase, glutamyltranspeptidase, FPG, triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol were determined by the Beckman Coulter clinical chemistry system (Pasadena, California, USA). Plasma concentrations of IL-22 were determined using a human IL-22 ELISA Kit (Bioassay Technology Laboratory, Shanghai, China) according to the manufacturer's instructions (intra-assay: coefficient of variation <10%; inter-assay: coefficient of variation <12%).

Statistical analysis

Continuous data were presented as the mean ± standard deviation, or median with interquartile range (IQR), where indicated. Differences between groups were evaluated using the unpaired Student's t-test for normally distributed data, and the Mann–Whitney test for data with skewed distributions. Multiple testing was corrected using the Bonferroni correction. The trends in categorical data were compared using the trend test. Multiple logistic regression analysis was carried out to assess the odds ratio (OR) for the incidence of the IFG and type 2 diabetes mellitus according to quartile groups of plasma IL-22 level (in comparison with quartile 4). Four statistical models were used. The preliminary model was crude and considered plasma IL-22 level only, whereas model 1 was adjusted for age, sex and BMI, and model 2 was adjusted for model 1 plus systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, total cholesterol, HDL-C and low-density lipoprotein cholesterol. Model 3 was adjusted for the variables in models 2 plus alanine aminotransferase, aspartate transaminase and glutamyltranspeptidase. All data were analyzed with the Stata/SE statistical software version 12.0 (Stata Corporation, College Station, Texas, USA).

Table 3 | Spearman's correlation coefficients between interleukin-22 level (pg/mL) and baseline characteristics in all participants

Characteristics	Coefficients	P-value
Male (%)	0.010	0.860
Age (years)	–0.039	0.487
BMI (kg/m^2)	–0.143	0.011
FPG (mmol/L)	–0.245	<0.001
TG (mmol/L)	–0.138	0.014
TC (mmol/L)	–0.073	0.193
HDL-C (mmol/L)	0.0920	0.102
LDL-C (mmol/L)	–0.014	0.804
SBP (mmHg)	–0.120	0.032
DBP (mmHg)	–0.150	0.008
ALT (U/L)	–0.095	0.091
AST (U/L)	–0.036	0.520
GGT (U/L)	–0.075	0.181

ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, glutamyltranspeptidase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

P-values were two-sided, and <0.05 was considered to show statistically significant differences.

RESULTS

Plasma IL-22 levels in the NG, IFG and type 2 diabetes mellitus groups

A total of 105 type 2 diabetes mellitus cases, 107 IFG cases and 106 NG participants were included in the present study cohort. IFG and type 2 diabetes mellitus participants had a higher BMI

and older age in comparison with NG participants (all $P < 0.001$). Except for the aforementioned factors, in terms of biochemical risk factors for type 2 diabetes, including TG, SBP, DBP and glutamyltranspeptidase, IFG and type 2 diabetes mellitus participants had significantly higher levels of all of these markers than NG participants. Furthermore, type 2 diabetes mellitus participants had significantly lower levels of HDL-C than NG participants. In all participants, fasting plasma IL-22 levels ranged from 64 to 2,132 pg/mL, and without sex differences ($P = 0.859$). Compared with NG participants (250 pg/mL [IQR 154–901]), fasting plasma IL-22 levels in IFG participants (185 pg/mL [IQR 145–414]) were significantly lower ($P < 0.05$), and fasting plasma IL-22 levels in type 2 diabetes mellitus participants (162 pg/mL [IQR 128–266]) were even lower in comparison with NG participants ($P < 0.001$; Table 1). Next, we carried out a subgroup analysis according to the plasma IL-22 levels. Table 2 shows the baseline characteristics of the study participants according to the plasma IL-22 level grouped by quartile. We observed that participants with decreased plasma IL-22 levels tended to show statistically significant linear elevated trends of BMI, FPG, TG, SBP, and DBP between quartile 1 and quartile 4.

Plasma IL-22 levels are independently associated with susceptibility to IFG and type 2 diabetes mellitus

In order to identify which factors are associated with plasma IL-22 level, we next carried out Spearman's correlation analysis between plasma IL-22 levels and a cluster of anthropometric parameters and biochemical indexes. The results showed that plasma IL-22 levels had a significantly negative association with BMI, FPG, TG, SBP and DBP (Table 3). To determine whether plasma IL-22 levels were independently associated with susceptibility to IFG and type 2 diabetes mellitus, multiple logistic regression analysis was carried out. In a crude model, decreased plasma IL-22 levels were significantly associated with more susceptibility to IFG and type 2 diabetes mellitus (Table 4). After adjusting for matching factors (age, sex, BMI), the OR comparing highest quartile was attenuated from 2.98 to 2.94. Further adjusting for diabetes risk factors, including SBP, DBP, TG, total cholesterol, HDL-C and low-density lipoprotein cholesterol, did not change these associations materially (OR 2.62, 95% CI: 1.17–5.86, *P*-value for trend <0.01). Finally, when we further controlled for the indicators of liver function, the OR was elevated to 2.78 (95% CI: 1.23–6.26, *P*-value for trend <0.01). When we analyzed plasma IL-22 levels as a continuous variable, in the crude model, for every 100-pg/mL decrease in the IL-22 levels, the susceptibility of type 2 diabetes increased 14%, and these associations did not change materially even after multivariable adjustment in model 3 (OR 1.11, 95% CI: 1.04–1.19, $P < 0.01$).

DISCUSSION

IFG is a transitional stage between NG and type 2 diabetes mellitus, and represents an important category of prediabetes[17–19].

Table 4 | Odds ratios and 95% confidence intervals for the incidence of the impaired fasting glucose and type 2 diabetes mellitus according to quartile groups of plasma interleukin-22 levels

Quartiles of IL-22 levels	IFG/Type 2 diabetes mellitus incidence% (*n*/*n* total)	ORs (95% CI)			
		Crude model	Model 1	Model 2	Model 3
Quartile 1 (lowest)	76.2 (61/80)	2.98 (1.51–5.86)	2.94 (1.38–6.27)	2.62 (1.17–5.86)	2.78 (1.23–6.26)
Quartile 2	70.9 (56/79)	2.26 (1.17–4.35)	1.58 (0.76–3.33)	1.45 (0.66–3.18)	1.47 (0.67–3.24)
Quartile 3	67.5 (54/80)	1.92 (1.01–3.66)	1.48 (0.71–3.06)	1.65 (0.77–3.55)	1.72 (0.79–3.74)
Quartile 4 (highest)	51.8 (41/79)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
P-value for trend		<0.01	<0.01	<0.01	<0.01
Per 100 pg/mL decrease		1.14 (1.08–1.21)	1.11 (1.04–1.19)	1.11 (1.04–1.19)	1.11 (1.04–1.19)
P-value		<0.01	<0.01	<0.01	<0.01

Model 1 was adjusted for age, sex and body mass index; model 2 was adjusted for model 1 plus systolic blood pressure, diastolic blood pressure, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol; and model 3 was adjusted for model 2 plus alanine aminotransferase, aspartate transaminase and glutamyltranspeptidase.

Chronic low-grade inflammation is well established in promoting IFG and type 2 diabetes mellitus. During the progression of type 2 diabetes mellitus, low-grade inflammation can be toxic to the pancreatic β-cells, leading to insufficient insulin production and exacerbating glucose homeostasis[20,21]. Compared with the well-known inflammatory cytokines, IL-22, a newly identified cytokine produced by special immune cell populations, was confirmed to have beneficial effects on chronic inflammation and metabolic diseases in animal-based studies[15,16]. However, the clinical relevance of IL-22 remains poorly characterized. Recently, some studies have shown a higher frequency of circulating Th22 and higher levels of peripheral IL-22 in type 2 diabetes mellitus patients than in the control group[22–24]. However, two other studies found an opposite result that peripheral IL-22 levels were lower in patients with type 2 diabetes mellitus[25,26]. Due to different races, diagnostic criteria and disease progression, there is still controversy about the clinical relevance of peripheral IL-22 levels and type 2 diabetes mellitus. Furthermore, we also did not know the variation of IL-22 levels in prediabetes subjects. In order to better reflect the relationship between the variation of IL-22 levels and glucose metabolism disorder categories, we recruited relatively large sample sizes compared with the previous studies, and joined the prediabetes (IFG) group into the present study.

In the present study, we found that fasting plasma IL-22 levels in IFG participants were significantly lower when compared with NG participants, and this decreased trend was further enhanced in type 2 diabetes mellitus participants. Furthermore, there were no significant differences in IL-22 levels between IFG and type 2 diabetes mellitus participants. Next, we carried out a subgroup analysis according to the plasma IL-22 levels, and observed that participants with decreased plasma IL-22 levels tended to show statistically significant linear elevated trends of some key risk factors of type 2 diabetes mellitus between quartile 1 and quartile 4, including BMI, FPG, TG, SBP and DBP.

The production of IL-22 by activated immune cells is associated with various chronic inflammatory diseases, such as rheumatoid arthritis, Crohn's disease, psoriasis and atopic dermatitis. However, unlike other cytokines, IL-22 receptors are absent on immune cells, being restricted to tissues instead, thus providing signal directionality from the immune system to tissues[11]. Therefore, IL-22 can play either a protective or a pathogenic role in chronic inflammatory diseases depending on the nature of the affected tissue and the local cytokine milieu[10,11]. Activated Janus activated kinase-signal transducer and activator of transcription 3 (JAK-STAT3) pathway has been summarized to contribute to obesity and peripheral insulin resistance[27,28]. Though the direct effects of IL-22 on metabolism were poorly reported, there were emerging studies involving the JAK-STAT3 regulation on metabolism, and IL-22 can regulate the JAK-STAT3 pathway *in vivo* and i*n vitro*[29–31]. These results raise the possibility that IL-22 level might play an independent role in the development of type 2 diabetes mellitus and metabolic syndrome.

In the present study, we analyzed the relationship between plasma IL-22 levels and a cluster of anthropometric parameters and biochemical indexes. Among the participants, a significantly negative association of plasma IL-22 with BMI, FPG, TG, SBP and DBP was found, and the correlations with indicators of liver function (liver enzymes) did not reach the level of significance. Then, multiple logistic regression analysis was carried out to investigate whether plasma IL-22 was independently associated with susceptibility to IFG and type 2 diabetes mellitus. The results showed that, after multiple adjustments, decreased plasma IL-22 levels were independently associated with increased susceptibility of IFG and type 2 diabetes mellitus.

The limitations of the present study warrant consideration. First, the analysis was retrospective. Therefore, a causal relationship between decreased plasma IL-22 levels and IFG and type 2 diabetes mellitus cannot be clearly determined. However, the adjustments for multiple confounders to the obtained data reduce the impact of potential biases. Second, our study participants were all of Han Chinese origin. It is unknown whether the present results can be generalized to other ethnicities. Third, our study participants were slightly older, and had a somewhat higher ratio of males relative to the general population in China. Nevertheless, in the present study, there were no sex differences in plasma IL-22 levels, and Spearman's correlation analysis showed that there were no associations of plasma IL-22 levels with age and sex. Fourth, we controlled for possible confounders, including age, sex, BMI and selected risk factors of type 2 diabetes mellitus, thus allowing conclusions that are largely generalizable. However, we cannot exclude the possibility that some other confounders were not included in the present study.

In conclusion, we present for the first time evidence that plasma concentrations of IL-22 are decreased in IFG and type 2 diabetes mellitus patients, and decreased plasma concentrations of IL-22 is an independently susceptible factor for IFG and type 2 diabetes mellitus. Future studies will clarify whether decreased plasma IL-22 levels increase the morbidity of diabetes in the general population, and investigate likely mechanisms that could explain the correlation between plasma IL-22 levels and type 2 diabetes mellitus.

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DISCLOSURE

The authors declare no conflict of interest.

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