JCTEI
JOURNAL OF CLINICAL TRIALS AND EXPERIMENTAL INVESTIGATIONS
Year: 2023 Volume: 2 Issue: 1

ORIGINAL ARTICLE

10.5281/zenodo.7671134

OPEN ACCESS

The diagnostic value of alterations in potassium and phosphate levels during an oral glucose tolerance test for hyperinsulinemia

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Received: 12 December 2022
Revised: 2 January 2023
Accepted: 5 February 2023
Published: 24 February 2023

Keywords
- Diabetes mellitus
- Hyperinsulinemia
- Oral glucose tolerance test
- Phosphate
- Potassium

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Abstract

Objective: We aimed to test whether the potassium and phosphate level alterations during the OGTT test are useful to diagnose hyperinsulinemia/insulin resistance.

Materials and methods: The study comprised patients who applied at our clinic for obesity or hyperglycemia and were scheduled for an oral glucose tolerance test (OGTT) because of high HbA1c levels or impaired fasting glucose levels. During the OGTT, blood glucose, insulin, potassium and phosphate patterns were measured at 0-30-60-90 and 120 minutes. Then potassium (K) and phosphate (P) changes were calculated (ΔK and ΔP).

Results: A total of 58 patients were included in the study, 63.8% (37 patients) were female and 36.2% (21 patients) were male. Mean age: 14.35±1.83 years, 79.3% were obese. A significant difference was found in the 90 min phosphate, ΔP2, and ΔP3 values of the patients with hyperinsulinemia were compared to the patients without hyperinsulinemia (respectively; p=0.018; p=0.040; p=0.005). There was no difference between ΔK values of the patients with and without hyperinsulinemia. While potassium level decreased to 3.6 mmol/L during OGTT, phosphate level decreased to 1.8 mg/dl.

Conclusions: ΔP2 and ΔP3 can be used as additional diagnostic parameters in the diagnosis of hyperinsulinemia. Phosphate and potassium should be checked before the test, as hypokalemia and hypophosphatemia may develop, especially in patients with significant hyperinsulinemia during the OGTT.

Introduction

Insulin resistance can generally be defined as a subnormal biological response to normal insulin concentrations (1). Although it is frequently associated with obesity, it may rarely be associated with genetic syndromes (2). Alongside the increase in the incidence of obesity in children, the incidence of insulin resistance/hyperinsulinemia also increases. Early detection of insulin resistance/hyperinsulinemia is important to prevent future comorbid conditions. There are many methods for monitoring of insulin resistance. These methods are based on the calculation of glucose levels and insulin levels with various formulas (3). Although the euglycemic clamp test is used as the gold standard among these methods, it is mostly used on a study basis because it is difficult to perform (4). Other methods vary in sensitivity and specificity (5,6). It is known that insulin reduces blood potassium and phosphate levels and is therefore used in the emergency treatment of hyperkalemia (7-9). This study was conducted to confirm the hypothesis that potassium and phosphate would cause further reductions in patients with hyperinsulinemia/insulin resistance during the oral glucose tolerance test (OGTT). The aim of this study was to determine the alterations in potassium and phosphate levels (Delta potassium: ΔK and delta phosphate: ΔP) during the OGTT test with simple insulin resistance indices calculated from glucose and insulin levels determined by OGTT in prediabetes children and to test whether ΔP and ΔK values can be used for diagnostic purposes for hyperinsulinemia.

Materials and methods

In the study, 58 patients between the ages of 12 and 18 who had impaired fasting glucose or HbA1c at the borderline of prediabetes and were scheduled for an OGTT test were included. Patients with abnormal thyroid function tests, acute illness, adrenal insufficiency, and electrolyte disorders were excluded from the study. The study protocol was approved by the University Ethics Committee (ethics committee number: 12.6.2020/144). Signed informed consent was obtained from the parents of the children. After at least 8 hours of fasting, the patient underwent an OGTT test in the morning. 1.75 g/kg (maximum 75 g) of powder glucose monohydrate was dissolved in 200 cc of water, and the patient was instructed to drink within 5 minutes. Venous blood samples were taken from the individuals included in the study. Yellow-capped biochemistry tubes without anticoagulants were used for the tests. Hemolyzed or lipemic samples were not included in the study. Biochemistry and hormone parameters were studied from the serum obtained. Within the scope of the study, serum potassium (K) level was measured by Ion Selective Electrode (ISE) method. Glucose, phosphorus (P) levels were measured by spectrophotometric method in Olympus AU5800 autoanalyzer (Beckman Coulter, Inc. Brea, CA92821 USA). Insulin level was measured by chemiluminescence method in ABBOTT ARCHITECT I 2000 SR (Abbott Laboratories Abbott Park IL, 60064, USA). During the OGTT, blood glucose and insulin, as well as potassium and phosphate patterns were measured at 0, 30, 60, 90 and 120 min, and delta potassium (ΔK) and delta phosphate (ΔP) values were calculated. (ΔK1: 30 min potassium – 0 min potassium, ΔK2: 60 min potassium – 0 min potassium, ΔK3: 90 min potassium – 0 min potassium, ΔK4: 120 min potassium – 0 min potassium; ΔP1: 30 min phosphate – 0 minute phosphate, ΔP2: 60 min phosphate – 0 min phosphate, ΔP3: 90 min phosphate – 0 min phosphate, ΔP4: 120 min phosphate – 0 min phosphate). The following simple insulin sensitivity/resistance indices were calculated from the blood glucose and insulin values during the OGTT.

HOMA-IR (10): Homeostasis Model Assessment): (fasting blood glucose [mmol/l] x fasting plasma insulin [µU/ml])/22.5

HOMA-B (Homeostasis Model Assessment–Beta-Cell Function) (10): Predicts steady state beta cell function (%B): (fasting plasma insulin [µU/ml]x20)/(fasting blood glucose [mmol/l]– 3.5)

HOMA-S (11): Predicts insulin sensitivity (%S). HOMA-S was calculated using the updated version of the HOMA calculator (12) using fasting glucose and insulin from OGTTs

QUICKI (Quantitative Insulin Sensitivity Check Index) index (13): 1/(log(fasting insulin µU/mL)+log(fasting glucose mg/dL))

Matsuda Index (14): 10,000/$\sqrt{}$(0 min glucose x 0 min insulin) x (mean glucose x mean insulin during OGTT), Insulin: µU/ml. Glucose: mg/dl

Insulinogenic Index (15): (30 min insülin – 0 min insulin)/(30 min glucose – 0 min glucose). Insulin: µU/ml. Glucose: mg/dl

Gutt index: Insulin sensitivity index (ISI 0,120) (16): 75,000 +(0 min blood glucose – 120 min blood glucose) (mg/dl)×0.19×BW/120×mean glucose (0 min, 120 min) (mmol/L)×Log Insulin (0 min, 120 min) (mU/L). BW: Body weight

Patients who met at least two of the total insulin >300 mU/L, 120 min insulin >75 mU/L and peak insulin >150 mU/L values during the OGTT, were grouped as hyperinsulinemia (17,18).

Table 1: Comparison of simple insulin indices of patients with and without hyperinsulinemia.

	Hyperinsulinemia (-) Median (25%–75% range)	Hyperinsulinemia (+) Median (25%–75% range)	p-values
Age	15.00 (12.87-16.38)	13.87 (12.75-15.50)	0.555
BMI (%)	95.44 (76,28-99.64)	99.77 (97.89-99.90)	**0.036**
HbA1c	5.65 (5.35-5.82)	5.70 (5.40-5.87)	0.693
0 min glucose	99.35 (89.55-112.25)	98.00 (92.62-103.00)	0.212
30 min glucose	138.70 (117.92-171.62)	153.85 (139.50-172.00)	0.242
60 min glucose	121.20 (105.25-162.42)	138.50 (121.62-155.30)	0.245
90 min glucose	129.00 (110.62-165.90)	130.50 (116.47-140.95)	0.506
120 min glucose	115.15 (104.15-152.10)	120.80 (105.82-135.00)	0.689

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 24.0 software (IBM Inc., Chicago, IL, USA). Numerical variables were summarized by median (25% – 75% range) as appropriate. The normality of the numerical variables was assessed with the Kolmogorov-Smirnov test. Independent-samples T-test was used to compare normally distributed independent groups, and the Mann-Whitney U test was used to compare non-normally distributed independent groups. A p-value less than 0.05 was considered statistically significant.

Results

A total of 58 patients were included in the study, 63.8% (37 patients) were female and 36.2% (21 patients) were male. Mean age: 14.35±1.83 years, 79.3% were obese. All patients had entered puberty. According to the insulin levels during the OGTT, while 44 of the patients had hyperinsulinemia, 14 patients did not have hyperinsulinemia. Simple insulin indexes of patients with hyperinsulinemia differed significantly from the patients without hyperinsulinemia. (HOMA-IR, HOMA-B, HOMA-S, Matsuda index, insülinojenik index, QUICKI index, Gutt index; sırasıyla p=0.002; p=0.004; p<0.001; p<0.001; p=0.020; p=0.004; p=0.027) (**Table 1**). In addition, there was a significant correlation between the total insulin level during the OGTT and the simple insulin index values (HOMA-IR, HOMA-B, HOMA-S, Matsuda index, insulinogenic index, QUICKI index, Gutt index; respectively r=0.508; r=0.502; r=-0.520; r=-0.884; r=0.385; r=-0.491; r=-0.438).

There was no difference in blood glucose levels during OGTT between patients with and without hyperinsulinemia (**Table 2**).

The 90 min phosphate, ΔP2, and ΔP3 values of patients with hyperinsulinemia were significantly different from those without hyperinsulinemia (respectively; p=0.018; p=0.040; p=0.005) (**Table 3**).

There was a moderate correlation (r=0.339 p=0.009) between total insulin level during the OGTT and ΔP3, and a weak correlation (r=0.310; p=0.018) with ΔP2. There was no difference between the ΔK values of patients with and without hyperinsulinemia (**Table 4**). However, there was a weak correlation between ΔK2 and Matsuda index (r=0.312; p=0.017), while a moderate correlation was found between ΔK2 and 60 min insulin (r=0.429; p=0.001).

The cut-off values, the area under the curve (AUC), and sensitivity and specificity values of these parameters, which are thought to be used in terms of hyperinsulinemia, are given in **Table 5**.

Discussion

Standards for insulin resistance in children have not been established. This is partly because different methods are used to test insulin sensitivity, there aren't enough cohort sizes to create normative distributions for insulin sensitivity, and there aren't enough longitudinal studies to connect insulin resistance definitions to long-term outcomes. There are numerous methods to predict insulin resistance. These methods are mostly based on the calculation of glucose levels and insulin levels with various formulas, where the sensitivity and specificity are different (3). The euglycemic hyperinsulinemic clamp is the "gold standard" for measuring insulin sensitivity, however, is burdensome, costly, and requires a research environment for participants (19). HOMA IR is the most

Table 2: Comparison of HbA1c and blood glucose values of patients with and without hyperinsulinemia.

	Hyperinsulinemia (-) Median (25%–75% range)	Hyperinsulinemia (+) Median (25%–75% range)	p-values
Age	15.00 (12.87-16.38)	13.87 (12.75-15.50)	0.555
BMI (%)	95.44 (76,28-99.64)	99.77 (97.89-99.90)	**0.036**
HbA1c	5.65 (5.35-5.82)	5.70 (5.40-5.87)	0.693
0 min glucose	99.35 (89.55-112.25)	98.00 (92.62-103.00)	0.212
30 min glucose	138.70 (117.92-171.62)	153.85 (139.50-172.00)	0.242
60 min glucose	121.20 (105.25-162.42)	138.50 (121.62-155.30)	0.245
90 min glucose	129.00 (110.62-165.90)	130.50 (116.47-140.95)	0.506
120 min glucose	115.15 (104.15-152.10)	120.80 (105.82-135.00)	0.689

widely used to define insulin resistance and was found to be highly associated with fasting insulin (r≥0.95) in children (20). Similarly, a high correlation was found between HOMA-IR and fasting insulin (r=0.974) and other insulins (30, 60, 90 and 120 minutes) in our study. However, we did not find any relationship between HOMA-IR and HOMA-S and fasting blood glucose in our study. A moderately significant relationship was found between fasting blood glucose and HOMA-B (r=0.361 p=0.05).

Because there is no standardization between manufacturers and clinical laboratories, some problems may occur in immunoassays used to measure circulating insulin. In addition, cross-reactivities of insulin assays with proinsulin and insulin-related peptides adversely affect the results (21,22). Although insulin standardization has improved in recent years, additional factors have been included in insulin to increase the diagnostic accuracy of insulin resistance (Alanine aminotransferase, Triglyceride, HDL cholesterol, gender, waist circumference, etc.) (23-25). It is known that insulin reduces blood potassium and is therefore used in the emergency treatment of hyperkalemia. The potassium-lowering effects of insulin are mediated by stimulation of Na+-K+-ATPase activity in skeletal muscle (25,26). In previous studies, it has been shown that insulin decreases the phosphate level in a dose-dependent manner (9). In addition, blood potassium and phosphate levels decrease with insulin infusion during the treatment of diabetic ketoacidosis (7,8). In our study, we supposed the alterations in potassium and phosphate levels in parallel with the increased insulin level during OGTT due to these effects of insulin, and we tested whether ΔK and ΔP can be used diagnostically in the diagnosis of insulin resistance/hyperinsulinemia. We found a

Table 3: Comparison of phosphate and ΔP values of patients with and without hyperinsulinemia.

	Hyperinsulinemia (-) Median (25%–75% range)	Hyperinsulinemia (+) Median (25%–75% range)	p-values
0 min Phosphate	4.51 (3.75-5.20)	4.38 (3.93-4.98)	0.641
30 min Phosphate	4.18 (3.58-4.83)	3.98 (3.44-4.48)	0.350
60 min Phosphate	4.09 (3.62-4.61)	3.70 (3.07-4.20)	0.080
90 min Phosphate	3.99 (3.48-4.57)	3.45 (2.91-4.00)	**0.040**
120 min Phosphate	3.85 (3.10-4.32)	3.40 (2.63-4.00)	0.170
ΔP1	0.28 (0.17-0.60)	0.40 (0.27-0.60)	0.275
ΔP2	0.48 (0.13-0.75)	0.79 (0.50-0.90)	**0.018**
ΔP3	0.65 (0.10-1.01)	0.97 (0.77-1.19)	**0.005**
ΔP4	0.14 (0.04-0.35)	0.20 (0.10-0.34)	0.165

Table 4: Comparison of potassium and ΔK values of patients with and without hyperinsulinemia.

	Hyperinsulinemia (-) Median (25%–75% range)	Hyperinsulinemia (+) Median (25%–75% range)	p values
0 min potassium	4.39 (4.07-4.57)	4.30 (4.10-4.50)	0.524
30 min potassium	4.05 (3.93-4.34)	4.10 (4.00-4.30)	0.777
60 min potassium	4.15 (3.90-4.46)	4.10 (3.88-4.39)	0.483
90 min potassium	4.18 (3.97-4.43)	4.10 (3.90-4.31)	0.408
120 min potassium	4.16 (3.97-4.40)	4.09-3.91-4.27)	0.339
ΔK1	0.24 (0.02-0.33)	0.20 (0.00-0.30)	0.381
ΔK2	0.16 (-0.20-0.43)	0.20 (0.01-0.31)	0.806
ΔK3	0,11 (-0.02-0.40)	0.20 (0.10-0.32)	0.607
ΔK4	0.14 (0.04-0.35)	0.20 (0.10-0.34)	0.642

significant difference in ΔP2 and ΔP3 values between the patients with and without hyperinsulinemia (p=0.018, p=0.005, respectively).

We found a sensitivity of 0.886 and a specificity of 0.500 to indicate hyperinsulinemia when the ΔP2 value was above 0.37 mg/dl during the OGTT. In addition, we found a sensitivity of 0.864 and a specificity of 0.500 in demonstrating hyperinsulinemia when the ΔP3 value was above 0.50 mg/dl during the OGTT (**Figure 1**). In our study, we also determined the cut-off values for HOMA-IR, HOMA-B, Insulinogenic index, 0-30-60-90 and 120 min insulin patterns during OGTT, which are used in the diagnosis of hyperinsulinemia (**Table 5**).

One study found that 0 min phosphate and 120 min blood glucose levels were correlated. (27). We found a weak correlation between 0 min phosphate and 90 min blood glucose in our study. In addition, we found weak correlations between 30 min phosphate and 90 and 120 min blood glucose, 60 min phosphate and 90 and 120 min blood glucose, and 90 min phosphate and 120 min blood glucose levels.

During the OGTT test, the plasma phosphate level decreased more significantly to 1.8 mg/dl and the potassium level also decreased to a minimum of 3.6 mmol/L (**Figure 2**).

It is well established that plasma phosphate facilitate the release of oxygen from hemoglobin to tissues due to its regulatory role on erythrocyte 2,3

Table 5: Serum levels significant parameters for the diagnosis of hyperinsulinemia

	AUC (95% CI)			p-value	Cut Off value	Sensitivity	Specificity
	LB	Area	UB				
HOMA-IR	0.651	0.776	0.901	**0.002**	**4.58**	0.727	0,786
HOMA-B	0.602	0.760	0.918	**0.004**	**117.40**	0.886	0.643
Insulinogenic index	0.537	0.709	0.880	**0.020**	**1.42**	0.773	0.643
0 min insulin	0.699	0.808	0.918	**< 0.001**	**15.65**	0.818	0.500
30 min insulin	0.705	0.823	0.941	**< 0.001**	**90.60**	0.864	0.643
60 min insulin	0.701	0.823	0.945	**< 0.001**	**70.10**	0.841	0.643
90 min insulin	0.692	0.828	0.964	**<0.001**	**81.50**	0.841	0.714
120 min insulin	0.734	0.862	0.990	**<0.001**	**75.15**	0.841	0.929
ΔP2	0.536	0.692	0.847	**0.032**	**0.37**	0.886	0.500
ΔP3	0.531	0.700	0.870	**0.025**	**0.50**	0.864	0.500

AUC: Area under the curve. 95% CI: 95% Confidence Interval. LB: Lower Bound UB: Upper Bound. ΔP2: 60.min phosphate-0. minute phosphate. ΔP3: 90. min phosphate-0.minute phosphate.

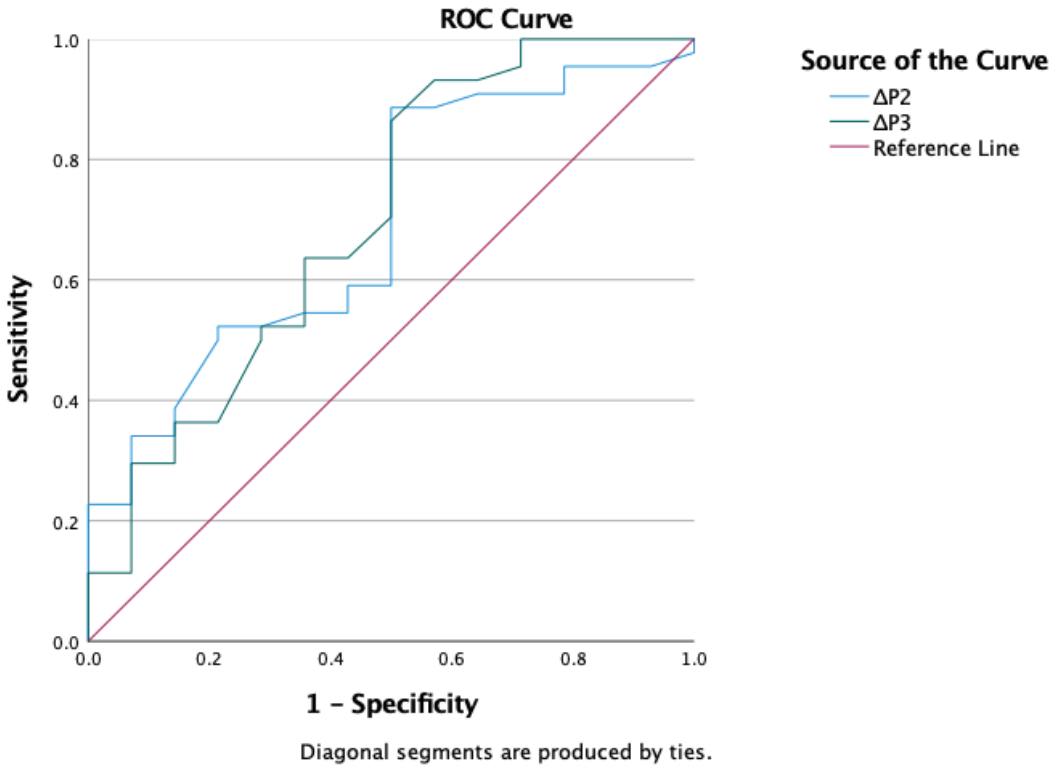

Figure 1: Sensitivity and specificity values of delta phosphate 2 (ΔP2) and delta phosphate 3 (ΔP3) in the diagnosis of hyperinsulinemia. ΔP2: 60. min phosphate value is – 0. min phosphate value, ΔP3: 90. min phosphate value – 0. min phosphate value.

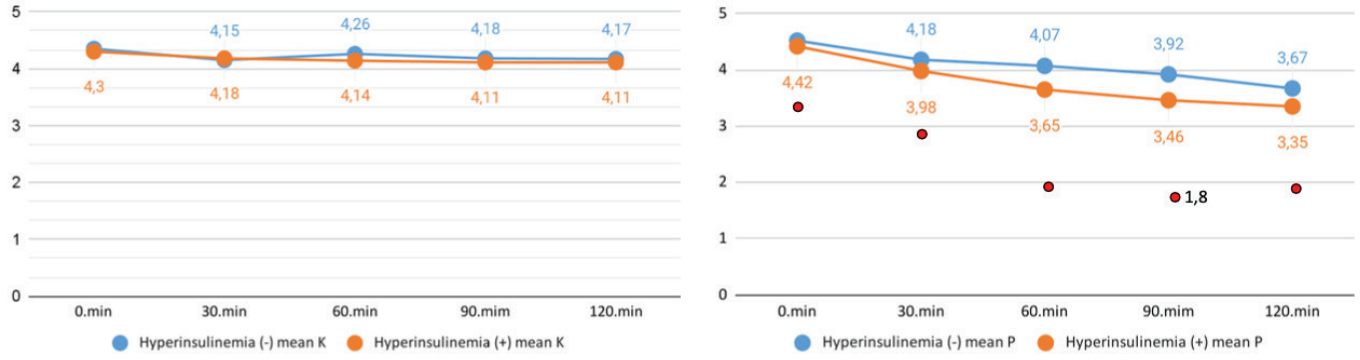

Figure 2: Change in potassium (mmol/L) and phosphate (mg/dl) during OGTT. Annotation: Red circles indicate minimum values

diphosphoglycerate. Hypophosphatemia leads to impaired oxygen delivery to tissues. It has also been shown in many researches (9,28-30) that hypophosphatemia causes deterioration in central nervous system functions, hemolysis and phagocytosis. Considering that the phosphate level decreased to 1.8 during the OGTT in our study, care should be taken in terms of side effects related to hypophosphatemia. Since there is a risk of severe hypophosphatemia during the OGTT test in patients with borderline hypophosphatemia, phosphorus level should be checked before the test.

Conclusions

ΔP2 and ΔP3 can be used as diagnostic parameters for detection of hyperinsulinemia. To confirm this, more comprehensive tests are needed to compare with the euglycemic hyperinsulinemic clamp test, which is accepted as the gold standard. Phosphate and potassium should be checked before the test, as hypokalemia and hypophosphatemia may develop, especially in those with significant hyperinsulinemia

during the OGTT.

Conflict of interest: The authors report no conflict of interest.

Funding source: No funding was required.

Ethical approval: Ethical approval Approval obtained from Sakarya University Faculty of Medicine (12.6.2020/144)

Acknowledgement: Biochemists Assoc. Dr. Erdem Çokluk and Dr. Fatıma Betul Tuncer

Contributions

Research concept and design: **RP**
Data analysis and interpretation: **RP**
Collection and/or assembly of data: **RP**
Writing the article: **RP**
Critical revision of the article: **RP**
Final approval of the article: **RP**

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