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ORIGINAL ARTICLE

Relationship between natural killer cell activity and glucose control in patients with type 2 diabetes and prediabetes

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ABSTRACT

Aims/Introduction: Natural killer (NK) cells are cytotoxic lymphocytes critical to human immunity. Previous studies showed correlations between NK cell function and blood glucose concentrations. The purpose of the present study was to assess the NK cell activity and various metabolic parameters in people with type 2 diabetes, prediabetes and normal glucose tolerance.

Materials and Methods: A total of 49 participants were enrolled in the study. Anthropometric and biochemical parameters including age, sex, body mass index, smoking status, blood pressure, fasting plasma glucose, C-peptide, insulin, glycated hemoglobin, total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol were assessed. The 75 g oral glucose tolerance test was carried out for 2-h postload glucose level. Homeostatic model assessment was calculated for insulin resistance and β-cell function. NK cell activity was measured by detecting the circulating interferon-gamma level secreted from NK cells.

Results: NK cell activity was lower in patients with type 2 diabetes (768.01 ± 650.35) compared with those with prediabetes (2,396.08 ± 653.76, $P < 0.001$) and normal glucose tolerance (2,435.31 ± 633.22, $P < 0.001$). In patients with type 2 diabetes, there was a significant inverse linear relationship between NK cell activity and fasting plasma glucose, glycated hemoglobin, and 2-h postload glucose level (all $P < 0.001$). Multiple regression analysis showed glycated hemoglobin to be an independent predictor of NK cell activity in patients with type 2 diabetes.

Conclusions: Compared with individuals with normal glucose tolerance or prediabetes, type 2 diabetes patients have a reduced NK cell activity, and it is significantly related to glucose control.

INTRODUCTION

People with type 2 diabetes mellitus have increased morbidity and mortality from diabetic vascular complications[1]. Recent studies have shown that patients with diabetes are also prone to various cancers, and efforts are being made to understand the underlying mechanisms for this increased cancer incidence[2–4]. The chronic inflammatory state in diabetes patients might be involved in the impaired immune function and, consequently, the higher susceptibility to infection[5,6]. Natural killer (NK) cell activity, in particular, has been shown to be involved in the immune dysfunction and increased risk of cancer in diabetes patients[7].

NK cells engage in innate immunity to remove pathogens and cancer cells[8]. They also release cytokines to transmit adaptive immunity[9]. Previous research has shown that different levels of cytokines produced by NK cells result in various levels of cell toxicity. NK cells, which strongly express cytokines, have strong cytotoxicity to target cells, whereas cells that have degraded cytokine expression have little or none of this function[10]. A method was recently developed to easily assess the activity of NK cells by measuring the level of secreted interferon-gamma (IFN-γ) derived from NK cells[7]. NK cell activity,

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expressed as a concentration of serum IFN-γ, is directly related to changes in the function and level of NK cells, and can indicate the degree of innate and adaptive immunity[11]. In light of this, several recent studies showed that the decline in NK cell activity is related to various types of cancer. As a result, NK cells are now known to play a role in cancer cell immunological surveillance[12–14].

Several studies were carried out to evaluate the NK cell function in diabetes patients. NK cells lost their function when exposed to hyperglycemia, as in patients with uncontrolled diabetes[15], and physical inactivity and poor metabolic status were associated with decreased NK cell activity[16]. Type 1 diabetes, as well as type 2 diabetes, patients were presented with a lower number of NK cells and a decline in NK cell function[17–19]. However, little is known about the NK cell activity in patients with prediabetes – who are in a hyperglycemic state, but not high enough to be diagnosed with diabetes – nor its relationship with metabolic parameters in these patients.

In the present study, we assessed and compared the NK cell activity in participants with type 2 diabetes, prediabetes and normal glucose tolerance (NGT), and analyzed the relationship between NK cell activity and various metabolic parameters in these participants.

METHODS

This was a cross-sectional study carried out on individuals with type 2 diabetes mellitus, prediabetes and NGT who visited the Endocrine & Diabetes Center of Gangnam Severance Hospital, Seoul, Korea, from April to June 2017. Type 2 diabetes was defined as both previously diagnosed and undiagnosed type 2 diabetes mellitus. Diagnosed diabetes mellitus was based on self-reported responses. The diagnosis of diabetes was based on the following American Diabetes Association criteria: fasting plasma glucose (FPG) ≥126 mg/dL, or symptoms of diabetes plus casual plasma glucose ≥200 mg/dL, or 2-h postload glucose level (2hPG) ≥200 mg/dL during a 75-mg oral glucose tolerance test, or glycated hemoglobin (HbA1c) ≥6.5%. Prediabetic patients were defined as those with FPG 100–125 mg/dL, 2hPG 140–199 mg/dL or HbA1c 5.7–6.4%. The NGT group was defined as individuals with FPG <100 mg/dL, 2hPG <140 mg/dL and HbA1c ≤5.6%. Individuals with human immunodeficiency virus, splenectomy, immunosuppressive therapy after organ transplantation, rheumatic diseases, Crohn's disease, use of other drugs that might affect immune status, severe liver or kidney disease, current or previous malignancy, blood aminotransferase level of ≥100 IU/L, or blood creatinine level of ≥1.4 mg/dL were excluded from the study.All procedures carried out in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the institutional review board of Gangnam Severance Hospital, and was carried out with prior informed consent from all participants.

The height, weight, and systolic and diastolic blood pressure were measured in the morning with light clothing without shoes. Body mass index was calculated as bodyweight in kilograms divided by height in meters squared (kg/m^2). Smoking and past medical and surgical history were assessed at the time of screening by a single interviewer. Fasting blood samples were drawn and analyzed for HbA1c, serum glucose, cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, insulin and C-peptide. The 75 g glucose tolerance test was carried out in all participants for post-loading glucose, insulin and C-peptide. To indirectly evaluate the insulin secretion function of pancreas β-cells and insulin resistance in the human body, the following formula was calculated using homeostatic model assessment (HOMA)[20].

$$\text{HOMA-IR} = \text{Fasting blood insulin (uU/mL)} \times \text{fasting plasma glucose (mmol/mL)}/22.5$$

$$\text{HOMA-\%B} = (20 \times \text{fasting blood insulin (uU/mL)})/(\text{fasting plasma glucose (mmol/mL)} - 3.5)$$

NK cell activity was measured using the NK-Vue Kit® (ATgen, Sungnam, Korea)[7]. A total of 1 mL of whole blood was collected from all participants and placed in an NK-Vue Tube®, which is a vacuum filter containing Promoca®. To ensure sufficient blood coating on the entire inner surface of the tube, it was gently mixed 10 times and then placed in an incubator at 37°C within 30 min. To ensure successful secretion of IFN-γ from activated NK cells, NK-Vue® Tubes were set up for 24 h in an incubator. The supernatant was then collected with a pipette and transferred to a 1.5 mL tube. After centrifugation at 16,000 r.c.f. for >1 min, the supernatant was collected in another 1.5 mL tube, and sent to enzyme-linked immunospecific assay plates to measure and quantify IFN-γ levels released from NK cells[7,21].

Statistical analysis

Statistical analysis was carried out with the SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA). The baseline characteristics were expressed as the mean ± standard deviation for continuous variables. The comparison of baseline characteristics and NK cell activity among patients with type 2 diabetes, prediabetes and NGT was carried out by Kruskal–Wallis tests with Bonferroni's method and the Mann–Whitney method. Correlation analysis and univariate, multivariate regression analysis were used to assess relationships between biochemical parameters and NK cell activity, and to identify factors that predict the NK cell activity. *P*-values <0.05 were considered statistically significant.

RESULTS

Of 49 study participants, 21 had type 2 diabetes, 15 had prediabetes and 13 had NGT. Patients with diabetes had lower NK cell activity compared with participants with NGT and prediabetes (768.01 ± 650.35 vs 2435.31 ± 633.22, 768.01 ± 650.35 vs 2396.08 ± 653.76, respectively, all $P < 0.001$). There was no significant difference in NK cell activity between NGT and prediabetes patients ($P = 0.821$; Table 1).

Correlation analysis was carried out to determine the association between NK cell activity and biochemical parameters. When all the study participants were included for analysis, NK cell activity was in negative correlations with FPG ($r = –0.745$, $P < 0.001$), 2hPG ($r = –0.778$, $P < 0.001$) and HbA1c ($r = –0.827$, $P < 0.001$). Insulin ($r = 0.357$, $P = 0.023$) and HOMA of β-cell function (HOMA-B; $r = 0.787$, $P < 0.001$) showed significant positive correlations with NK cell activity. These correlations remained significant after adjusting for age, sex, blood pressure and smoking status (Table 2).

When diabetes patients were divided into different levels of glucose control and separate analysis was carried out, NK cell activity showed significant negative correlations with FPG ($r = –0.705$, $P = 0.002$), 2h-PG ($r = –0.795$, $P = <0.001$) and HbA1c ($r = –0.790$, $P < 0.001$), and a significant positive correlation with HOMA-B ($r = 0.649$, $P = 0.005$) after adjusting for age and sex, blood pressure, and smoking status. In the prediabetes and NGT groups, no significant relationships were observed between measured parameters and NK cell activity (Table 2).

Multiple regression analysis with all study participants showed HbA1c and HOMA-B to be independently associated with decreased NK cell activity ($B = –317.849$, 95% confidence interval –384.927 to –250.771, $P < 0.001$; and $B = 5.596$, 95% confidence interval 3.199–7.993, $P = 0.024$, respectively). Among patients with type 2 diabetes, HbA1c was independently associated with decreased NK cell activity ($B = –280.787$, 95% confidence interval –347.053 to –214.521, $P < 0.001$; Table 3).

DISCUSSION

Impaired immune function has been proposed as a possible underlying mechanism linking the increased risk of infection and cancer incidence among diabetes patients[3,4]. In the present study, NK cell activity was measured in normal individuals, prediabetes patients and type 2 diabetes patients, and diabetes patients had lower NK cell activity compared with the other two groups, whereas prediabetes and NGT participants had

Table 1 | Baseline characteristics of study participants

	Type 2 DM	Non-DM		*P*-value
		Prediabetes (IGT or IFG)	NGT	
n	21	15	13	
Sex				
Men (*n*)	8	5	4	
Women (*n*)	13	10	9	
Age (years)	60.71 ± 6.99	58.80 ± 10.27	53.69 ± 13.76	0.153
Current smoker (%)	38.1	40	15.4	0.307
SBP (mmHg)	128.00 ± 14.84	130.53 ± 17.79	118.62 ± 14.00	0.104
DBP (mmHg)	76.33 ± 9.79	84.27 ± 14.42	79.00 ± 13.47	0.307
BMI (kg/m^2)	23.55 ± 2.75	24.71 ± 2.35	23.10 ± 3.54	0.304
FPG (mmol/L)	10.55 ± 3.47†‡§	5.82 ± 0.53¶	5.13 ± 0.31	<0.001
HbA1c (%)	8.86 ± 1.61†‡§	5.85 ± 0.36¶	5.35 ± 0.35	<0.001
2hPG (mmol/L)	15.54 ± 4.75†‡§	6.94 ± 1.48	5.85 ± 0.69	<0.001
Total cholesterol (mmol/L)	5.13 ± 0.96	4.90 ± 0.93	4.86 ± 1.15	0.699
Triglyceride (mmol/L)	2.08 ± 1.21	1.72 ± 0.80	1.43 ± 0.79	0.182
HDL cholesterol (mmol/L)	1.31 ± 0.33	1.36 ± 0.26	1.40 ± 0.35	0.708
LDL cholesterol (mmol/L)	3.39 ± 0.75	3.25 ± 0.92	3.26 ± 1.03	0.865
Fasting C-peptide (nmol/L)	0.59 ± 0.25†§	0.75 ± 0.23	1.05 ± 0.43	0.007
Fasting insulin (pmol/L)	46.53 ± 37.78†§	62.30 ± 31.67¶	118.76 ± 129.59	<0.001
HOMA-B	34.40 ± 17.09†‡§	100.33 ± 22.56¶	152.15 ± 35.38	<0.001
HOMA-IR	1.89 ± 1.45	1.73 ± 0.52	2.21 ± 0.94	0.224
NK cell activity	768.01 ± 650.35†‡§	2396.08 ± 653.76	2435.31 ± 633.22	<0.001

Data are presented as the mean (standard deviation). The *P*-value represents the analysis of variance *P* for the baseline measures among the groups. $^{†}P < 0.05$ between normal glucose tolerance (NGT) and type 2 diabetes mellitus (DM), $^{‡}P < 0.05$ between prediabetes (impaired glucose tolerance [IGT] and impaired fasting glucose [IFG]) and type 2 DM, $^{§}P < 0.05$ between non-DM (NGT and prediabetes) and type 2 DM, $^{¶}P < 0.05$ between NGT and prediabetes (IGT and IFG). 2hPG, 2-h postload glucose; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-B, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; NK, natural killer; SBP, systolic blood pressure.

Table 2 | Correlation analysis between biochemical parameters including natural killer cell activity after adjusting for age, sex, blood pressure and smoking status

	NK cell activity							
	Type 2 DM		Prediabetes		NGT		All participants	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
BMI	0.193	0.459	0.409	0.240	−0.040	0.925	0.162	0.294
FPG	−0.705	<0.001	−0.208	0.565	−0.395	0.333	−0.745	<0.001
HbA1c	−0.790	<0.001	−0.470	0.170	−0.751	0.032	−0.827	<0.001
2hPG	−0.795	<0.001	0.268	0.453	−0.608	0.109	−0.778	<0.001
Total cholesterol	−0.264	0.306	0.032	0.929	−0.407	0.317	−0.245	0.109
Triglyceride	−0.003	0.990	0.624	0.054	−0.419	0.302	−0.183	0.235
HDL cholesterol	−0.131	0.616	−0.427	0.219	0.332	0.422	0.036	0.818
LDL cholesterol	−0.267	0.300	0.188	0.604	−0.448	0.265	−0.186	0.228
Fasting C-peptide	−0.350	0.169	0.179	0.621	0.196	0.642	0.219	0.153
Fasting insulin	−0.297	0.247	−0.009	0.980	0.749	0.032	0.302	0.046
HOMA-B	0.649	0.005	0.387	0.269	0.244	0.560	0.738	<0.001
HOMA-IR	−0.489	0.046	0.187	0.606	0.090	0.833	−0.212	0.166

Data are presented as the mean (standard deviation). 2hPG, 2-h postload glucose; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-B, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance; LDL, low-density lipoprotein; NK, natural killer; NGT, normal glucose tolerance.

Table 3 | Multiple stepwise regression analysis between natural killer cell activity and biochemical parameters in type 2 diabetes mellitus and all participants

	B (95% CI)	β	R^2	*P*-value
NK cell activity in type 2 DM				
FPG	4.499 [0.894, 8.104]	0.432	0.459	0.233
HbA1c	−280.787 [−347.053, −214.521]	−0.697	0.459	<0.001
2hPG	−2.381 [−4.724, −0.038]	−0.313	0.459	0.327
HOMA-B	14.096 [4.745, 23.447]	0.370	0.459	0.154
NK cell activity in all participants				
FPG	4.702 [0.208, 9.196]	0.277	0.713	0.302
HbA1c	−317.849 [−384.927, −250.771]	−0.599	0.713	<0.001
2hPG	−2.345 [−4.602, −0.088]	−0.228	0.713	0.305
Fasting C-peptide	−96.849 [−249.246, 55.548]	−0.098	0.713	0.529
Fasting insulin	5.527 [−3.117, 14.171]	0.059	0.713	0.526
HOMA-B	5.596 [3.199, 7.993]	0.295	0.713	0.024

Data are presented as the mean. 2hPG, 2-h postload glucose; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-B, homeostatic model assessment of β-cell function; NK, natural killer.

comparable NK cell activity. Also, NK cell activity was associated with various parameters related to glucose metabolism only in diabetes patients.

The present study results are in line with previous studies that demonstrated a reduced NK cell activity in diabetes patients compared with controls. The role of NK cells is to engage in innate immunity and transmit adaptive immunity[8,9]. NK cells have characteristic activating receptors, such as NKp45 and NKG2D, that are activated by contact with ligands on the surface of infected cells or tumor cells[22,23]. Several cytokines, such as interleukin-12 and interleukin-15, promote NK cell activation through differentiation and maturation[24]. Activated NK cells release proteases called perforins and granzymes[25] that have cytotoxic effects on target cells. They also regulate the immune response by releasing cytokines, such as IFN-γ and tissue necrosis factor-alpha[26]. Therefore, the impairment in immune system maintenance, as well as restriction of cancer growth resulting from the reduced NK cell activity in diabetes patients, might lead to the increased susceptibility to infectious diseases and cancer.

Meanwhile, there was no difference in NK cell activity between prediabetes patients and individuals with NGT, whereas there was a difference between participants with diabetes and prediabetes. Also, a significant correlation was noted only in the diabetes group, and not in the NGT and prediabetes groups between HbA1c, FPG, 2hPG and NK cell activity.

In multiple regression analysis, HbA1c independently showed a significant relationship with NK cell activity only in the diabetes group. This is in agreement with a previous study that showed that the cytolytic function of NK cells significantly deteriorates with the exposure to elevated glucose concentrations in the range seen in poorly controlled diabetes[15]. In other words, it can be inferred that while NK cell activity deteriorates linearly with the degree of hyperglycemia, hyperglycemia starts to interfere with NK cell activity once it reaches a certain degree, at least higher than a prediabetes range.

HOMA-B, which indirectly represents the β-cell function in pancreas, clearly had a significant positive correlation with NK cell activity in type 2 diabetes. Also, fasting plasma C-peptide and insulin showed significant correlations with NK cell activity. A study by Zhang *et al.*[17] found that type 1 diabetes patients with severely reduced insulin levels also had decreased NK cells. In addition, expression of NKG2D, an NK cell receptor, was reduced. NK cell production of IFN-γ, which is essential for immune system function, was also impaired. A study by Rodacki *et al.*[18] also found that NK cell activity in patients with long-standing type 1 diabetes was lower than that of normal controls, in addition to NKG2D expression. These data, along with the present results, suggest that insulin deficiency might be associated with impaired NK cell function. In the prediabetes state, there is a compensatory increase in insulin secretion to overcome hyperglycemia, and it might explain why there was no reduction in NK cell activity in prediabetes patients. However, when prediabetes patients progress to overt diabetes, their islet function is reported to be approximately 50% of individuals with NGT, and consequently might be related to a reduced NK cell activity.

In addition, previous reports show that low physical inactivity or unhealthy metabolic status contributes to impaired NK cell function[16]. Based on these reports, we investigated correlations between NK cell activity and biochemical parameters related to diabetes, obesity and metabolic syndrome. However, other than FPG, 2hPG and HbA1c, no significant correlation was noted between NK cell activity and body mass index, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Furthermore, although some studies showed differences in NK cell function at different levels of hyperglycemia, when we carried out subgroup analysis on the relationship between NK cell activity and these metabolic parameters, we did not find any significant differences. The lack of significance might be due to a small number of study participants in our study.

The present study had several limitations. First, this was a small cross-sectional study of 49 people at a single center. Accordingly, there is a risk of bias in this study. Due to the characteristics of a cross-sectional study, changes in NK cell activity related to differences in fasting plasma glucose or HbA1c over time cannot be identified, and it is difficult to explain the actual relationship between blood glucose management and NK cell activity in patients with type 2 diabetes. A future large-scale study with more participants is required to investigate the relationship between NK cell activity and diabetes, blood glucose control, and dyslipidemia. It is also necessary to determine the relevance of changes in NK cell activity through classification and analysis of blood glucose or HbA1c results.

In conclusion, NK cell activity is significantly lower in patients with type 2 diabetes compared with NGT and prediabetes patients. NK cell activity significantly decreases linearly with the increase in blood glucose level. The study supports the hypothesis that the increasing prevalence of infectious diseases and malignancy in type 2 diabetes patients is associated with decreased immune function. Future efforts are required to redefine the relationship between type 2 diabetes mellitus and NK cell activity, and to provide a way to reduce the incidence of infectious diseases and cancer by carrying out large-scale studies of patients with type 2 diabetes.

DISCLOSURE

The authors declare no conflict of interest.

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