PREVALENCE OF INSULIN RESISTANCE IN PREDIABETIC PATIENTS WITH HYPERTENSION

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ABSTRACT

Background: Prediabetes is an intermediate stage between normal people and patients with type 2 diabetes mellitus. The pathogenesis is mainly related to insulin resistance (IR). The relationship between IR and hypertension is a complex and multifactorial phenomenon. We examined the prevalence of IR in prediabetic patients with hypertension.

Objectives: The present study aimed to determine the incidence of IR according to the HOMA2 model in the group of prediabetes with hypertension, compared with the group of prediabetes without hypertension.

Subjects and Methods: The cross-sectional study described and collected data from 191 people with prediabetes from February 2023 to September 2023 at the Examination Department of Cho Ray Hospital. IR was determined by the HOMA2 calculator, using a threshold of 1.29 for IR. Prediabetes and hypertension were diagnosed according to ADA 2022 and ISH 2020 criteria, respectively.

Results: The number of subjects selected to analyze the data was 179 patients, including 89 prediabetes patients without hypertension and 90 prediabetes patients with hypertension. The prevalence of IR in the overall prediabetes group was 56.9%. The prevalence of IR in the hypertensive group was 66.7%, higher than the non-hypertensive group at 47.2%, which was statistically significantly different. The values of the index in HOMA2 did not differ statistically significantly between non-hypertensive and hypertensive populations.

Conclusions: The prevalence of IR in prediabetes patients with hypertension was 66.7%, greater than the prediabetes patients without hypertension of 47.2%, P = 0.013. Attention should be paid to good control of blood pressure in patients with prediabetes.

Keywords: *prediabetes, hypertension, insulin resistance, HOMA2*

I. BACKGROUND

Prediabetes is a terminology used to give a rundown of individuals with impaired glucose tolerance, or impaired fasting blood sugar, or increasing HbA1c. This carries a very high risk of progressing to diabetes mellitus and the complications associated with diabetes. Prediabetes is an intermediate stage between normality and type 2 diabetes. About 5-10% of prediabetics will become diabetics annually and a total of 70% of prediabetics will become actual diabetics. Prediabetes is associated with diabetes-like risk factors, including overweight, obesity, dyslipidemia, chronic kidney disease, hypertension, and physical inactivity.

According to a report by the International Diabetes Federation (IDF), in 2021 an estimated 541 million mature people, or 10.6% of all adults had impaired glucose tolerance. By 2045, this number is expected to rise to 730 million persons, or 11.4% of all

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Date of receipt: 5/2/2024
Date of scientific judgment: 1/4/2024
Reviewed date: 8/4/2024

international adults. At the same time as the risk of developing diabetes, people with prediabetes are likely to develop several cardiovascular diseases, especially hypertension[1].

The relationship between IR and hypertension is a complicated and multifactorial event including genetic and environmental factors. It has been observed that people with hypertension in Western countries have sedentary lifestyles and consume high-calorie food, which also plays an important role in developing IR, primarily through altered gene expression. In addition, DNA methylation, histone transformation, and noncoding RNA activity are key mechanisms in hypertension that change protein transcription and expression as well as cell phenotypic variation. The translocation of GLUT4 to cell membranes is the first step of insulin-induced glucose uptake. Lower degree of expression and impaired translocation capacity of GLUT4 characterize the state of IR. As a result, IR and hyperinsulinemia are in charge of hypertension-related target organ injury as a result of defects in insulin's reverse regulatory effects. Several pathophysiological mechanisms reduce the signaling of insulin in hypertension, such as the renin-angiotensin-aldosterone system, the sympathetic nervous system, and oxidative stress. Besides, there is a weakening of mechanisms serving as defenses against IR in hypertension. The renin-angiotensin-aldosterone system plays an important role in the pathogenesis of IR. By way of the generation of reactive oxygen species, angiotensin II causes proteasome-mediated degradation of insulin-induced insulin receptor substrate-1, leading to impaired insulin activity. This effect triggers low-grade inflammation in blood vessels, causing the progress of insulin resistance and following cardiovascular events[2].

The primary pathogenesis of diabetes is increased IR. Therefore, identifying IR in this population is very important, in order to reduce the incidence of developing diabetes mellitus and reduce cardiovascular events in the future, especially when hypertension is a co-morbidity. There are many models to determine IR, which HOMA2 was built by Oxford University (UK) in 1996 from the original HOMA but has advantages over the HOMA1 model: HOMA2 calculates by computer program the original non-linear equations of the model more accurately, HOMA2 also takes into account hepatic glucose resistance (reducing the effect of hyperglycemia, inhibiting hepatic glucose production) and peripheral glucose resistance (reducing the effect of hyperglycemia, stimulating glucose absorption into muscles and adipose tissue).

Studies on IR in Vietnam or Ho Chi Minh City and southern provinces are currently focusing on obese or type 2 diabetes who have been diagnosed. There is currently no study on IR in the prediabetic population, especially those diabetes with hypertension, so this study was conducted to clarify this issue at Cho Ray Hospital. Based on the aforementioned reasons, the goal of this present study was to find out the prevalence of IR by using the HOMA2 calculator in the group of prediabetes patients with hypertension, compared with the group of prediabetes patients without hypertension.

II. SUBJECTS AND METHODS

2.1. Study design and participants

The study was patterned as a cross-sectional investigation, which was conducted

on two groups of subjects including prediabetes patients with and without hypertension.

Participants in the group of prediabetes patients without hypertension were at least 18 years old, diagnosed with diabetes according to the diagnostic criteria of ADA 2022, and did not have hypertension. Participants in the group of prediabetes patients without hypertension were at least 18 years old, diagnosed with diabetes according to the diagnostic criteria of ADA 2022 and with hypertension according to criteria of ISH 2020, or had been diagnosed with hypertension and were being treated for hypertension.

Severe patients, at risk of death; pregnant women; patients with indications for surgery; and patients with eGFR ≤ 30ml/min/1.73m2 were excluded from the study.

The sample size of the study is calculated from the study objective, applying the formula of estimating the incidence rate to calculate the minimum sample size for each group is n = 76.

Study period: February to September 2023. Location of study: Examination Department and Biochemistry Department – Cho Ray Hospital.

2.2. Data collection method:

Prediabetes patients with and without hypertension were selected from those who went for regular check-ups at Cho Ray Hospital's Examination Department.

The data collected included characteristics of age, gender, height, weight, BMI, systolic and diastolic blood pressure, fasting blood glucose, fasting insulin levels, and other biochemical tests. The indicators of HOMA2 were calculated by software from https://www.dtu.ox.ac.uk/homacalculator/.
The cut-off value for determining IR of HOMA2-IR is the 75th percentile of normal people. According to previous research, the cut-off value was HOMA2-IR ≥ 1,29[3].

We used ADA Diagnostic Criteria 2022 to diagnose prediabetes and 2020 ISH Global Hypertension Practice Guidelines criteria to diagnose hypertension. Fasting blood glucose quantification was performed on the Advia 1800 assay machine using the chemiluminescence method with the enzyme hexokinase. Fasting blood insulin quantification was performed on the Liaison assay machine using luminescent immunochemistry. Two levels of internal quality control were performed in accordance with the tests carried out in the study.

2.3. Statistical analysis

The data was carried out in the R environment. For quantitative variables, if the data had a normal distribution, it would be expressed in mean and standard deviation (M ± SD); if not, data would be expressed in the median and quartile range (Median [IQR]). Qualitative variables were represented as counts or frequencies (%). The chi-squared test was used to compare the difference in proportion in two groups. The t or Wilcoxon rank-sum test was used for the comparison of the means of two separate groups. The test of statistical significance was confirmed by a p-value of less than 0.05.

2.4. Ethics

The study had been approved by the Ethics Committee in Biomedical Research of Cho Ray Hospital (approval letter No. 1494/GCN-HĐĐĐ dated February 7, 2023). All candidates provided written informed consent.

III. RESULTS

The study collected data from 191 prediabetes patients: 95 people without

hypertension, of whom 6 had fasting insulin levels < 2.9 µU/mL, while the remaining 89 subjects were eligible for analysis; 96 people with hypertension, of whom 5 had fasting insulin levels < 2.9 µU/mL, 1 had fasting insulin levels > 57.6 µU/mL, and the remaining 90 subjects were eligible for analysis (Figure 1).

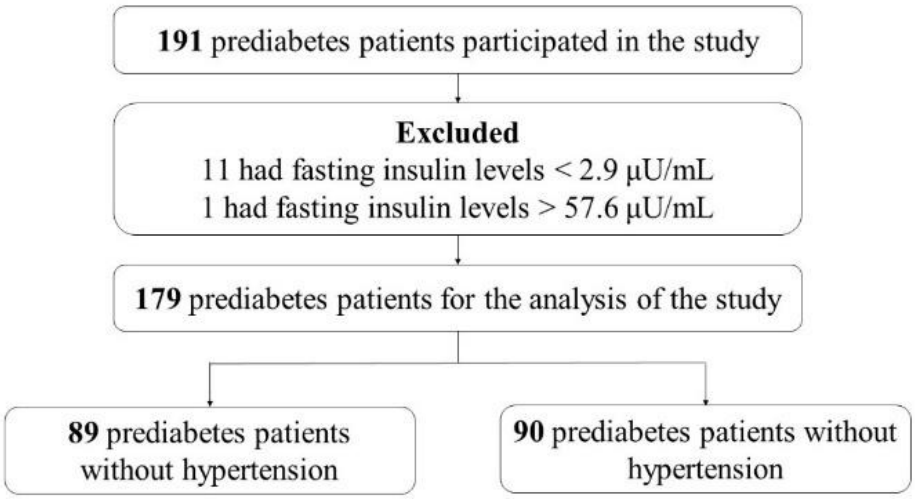

Figure 1. ***Flow diagram narrating the assemblage of the study sample***

3.1. General characteristics of study subjects

The average age of prediabetics without hypertension was 55.5 ± 12.1, with the oldest patient at 86 and the youngest at 29. The average age of prediabetics with hypertension was 61.9 ± 12.1, with the oldest patient at 89 and the youngest at 29. The average age of the group of people with hypertension was greater than that of the group of people without hypertension, which was statistically significant (P < 0.001). The proportion of females in the group of non-hypertension and hypertension was 64.0% and 64.4%, respectively. Gender ratio comparison showed no statistically significant difference between the non-hypertension and hypertension groups. Height, weight, and BMI in the hypertension group were not different from those in the non-hypertension group. Systolic and diastolic blood pressure in prediabetics with hypertension were greater than those in prediabetics without hypertension. (Table 1)

Table 1. ***Some of the anthropometric characteristics of the research subjects***

Variable	Prediabetics without hypertension (n = 89)	Prediabetics with hypertension (n = 90)	P
Age (years) M ± SD	55.5 ± 12.1	61.9 ± 12.1	<0.001*
Gender Female (%)	57 (64.0)	58 (64.4)	0.99**
Height (m) M ± SD	1.59 ± 0.05	1.58 ± 0.05	0.30*
Weight (kg) M ± SD	59.8 ± 5.59	60.1 ± 5.99	0.051*

Variable	Prediabetics without hypertension (n = 89)	Prediabetics with hypertension (n = 90)	P
BMI (kg/m²) M ± SD	22.9 ± 1.56	23.0 ± 1.93	0.06*
Systolic BP (mmHg) M ± SD	128.7 ± 11.3	141.1 ± 16.8	<0.001*
Diastolic BP (mmHg) M ± SD	74.4 ± 7.34	81.6 ± 9.95	<0.001*

* two-sample t-test
** chi-squared test

3.2. Laboratory tests of the study subjects

The results showed that eGFR and HDL-Cholesterol in the hypertensive group were different from the non-hypertensive group, which was statistically significant. Other subclinical indicators in the table have no differences between the two groups. (Table 2)

Table 2. ***Features of some laboratory tests of the research subjects***

Variable	Prediabetics without hypertension (n = 89)	Prediabetics with hypertension (n = 90)	P
Creatinine (mg/dL) M ± SD	0.76 ± 0.27	0.84 ± 0.29	0.07*
eGFR (mL/phút/1,73m²) M ± SD	95.3 ± 15.6	84.5 ± 20.4	<0.001*
Cholesterol (mg/dL) M ± SD	218.0 ± 45.5	220.0 ± 47.7	0.77*
HDL-Cholesterol (mg/dL) M ± SD	42.6 ± 11.9	47.6 ± 12.9	0.008*
LDL-Cholesterol (mg/dL) M ± SD	135.6 ± 42.8	143.3 ± 45.2	0.24*
Triglycerides (mg/dL) Median (IQR)	177 (140 – 235)	169.5 (133 – 222.5)	0.38**

* two-sample t-test
** Wilcoxon rank-sum test

There were no statistically significant differences in fasting glucose, HbA1c, and fasting insulin between the non-hypertensive and hypertensive groups. (Table 3)

Table 3. ***Fasting blood glucose, HbA1c, and fasting insulin of the study subjects***

Variable	Prediabetics without hypertension (n = 89)	Prediabetics with hypertension (n = 90)	P
Fasting glucose (mg/dL) M ± SD	101.9 ± 10.81	103.9 ± 10.87	0.21*
HbA1c (%) M ± SD	5.91 ± 0.83	6.10 ± 0.21	0.051*
Insulin (µU/mL) Median (IQR)	13.1 (6.7 – 15.9)	12.7 (9.7 – 19.1)	0.052**

* two-sample t-test
** Wilcoxon rank-sum test

3.3. Prevalence of insulin resistance in the study group

The prevalence of IR with the threshold values of 1.29 in HOMA2 in the overall prediabetes group was 56.9% The prevalence of IR in the hypertensive group was 66.7%, which was statistically significantly different from the non-hypertensive group of 47.2%. (Table 4)

Table 4. ***Prevalence of insulin resistance in the study group***

Insulin resistance HOMA2-IR ≥ 1.29	Prediabetics without hypertension (n = 89)	Prediabetics with hypertension (n = 90)	Prediabetics (n = 179)	P[1]
Frequency	42	60	102	
Ratio (%)	47.2	66.7	56.9	0.013*

[1] Test the difference between the prediabetics without hypertension and the prediabetics with hypertension

* chi-squared test

After statistical analysis, the results showed that the values of the indicators in the HOMA2 calculator did not differ statistically significantly between non-hypertensive and hypertensive groups. (Table 5)

Table 5. ***Comparison of indicators in the HOMA2-IR calculator between non-hypertensive and hypertensive groups***

	Prediabetics without hypertension (n = 89)	Prediabetics with hypertension (n = 90)	P
HOMA2-IR			
M ± SD	1.52 ± 0.91	1.73 ± 0.88	
Median (IQR)	1.27 (0.87 – 1.95)	1.56 (0.97 – 2.28)	0.051*
HOMA2-%B			
M ± SD	95.58 ± 38.57	101.75 ± 36.76	
Median (IQR)	91.2 (69.90 – 112.70)	95.50 (78.33 – 126.03)	0.18*
HOMA2-%S			
M ± SD	91.37 ± 52.25	76.06 ± 43.09	
Median (IQR)	78.6 (51.3 – 115.4)	64.0 (43.83 – 102.55)	0.053*
* Wilcoxon rank-sum test			

IV. DISCUSSION

There were 179 adults with prediabetes selected for the study, including 89 non-hypertensive and 90 hypertensive adults. The average age of both groups was over 50 years old, with women accounting for over 60%. The ages of the prediabetic patients in our study are consistent with the pathophysiological course of type 2 diabetes. According to the 2022 ADA recommendations, all people who are not at risk for early type 2 diabetes should be screened at age 45 and older[4]. Type 2 diabetes was formerly known as older adult diabetes or non-insulin-dependent diabetes. Insulin secreted by the pancreas, although reaching normal amounts, decreases, or does not play a role in regulating blood sugar levels due to a progressive decrease in pancreatic beta cell function on the background of IR. Impaired beta cell function and IR increase with age, in addition to overweight, obesity, and lack of physical activity.

The proportion of women in the prediabetes group in general and both non-hypertensive and hypertensive subgroups in particular is about 64%. This is in line with Pham Huu Tien's (2022)[5] previous study at Binh Thanh District Hospital of 60.3%. Most reports of meta-analysis of diabetes or prediabetes in Vietnam indicate that the incidence is higher in women than in men. This can be due to the following causes: women often suffer from a wider variety of diseases than men, hormonal changes, and immune-mediated inflammation in women are more complicated. In particular, women who are pregnant and may be associated with gestational diabetes, are at hazard in development to type 2 diabetes, whose mediated process is prediabetes.

The results of our study showed no statistically significant difference between non-hypertensive and hypertensive diabetics in fasting blood glucose, HbA1c, and fasting insulin levels. This was advantageous for the analysis of HOMA2-IR index values because the formula established in the HOMA2 is based on the subject's fasting glucose and insulin levels.

In our study, the prevalence of IR in the hypertensive group (n = 90) was 66.7%, greater than in the non-hypertensive group (n=89) of 47.2%, which was statistically significant, P = 0.013.

According to the literature and previous studies, the pathogenesis of prediabetes is mainly related to insulin reduction and insulin resistance. The first mechanism is a decrease in insulin secretion. The pancreas at this time does not produce enough insulin levels. Although not to the extent of type 1 diabetes, when the body is almost completely depleted of insulin because pancreatic cells are destroyed, in prediabetes, the pancreas still decreases insulin secretion. Studies have found that people with impaired fasting glycemia reduce insulin secretion early after meals, while people with impaired glucose tolerance may have reduced secretions. The second mechanism, as mentioned above, is when insulin is still fully secreted but cannot function properly because cells in sites such as muscle, liver, and fat tissue do not respond to insulin. The level of IR in people with prediabetes is not the same between these places. Specifically, people with impaired glucose tolerance exhibit significant IR in muscles, while people with impaired fasting glycemia often have stronger IR in the liver. The other site, adipose tissue, is related with the aforementioned phenomenon in both forms of prediabetes. These abnormal processes lead to different characteristics of the glycemic progression of these two forms. People with impaired fasting glycemia have preprandial blood glucose levels higher than normal but still lower after meals, while in people with impaired glucose tolerance, blood glucose increases continuously and does not decrease to normal levels after 2-3 hours[6,7].

Risk factors for diabetes include age ≥ 45, women, obesity, dyslipidemia, genetic factors, and hypertension. Hypertension and IR are components of metabolic syndrome and often integrate. Along with its metabolic effects, insulin causes vasodilation by stimulating the creation of nitric oxide (NO) in the endothelium and regulating sodium homeostasis by increasing sodium reabsorption in the kidneys thus contributing to blood pressure regulation[8].

Endothelial dysfunction may be one of the pathophysiological passageways clarifying the strong relationship between hypertension and IR in prediabetes. Some studies have

demonstrated that markers of endothelial dysfunction are affiliated with prediabetes, and endothelial dysfunction is associated with IR and hypertension. Inflammation could be another explanatory component for the relationship between the two phenomena. IR can develop not only in classical insulin-responsive tissues but also in others like cardiovascular tissues, in which insulin is involved in the development of cardiovascular diseases and hypertension[6-8].

The above explains the results of our study consistent with the pathogenesis and risk factors of the disease.

V. CONCLUSION

The rate of insulin resistance according to HOMA2 in prediabetic patients (n = 179) was 56.9%; in the prediabetics with hypertension (n = 90) was 66.7%, greater than in the prediabetics without hypertension (n = 89) of 47.2%, P = 0.013. Attention should be paid to good control of blood pressure in prediabetic patients in clinical practice.

FUNDING

Our research received no funding from any external person, company, or organizations.

CONFLICT OF INTEREST

All authors confirm that there are no potential conflicts of interest to declare.

ACKNOWLEDGEMENT

We would like to express our sincere gratitude to Cho Ray Hospital for facilitating the completion of this study.

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