Original Research

Analysis of Risk Factors for Normal Glucose Tolerance-Hyperinsulinemia

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The aim of this paper is to study the prevalence of individuals with normal glucose tolerance-hyperinsulinemia in Nanshan of Shenzhen, determine the cut point values of normal glucose tolerance-hyperinsulinemia, and investigate the risk factors for it. All subjects were followed 75g oral glucose tolerance test (OGTT) and insulin releasing test. Glucose metabolic disorders were determined according to WHO definition (1999). Hyperinsulinemia was determined if fasting serum insulin and/or 2-hour serum insulin ≥ the 90th percentile, so subjects with normal glucose tolerance were divided into two groups: hyperinsulinemia and normoinsulinemia. The islet cell function and metabolic characteristics of individuals with normal glucose tolerance-hyperinsulinemia were analyzed and its related risk factors were investigated by Logistic regression analysis. The cut point values of normal glucose tolerance-hyperinsulinemia in Nanshan of Shenzhen is fasting serum insulin ≥ 13.85 mU/L and/or 2-hour serum insulin ≥ 74.97 mU/L. The prevalence of NGT- HINS in the community was 7.84%. The differences of the prevalence of high blood, HDL, LDL, TG, UA were significant between subjects with NGT-HINS and NGT-NINS ($P < 0.05$); and the differences are nonsignificant between subjects with NGT-HINS and IGR ($P > 0.05$). There were significant differences on 2hPG between subjects with NGT-HINS and IGR ($P < 0.05$), and no difference between individuals with NGT-HINS and NGT-NINS ($P > 0.05$). The differences of the smoking rates, Baecke index, BMI, WHR, TC, FPG, HbA1C, HOMA-IR, and HBCI/R were significant among these groups. There were nonsignificant differences on age, sex, drinking rate among three groups ($P > 0.05$). Logistic regression analysis showed that BMI (OR = 14.019, 95% CI: 4.111, 47.800; $P = 0.000$); TG (OR = 9.336, 95% CI: 2.697, 32.313; $P = 0.000$); HDL (OR = 0 .181, 95% CI: 0 .053, 0.625; $P = 0.007$); FPG (OR = 5.276, 95% CI: 1.588, 17.535; $P = 0.007$); HOMA-IR (OR = 22.727, 95% CI: 6.895, 74.915; $P = 0.000$); HBCI/IR (OR = 6.611, 95% CI: 2.238, 19.529; $P = 0.001$) were the independent predictors for NGT-HINS. Our results show that the cut point values of normal glucose tolerance-hyperinsulinemia in Nanshan of Shenzhen is fasting serum insulin ≥ 13.85 mU/L and/or 2-hour serum insulin ≥ 74.97 mU/L. Individuals with NGT-HINS suffered more metabolic risk factors and had a decreased β-cell function. NGT-HINS is a transitional state between NGT and IGR. BMI, TG, HDL, FPG, HOMA-IR, and HBCI/IR were the independent predictors for NGT-HINS.

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Key Words: *normal glucose tolerance-hyperinsulinemia, normal glucose tolerance-normoinsulinemia, impaired glucose regulation, risk factors*

INTRODUCTION

Background

According to the five national epidemiological surveys of diabetes in China in the past 30 years, the prevalence of diabetes in China has increased significantly. From 2007 to 2008, the Chinese Diabetes Society of the Chinese Medical Association conducted an epidemiological survey of diabetes in 14 provinces and cities nationwide. It is estimated that the prevalence of diabetes in adults over 20 years old in China is 9.7%, and the total number of adult diabetes in China is 92.4 million. It is very likely that China has become the country with the largest number of diabetes patients in the world.[1] Multiple complications of diabetes jeopardize people's health while increasing medical costs and social burden. Therefore,

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screening sugar metabolism in high-risk groups as early as possible is extremely important for early prevention, diagnosis, and treatment.

It is currently believed that insulin resistance (IR) and insulin-deficient function of islet β-cell are common pathogenic factors of type 2 diabetes mellitus (T2DM). Reaven et al[2] found that the majority of patients initially had insulin resistance, and the body's tissue glucose utilization capacity decreased, leading to high blood sugar tendency; in order to maintain a normal blood glucose regulation, islet β cells compensatory secretion of more insulin and Hyperinsulinemia (HINS) occurs, while blood glucose rises when the islet β cells are decompensated. Therefore, hyperinsulinemia can be considered as a metabolic disorder occurring earlier than prediabetes.

Studies show that normal glucose tolerance-hyperinsulinemia is an independent risk factor for atherosclerosis, which increases the incidence of cardiovascular and cerebrovascular diseases;[3-7] normal glucose tolerance-hyperinsulinemia (NGT-HINS) is also an early warning sign of diabetes, which is more likely to be converted to diabetes than normal glucose tolerance-normoinsulinemia (NGT-NINS).[8-11] Therefore, the study of the NGT-HINS stage is of great significance for the early prevention of type 2 diabetes as well as cardiovascular and cerebrovascular diseases.

Currently, there is no clear determination of the cut-off value of NGT-HINS in China; the etiology of NGT-HINS is still lacking. The differences between the clinical characteristics of the NGT-HINS and NGT-NINS populations, whether they are similar to the impaired glucose regulation (IGR) stage, and the risk factors associated with metabolic syndrome are the focus of this study. This study investigated the prevalence of NGT-HINS in Nanshan District, Shenzhen by epidemiological methods, determined the cut-point value of hyperinsulinemia in normal blood glucose population in the region and analyzed its risk factors to provide a theoretical basis for early clinical intervention. It also provides an important reference value for further exploration of the etiology.

Specific Aims

This study aims at investigating and analyzing the prevalence of normal blood glucose-hyperinsulinemia (NGT-HINS) in Nanshan District, Shenzhen, establishing the cut-off value of hyperinsulinemia in this population, and exploring the relating risk factors.

Study Procedure

1. Measure the height, weight, waist circumference (WC), hip circumference, sitting systolic pressure (SBP), and diastolic blood pressure (DBP) of the subjects, calculate the body mass index (BMI), and assess the physical activity status of the targeted population with the Baecke index.

2. Measurement of biochemical indicators: The subjects underwent uniform OGTT test to measure fasting blood glucose. Their PG and INS levels were also measured respectively 30 min, 1 h, 2 h, 3 h after 75 g glucose load. Blood lipids including triglyceride (TG) and total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), uric acid (UA), liver and kidney function indicators, and glycosylated hemoglobin (HbA1C) were also measured.

3. The normal blood glucose population was screened according to the 1999 World Health Organization (WHO) Diabetes Diagnostic Criteria. Hyperinsulinemia was determined by fasting blood glucose level and by the insulin ≥ 90th percentile at 2 hours after glucose load. Logistic regression analysis was used to investigate the risk factors for hyperinsulinemia in normal blood glucose population.

METHODS

Apparatus and Biomarker Measurements

The following apparatus were used during this study: Beckman Coulter Chemistry Analyzer DxC 800, Siemens IMMULITE 1000 Immunoassay System, BIO-RAD D-10 Hemoglobin Testing System, TDZ4-WS/TDZ4WS (produced by Hunan Xiangyi Laboratory Instrument Development Co., Ltd.), YHC-360 Medical refrigerator (produced by Qingdao Haier Co., Ltd.), pipettes (made in Finland), and MSI Minishaker (made in Malaysia). Insulin levels were measured by Beckman Coulter hypersensitive insulin assay kits. Blood glucose levels were measured by glucose assay kits which were produced by Mindray Bio-Medical Electronics Co., Ltd.

Methods

Study design

A cross-sectional study

Subject recruitment

Health check-ups participated in the diabetes screening of the Nanshan District People's Hospital in Shenzhen (689 subjects in total).

Study procedure

(1) We established epidemiological questionnaires before the research began. The professional researchers collected general information from the studied population, inquired about diabetes, dyslipidemia, hypertension and other related medical history and family genetic history, and also collected daily physical activity, smoking and drinking status. Height, weight, waist circumference, hip circumference, sitting systolic pressure, and diastolic blood pressure were also measured, and body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. The Baecke index was used to assess the physical activity of the study population[12] (see Appendix II for scoring methods).

(2) Subjects consumed no less than 200 grams of carbohydrates per day for three days before the OGTT test. Subjects had fasted for more than 10 hours before the test. No smoking or coffee was allowed for 8 hours before the test. Drinking water was allowed in small amounts. During the test, mental stress and strenuous activities were avoided.

(3) All subjects (except for those diagnosed with type 2 diabetes) underwent OGTT test. They were taken 4 mL of anterior elbow venous blood in fasting condition and 30 min, 1 h, 2 h, 3 h after 75 g of anhydrous glucose intake respectively. Centrifuged for 10 minutes at a speed of 2500 r/min, took the upper serum, checked the blood glucose levels and insulin levels at each time point, and detected biochemical indicators including triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), blood uric acid (UA), liver and kidney function indicators, and glycated hemoglobin (HbA1C).

(4) Blood glucose (hexose kinase) and blood lipids (lipase method) were measured by DXC-800 automatic biochemical analyzer operated by professionals. BIO-RAD D-10 Hemoglobin Testing System was used to measure glycated hemoglobin. Insulin levels were measured by DBC kit and IMMULITE 1000 Immunoassay System operated by professionals. The coefficient of variation between batches was 5.9-8.0, and the intra-assay coefficient of variation was 5.2-6.4%.

Diagnostic Criteria

(1) Determination of glucose metabolism status according to 1999 WHO diagnostic criteria[13]

NGT: FPG < 6.1 mmol/L and 2hPG < 7.8 mmol/L:
IFG: FPG 6.1 ～ 7.0 mmol/L and 2hPG < 7.8 mmol/L:
IGT: FPG < 7.0 mmol/L and 2hPG 7.8 ～ 11.1 mmol/L:
IGR: FPG 6.1 ～ 7.0 mol/L and/or 2hPG 7.8 ～ 11.1 mmol/L:
DM: FBG > 7.0 mmol/L and/or 2hPG > 11.1 mmol/L.

(2) Determination of hyperinsulinemia

The research team used the ≥ 90th percentile for the detected value of the OGTT 2-hour plasma insulin test (2h-INS) and/or fasting test as criteria for determining insulinemia (HINS).[7,14] This divides hyperinsulinemia into simple fasting hyperinsulinemia, simple 2h hyperinsulinemia, and fasting/2h hyperinsulinemia three different types. The normal blood glucose population was divided into two groups: normal blood glucose-hyperinsulinemia (NGT-HINS) and normal blood glucose-non-hyperinsulinemia (NGT-NINS).

(3) Assessment of the metabolic syndrome

① Overweight and/or obesity: BMI ≥ 25kg/m2;[15]
Waist to hip ratio > 0.90 (male), > 0.85 (female).[16]
② Combine two or more components in the following:[17]

Triglyceride (TG) ≥ 1.7mmol/L or those previously received lipid-lowering treatment;

High-density lipoprotein cholesterol (HDL-c) reduction: male < 1.03mmol/L, female < 1.29mmol/L or those previously received lipid-lowering treatment;

Increase in blood pressure (BP): BP≥130/85mmHg and/or those who have been diagnosed with hypertension and treated;

Fasting plasma glucose (FPG) increased by ≥ 5.6mmol/L and/or those who have been diagnosed with diabetes and treated.

(4) Insulin sensitivity index: homeostasis-insulin resistance index (HOMA-IR) = FPG×Fins/22.5; homeostasis-β-cell-function index (HBCI) = 20×FINS/(FPG-3.5); The HOMA β-cell function index/HOMA insulin resistance index (HBCI/IR) = HBCI/HOMA-IR.[18]

Exclusion Criteria

Individuals with diabetes, liver/kidney/endocrine system disease, and those who previously went through medications affecting glucose/fat/insulin metabolism were excluded.

Statistical Analysis

Data are presented as mean ± standard deviation ($\bar{X}$ ±s, normal distribution). The t-test was used for comparison between groups; the one-way ANOVA was used to compare the mean of multiple samples, and the comparison between the two groups was tested by the LSD method. The comparison between the groups was performed using the $\chi 2$ test. All data were analyzed by SPSS 19.0, and the inspection level was α = 0.05 (two sides). Logistic regression analysis was used to investigate the relationship between disease occurrence and potential risk factors.

Table 1. Distribution of glucose metabolism status of the subjects (% cases).

Subjects	NGT	IGR	T2DM
689	291(42.24)	275(39.91)	123(17.85)

*T2DM: Diabetes Mellitus type 2; IGR: Impaired Glucose Regulation; NGT: Normal glucose tolerance

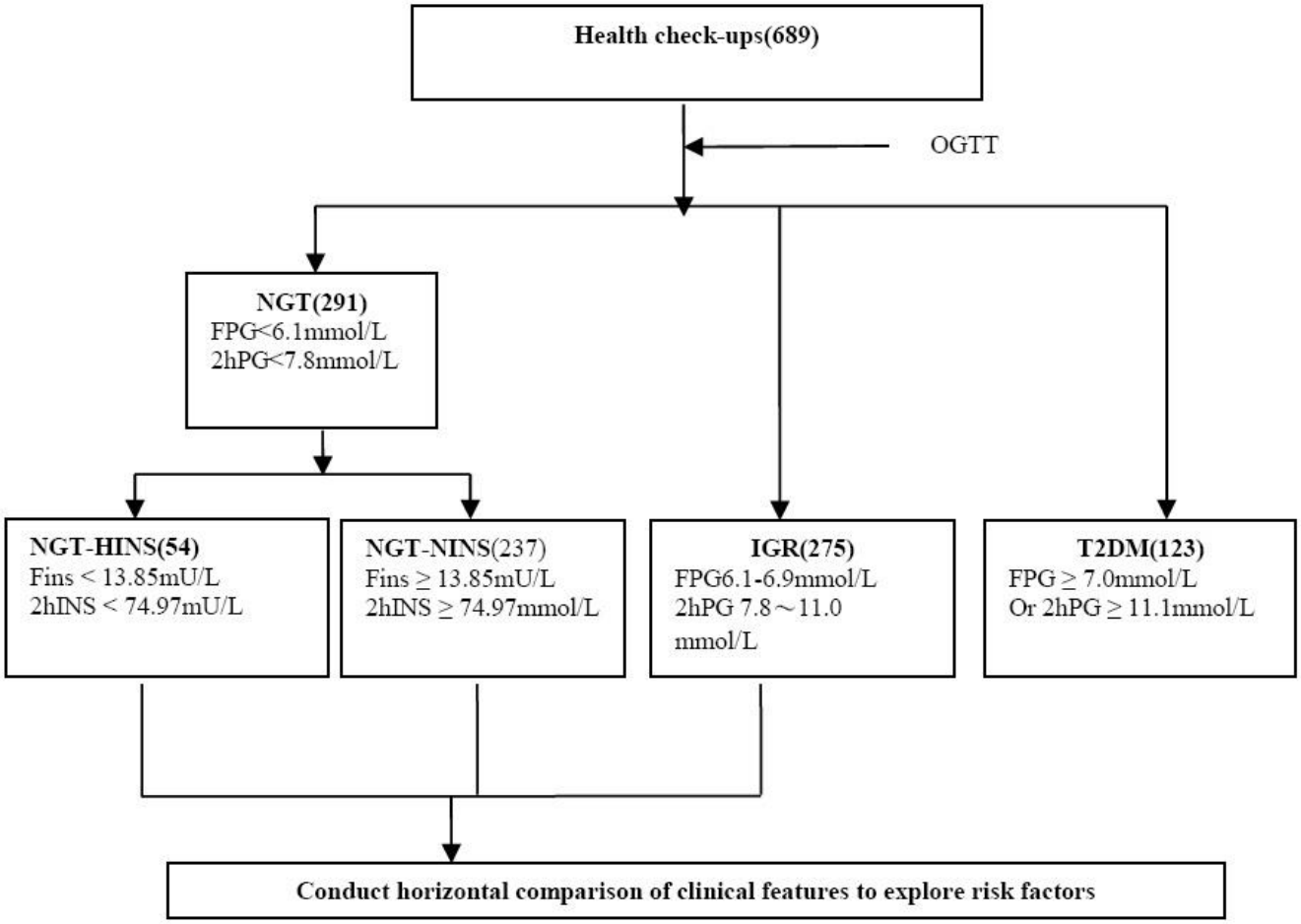

Figure 1. Illustration of grouping.

Table 2. Clinical data and biomedical indicators in NGT-NINS, NGT-HINS and IGR populations.

Indicators	NGT-NINS	NGT-HINS	IGR
Age（y/o）	43.29±12.13	43.83±14.21	46.33±12.66
Sex（M/F）	110/127	26/28	118/157
Smoking rate（%）	40/237	16/54	85/275
Drinking rate（%）	42/237	11/54	52/275
Baecke Index	2.76±0.18	2.36±0.23	2.23±0.49
BMI（kg/m^2）	22.68±2.59	25.06±3.56	16.23±2.73
WHR (%)	0.85±0.04	0.89±0.05	0.92±0.04
Hypertension rate（%）	50/237	19/54	103/275
TC (mmol/L)	4.75±0.65	5.09±0.71	5.38±0.68
HDL(mmol/L)	1.42±0.29	1.23±0.30	1.23±0.23
LDL(mmol/L)	3.01±0.67	3.46±0.71	3.43±0.45
TG(mmol/L)	1.24±0.41	1.8±0.54	1.86±1.11
UA(umol/L)	299.52±81.43	364.36±75.93	368.22±61.67
FPG(mmol/L)	5.06±0.47	5.48±0.41	5.95±0.63
2hPG(mmol/L)	5.92±1.88	6.36±0.96	8.71±3.84
HbA1C (%)	4.98±0.47	5.73±0.50	5.91±0.46
HOMA-IR	1.32±0.56	3.34±1.58	2.14±1.24
HBCI／IR	65.98±31.87	45.01±17.29	35.34±17.40

Cut Point Values of Hyperinsulinemia

For the population with normal glucose metabolism, the 90th percentile of fasting glucose level is 13.85 mU/L while the 90th percentile of OGTT 2-hour insulin level is 74.97 mU/L. The normal glucose metabolism population was divided into NGT-HINS and NGT-NINS groups according to their fasting and/or OGTT 2-hour insulin level (Hyperinsulinemia is determined when the test value is greater than or equal to the 90th percentile). Among all the subjects, 54 were NGT-HINS accounting for 7.84% of the total; 237 were NGT-NINS, accounting for 34.40% of the total.

Comparison of Clinical Data and Biomedical Indicators In NGT-NINS, NGT-HINS and IGR Populations (Table 2)

1. The differences in smoking rate, Baecke index, BMI and WHR among the NGT-NINS, NGT-HINS and IGR groups were statistically significant. $\chi^2 = 14.108$, $P = 0.001$ (smoking); F=135.706, P=0.000 (Baecke index); $F = 105.794$, $P = 0.000$ (BMI): $F = 151.182$, $P = 0.000$(WHR); These indicators had significant differences after being compared two by two respectively. There were no significant differences in age, gender and drinking rate between NGT-HINS, NGT-NINS and IGR (P > 0.05).

2. There were significant differences in the prevalence of hypertension, TC, HDL, LDL, TG, UA, FPG, 2hPG and HbA1C among NGT-NINS, NGT-HINS and IGR populations χ^2=16.750, P=0.000 (prevalence of hypertension); F = 56.607, P = 0.000 (TC); F = 35.795, P = 0.000 (HDL); F = 36.691, P = 0.000 (LDL); F = 35.568, P = 0.000 (TG); F = 61.602, P = 0.000 (UA); F = 170.356, P = 0.000 (FPG); F = 59.898, P = 0.000 (OGTT 2hPG); F = 256.420, P = 0.000 (HbA1C). After the indicators were compared, the NGT-HINS and NGT-NINS populations had significant differences in the prevalence of hypertension, HDL, LDL, TG, and UA (P < 0.05), but no significant difference compared with the IGR population (P > 0.05). There was no significant difference between the 2hPG of NGT-HINS and NGT-NINS (P > 0.05), but there were significant differences between the 2hPG of NGT-HINS and IGR ($P < 0.05$). The comparisons of TC, FPG, and HbA1C in every two groups were statistically significant (P < 0.05).

3. The difference of HOMA-IR between NGT-NINS, NGT-HINS and IGR population was statistically significant (F=92.540, P=0.000). There were significant differences between every two groups after they were paired two by two (P < 0.05). There were significant differences in the HBCI/IR of three groups (F = 100.205, P = 0.000) and between every two groups after they were paired two by two (P < 0.05).

Analyzing the Risk Factors of NGT-HINS with Logistic Regression (Table 3)

A logistic regression analysis was conducted in the normal glucose tolerance population, using hyperglycemia as a dependent variable, and gender ("1" for males, "0" for females), age, smoking rate, drinking rate, WHR, BMI, prevalence of hypertension, UA, FPG, TG, HDL (“1” for too high, “0” for normal, comparing to the evaluation criteria of metabolic syndrome), HOMA-IR (using the 75th percentile for normal glucose tolerance population as cut point value), and HBCI /IR (using the 25th percentile of the normal glucose tolerance population as the cut point value)[15] as independent variables. Results show that BMI, TG, HDL, FPG, HOMA-IR, HBCI/IR are independent risk factors for NGT-HINS (P < 0.05), while there is no correlation between age, gender, smoking rate, drinking rate, WHR, prevalence of hypertension, uric acid level and the occurrence of NGT-HINS (P > 0.05).

Table 3. Risk factors of NGT-HINS.

Independent variable	*OR* value	*P* value	95% confidence interval for OR
Sex	1.016	0.981	0.225~3.340
Age	0.989	0.622	0.945~1.034
Smoking rate	2.315	0.222	0.826~13.015
Drinking rate	1.080	0.914	0.255~4.197
BMI	13.070	0.000	4.111~47.800
WHR	1.901	0.250	0.654~5.964
Prevalence of hypertension	1.640	0.437	0.460~5.720
TG	8.943	0.000	2.697~32.313
HDL	0.181	0.007	0.053~0.625
UA	2.271	0.177	0.709~7.826
FPG	4.994	0.008	1.588~17.535
HOMA-IR	21.162	0.000	6.895~74.915
HBCI/IR	6.540	0.001	2.238~19.529

DISCUSSION

According to the data from the National Institute of Health and Nutrition,[11] NGT-HINS is an important warning sign for diabetes and cardiovascular disease. If we can identify the relevant risk factors for NGT-HINS and screen the relevant population, we can carry out primary prevention of diabetes and cardiovascular disease as early as possible. At present, the cause of NGT-HINS has not yet been clarified, and a clear cut-off value of NGT-HINS in China is still lacking. This study

investigated the prevalence of NGT-HINS in Nanshan District, Shenzhen by epidemiological methods, determined the cut-point value of hyperinsulinemia in normal blood glucose population in the region, and analyzed the risk factors for it, providing a theoretical basis for early clinical intervention as well as further study.

The Cut-point Value of NGT-HINS and its Prevalence

NGT-HINS is closely related to insulin resistance.[19,20] As an intermediate transitional metabolic state between normal glucose tolerance and impaired glucose regulation, NGT-HINS reflects a series of pathophysiological changes before the onset of type 2 diabetes. Mercedes et al[14] used the 90th percentile of insulin level in normal glucose tolerance population as the cut-point value of hyperinsulinemia (FINS = 20.1 mU/L). There was also a study in China using the 95th percentile of insulin level of 1221 participants in Beijing as the cut-point value (FINS = 15 mU/L, 2hIns = 80 mU/L, and the detection rate of NGT-HINS is 6.47%).[10] This study chose the 90th percentile of insulin level of the health check-ups in Nanshan district, Shenzhen as the cut-point value and got the results of FINS = 13.85 mU/L, 2hIns = 74.97 mU/L, and the detection rate of NGT-HINS = 7.84%.

Metabolic Characteristics and Islet Cell Function in NGT-HINS Population

The results in **Table 1** show that the HOMA-IR of the NGT-HINS population is significantly higher than that of the NGT-NINS and IGR populations, indicating that there is a higher degree of insulin resistance in the NGT-HINS population. The HBCI/ IR in NGT-HINS population is lower than that of NGT-NINS population ($P < 0.01$), but higher than that of IGR population. The occurrence of metabolic-related risk factors (hypertension, HDL, LDL, TG, UA) in NGT-HINS population is similar to that of IGR population but significantly higher than that of NGT-NINS population. The smoking rate, Baecke index, BMI, WHR, TC, FPG, and HbA1C in the NGT-HINS population are between those of NGT-NINS population and those of IGR population. Based on these, NGT-HINS can be considered as a transitional metabolic state between normal glucose metabolism and impaired glucose tolerance.

Exploring the Risk Factors of NGT-HINS

The results of logistic regression analysis show that the occurrence of NGT-HINS is directly proportional to BMI, TG, HDL, FPG, HOMA-IR, HBCI/IR, and inversely proportional to HDL.

A study by Boden et al [21] finds that the mechanism by which weight gain causes a decrease in insulin sensitivity in muscle tissue may be caused by an increase in free fatty acids in the blood that mediates insulin resistance. As the result, the body needs to secrete more insulin to regulate blood sugar, causing hyperinsulinemia.[22,23] Obesity and weight gain are associated with some inflammatory mediators in the blood circulation, including Tumor Necrosis Factor (TNF),[24] and these inflammatory mediators have been shown to interfere with insulin receptor activity.[25] The proportion of waist-to-hip ratio reflects the degree of abdominal obesity, and the results of this study show that BMI and dyslipidemia (high TG, low HDL) increase the risk of NGT-NINS. The fact that there is no correlation between the occurrence of NGT-NINS and WHR indicates that where the fat accumulates is irrelevant to the occurrence of NGT-HINS in the studied area.

Several cross-sectional studies suggest that smoking has a significant association with decreased insulin sensitivity and elevated fasting insulin, regardless of diabetes or non-diabetic population.[26-28] Mercedes et al [24] believe that recent smoking, rather than continuous smoking, increases the risk of hyperinsulinemia. The results of this study show that smoking is not a risk factor for NGT-HINS, which might be a false negative result caused by the fact that this study has included both recent smokers and continuous smokers.

Although uric acid has not been shown to be a component of the metabolic syndrome, there is ample evidence showing that uric acid always occurs along with components of the metabolic syndrome.[29-30] The correlation between hyperuricemia and hyperinsulinemia still remains unclear, and some hypothesize that it is an increase in insulin levels in the blood that causes a decrease in the clearance of uric acid to the kidneys, which is accompanied by an increase in insulin resistance, leading to an increase in blood uric acid level.[31] The results of this study show that there is no correlation between hyperuricemia and NGT-HINS. This could be due to that some certain factors other than uric acid cause elevated blood uric acid level and NGT-HINS, or just a false negative result caused by insufficient sample representation.

In order to reduce missed diagnosis caused by the use of FPG screening for diabetes, the American Diabetes Association (ADA) lowered the cut point separating diabetes from nondiabetes from FPG $\geq$ 7.8 mmol/l to $\geq$ 7.0 mmol/l. In 2003, The ADA again lowered the IFG cut point to 5.6 mmol/l.[32] The results of this study show that elevated FPG is a risk factor for NGT-HINS; the FPG levels of NGT-HINS population are significantly higher than those of NGT-NINS population. It can be inferred that in order to reduce the missed diagnosis rate of abnormal glucose metabolism through FPG screening, the upper limit of normal blood glucose in the population should also be lowered. To ensure the accuracy and reliability of this inference, further studies with bigger sample sizes and better sample representative are needed.

Currently, the etiology and pathogenesis of NGT-HINS are yet to be clarified. Exploring the risk factors for NGT-HINS is not only the basis for further etiological research but also of great significance to the early prevention of type 2 diabetes and cardiovascular diseases.

CONCLUSION

In this study, we draw the following conclusions: 1. The cut point values of hyperinsulinemia for normal glucose metabolism population in Nanshan district, Shenzhen. 2. NGT-HINS population has increased metabolic risk factors and decreased islet cell function. NGT-HINS is a transitional metabolic state between normal glucose tolerance and

impaired glucose regulation. 3. BMI, TG, HDL, FPG, HOMA-IR, and HBCI／IR are independent risk factors for normal glucose tolerance-hyperinsulinemia.

CONFLICT OF INTEREST DISCLOSURE

The authors have no conflict of interest to disclose.

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Appendix I. Abbreviations.

2hINS	OGTT 2-hour plasma INS
ADA	American Diabetes Association
BMI	body mass index
CL	confidence interval
FINS	fasting plasma insulin
FPG	fasting plasma glucose
HDL-c	high density lipoprotein cholesterol
HBCI	homeostasis-B-cell-function index
HOMA-IR	homeostasis-insulin resistance index
HINS	hyperinsulinemia
IGR	impaired glucose regulation
INS	insulin
IR	insulin resistant
LDL-c	low density lipoprotein cholesterol
NGT	normal glucose tolerance
NGT-HINS	normal glucose tolerance- hyperinsulinemia
NGT-NINS	normal glucose tolerance-normoinsulinemia
OGTT	oral glucose tolerance test
OR	odds ratio
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TG	triglyceride
UA	uric acid
WHO	World Health Organization
WHR	waist-to-hip ratio

Appendix II. Questionnaire for physical activity assessment.

1What is your main occupation?	1-3-5
2 How long do you sit during work hours	1-2-3-4-5（None-Barely-Sometimes-Usually-Always）
3 How long do you stand during work hours	1-2-3-4-5（None-Barely-Sometimes-Usually-Always）
4 How long do you walk during work hours	1-2-3-4-5（None-Barely-Sometimes-Usually-Always）
5 How long do you lift heavy things during work hours	1-2-3-4-5（None-Barely-Sometimes-Usually-Always）
6 The frequency of feeling tired after work	5-4-3-2-1（Always-Usually-Sometimes-Barely-None）
7 The frequency of sweating during work hours	5-4-3-2-1（Always-Usually-Sometimes-Barely-None）
8 How you feel about the physical burden of your job comparing to other people of your age	5-4-3-2-1（Much heavier-heavier-same-lighter-much lighter）
9 Do you exercise usually?（Yes/No）	
If yes:	
What sport do you play the most frequently	How Strenuous it is（0.76-1.26-1.76）
How many hours per week	Time（1<1-2/2-3/3-4>4）0.5-1.5-2.5-3.5-4.5
How many months per year	Ratio（1<1-3/4-6/7-9>9）0.04-0.17-0.42-0.67-0.92
Do you have a second favorite sport	
What sport it is	How Strenuous it is（0.76-1.26-1.76）
How many hours per week	Time（1<1-2/2-3/3-4>4）0.5-1.5-2.5-3.5-4.5
How many months per year	Ratio（1<1-3/4-6/7-9>9）0.04-0.17-0.42-0.67-0.92
10 How do you feel about your exercising time comparing to other people of your age	5-4-3-2-1（Much more - more - the same - less - less much）
11 Frequency of sweating during leisure time	5-4-3-2-1（Always-Usually-Sometimes-Barely-None）
12 Frequency of exercising during leisure time	1-2-3-4-5（None-Barely-Sometimes-Usually-Always）
13 Frequency of watching tv during leisure time	1-2-3-4-5（None-Barely-Sometimes-Usually-Always）
14 Frequency of taking a walk during leisure time	1-2-3-4-5（None-Barely-Sometimes-Usually-Always）
15 Frequency of riding a bike during leisure time	1-2-3-4-5（None-Barely-Sometimes-Usually-Always）
16 How many minutes do you spend each day on walking or riding to your workplace/school/shopping mall	1-2-3-4-5（<5/5-15/15-30/30-45>45minutes）

$$I_9 = \sum_{i=1}^{2} (\text{How Strenuous the sport is} \times \text{weekly exercising time(hour)} \times \text{ratio of months with sport per year})$$

= 0/0.01- <4- <8- <12 / ≥ 12（0 when choose “No” at question 9）

Calculating physical activity index (Baecke index)
Working index=I_1+（6-I_2）+ I_3 + I_4 + I_5 + I_6 + I_7 + I_8 / 8

Exercising index=I_9 + I_{10} + I_{11} + I_{12}/4

Working leisure time index =（6-I_{13}）+ I_{14} + I_{15} + I_{16} / 4
*too low: Baecke index < 1 too high: Baecke index > 5