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Impact of glucagon response on postprandial hyperglycemia in men with impaired glucose tolerance and type 2 diabetes mellitus

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Abstract

Glucagon is the physiological antagonist of insulin. Postprandial (pp) hyperglycemia in impaired glucose tolerance (IGT) and in type 2 diabetes mellitus (T2DM) may also depend on irregularities in glucagon secretion. This study investigated the glucagon excursion after a lipid-glucose-protein tolerance test in subjects with different stages of glucose intolerance. We also analyzed the relationship between pp glucagon secretion and hyperglycemias. A total of 64 men (27 healthy subjects with normal glucose tolerance [NGT], 15 with IGT, and 22 with T2DM) were examined. Plasma glucose (PG), insulin, proinsulin, free fatty acids, and triglycerides were measured in the fasting state and at 30 minutes and 2, 3, 4, and 6 hours after the intake of the test meal, which contained 126 g carbohydrates, 92 g fat, and 17 g protein. Postprandial concentrations of metabolic parameters were calculated as area under the curve (AUC). Glucagon was measured in the fasting state and at 30 minutes and 2 and 4 hours pp. Early glucagon increment was defined as glucagon at 30 minutes minus fasting glucagon. The insulin response was quantified as insulin increment divided by PG increment in the corresponding time. Insulin resistance was calculated using homeostasis model assessment (HOMA). Fasting glucagon was significantly increased in IGT vs NGT ($P < .05$), and early glucagon increment was significantly higher in T2DM vs NGT and IGT ($P < .05$). The 2-hour glucagon concentration after the load (AUC) was increased in IGT and T2DM vs NGT ($P < .05$). Early glucagon increment and the 2-hour AUC of glucagon were strongly correlated to pp glycemia ($r = 0.494$ and $P = .001$, and $r = 0.439$ and $P = .003$, respectively). An inverse correlation was observed between early glucagon increment and insulin response at 30 minutes and 2 hours after the meal load ($r = -0.287$ and $P = .026$, and $r = -0.435$ and $P = .001$, respectively). The 2-hour AUC of glucagon was significantly associated with insulin resistance ($r = 0.354$, $P = .020$). Multivariate analysis revealed 2-hour insulin response and early glucagon increment as significant independent determinants of the AUC of PG in IGT ($R = 0.787$). In T2DM, 2-hour insulin response, insulin resistance, and early glucagon increment were significant determinants of the AUC of PG ($R = 0.867$). Our study suggests an important role for the irregularities in glucagon response in the pp glucose excursion after a standardized oral mixed meal in IGT and in T2DM. According to our data, a bihormonal imbalance starts before diabetes is diagnosed. Prospective studies are needed to evaluate the impact of glucagon on the progression of glucose intolerance and the possible effects of medicinal suppression of glucagon increment to prevent the progression of glucose tolerance.

1. Introduction

Diabetes develops as a bihormonal disease. Glucagon is the physiological antagonist of insulin. Thus, postprandial (pp) hyperglycemia may also depend on irregularities in glucagon secretion possibly before diabetes is diagnosed. As far as insulin is concerned, in the prediabetic stage, there is already a deficit in early insulin response as well as increased insulin resistance [1-4]. At the same time, glucagon suppression is impaired after an oral or intravenous (IV) glucose load [5-13] in impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM). It has been noted that the glucose-induced insulin response is greater after an oral load as compared with an IV glucose injection because of the effect of incretins [14]. So it follows that it is important to investigate pp metabolic regulations under physiological conditions such as after the intake of a mixed meal. A standardized mixed meal with a relatively high fat and protein concentrations, and a glucose concentration corresponding to a standardized oral glucose tolerance test

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(OGTT) may yield a more physiological and suitable model to test the impact of glucagon on pp glucose regulation.

Only scarce information exists about the relevance of pp glucagon excursions in subjects with IGT and T2DM after a mixed meal [15-18]. According to literature data, the pp metabolic response can be influenced by sex, age, obesity, smoking, drugs (particularly β-blockers) [18-21], and the composition of food [17,22,23]. Therefore, a homogenous study population of male sex was carefully selected for this study to avoid bias by the aforementioned cofactors.

This study aims to answer the following questions: (1) how does the glucagon excursion change after a lipid-glucose-protein tolerance test (LGTT) in the different stages of glucose intolerance? (2) And, what is the impact of the irregularities in pp glucagon response on glucose tolerance?

2. Materials and methods

2.1. Subjects and study design

A total of 64 men, aged 44 to 70 years, with body mass index (BMI) of less than 35 kg/m^2, were examined [24]. All study participants were nonsmokers and had fasting triglycerides of less than 4.6 mmol/L. Additional exclusion criteria were liver, kidney, or thyroid disease; acute infectious diseases; medication affecting glucose metabolism (β-blocker agents, lipid-lowering drugs, thiazide diuretics, and glucocorticoids). Patients with T2DM were drug naive or on monotherapy with oral antidiabetics. Only 11 of 22 patients with diabetes were on oral agents: 2 on each of repaglinide, glibenclamide, and metformin, and 5 on acarbose. All subjects with IGT were free of antidiabetic medication.

A standard OGTT with 75-g glucose was used in accordance with the recommendations of the American Diabetes Association and the World Health Organization as a screening test for the classification of the glucose intolerance stages [25,26].

The group of normal glucose tolerance (NGT) included subjects with fasting plasma glucose (PG) less than 7.0 mmol/L and 2-hour PG less than 7.8 mmol/L. The group of IGT included subjects with fasting PG less than 7.0 mmol/L and 2-hour PG of 7.8 mmol/L or higher and less than 11.1 mmol/L. Twenty-seven subjects had NGT and 15 IGT.

2.2. Lipid-glucose-protein tolerance test

The lipid-glucose-protein drink consisted of a mixture of ScandiShake (Pfimmer Nutricia GmbH, Erlangen, Germany) plus 200 g of 30% cream and 50 g glucose. It had to be consumed within 5 minutes. ScandiShake is a milk powder that is enriched with carbohydrates and vegetable oils; 85 g of powder is mixed in 240-mL milk (69.5 g carbohydrates, 30.4 g fat, and 11.7 g protein). In total, the test meal contains 126 g carbohydrates, 92 g fat, and 17 g protein (5983.12 kJ [1430 kcal]). The subjects remained during the test in a sitting position to avoid physical activity. The study participants were requested to refrain from alcohol consumption and to be on their usual diet for 2 days before the test day. Blood was collected in the fasting state and at 30 minutes and 2, 3, 4, and 6 hours after the intake of the lipid-glucose-protein shake, which had to be consumed

Table 1
Basic characteristics of the study participants with NGT, IGT, and T2DM

	NGT	IGT	T2DM	*P*
n	27	15	22	
Age (y)	58.7 ± 8.9	54.7 ± 10.3	59.3 ± 7.3	NS
BMI (kg/m^2)	26.2 ± 2.5	27.6 ± 3.5	27.3 ± 3.2	NS
Waist-to-hip ratio	0.95 ± 0.52	0.96 ± 0.76	0.97 ± 0.49	NS
Blood pressure systolic (mmHg)	134 ± 19	131 ± 15	141 ± 17	NS
Blood pressure diastolic (mmHg)	80 ± 8	81 ± 8	84 ± 8	NS
PG, fasting[c] (mmol/L)	5.71 ± 0.62	6.12 ± 0.70	9.69 ± 3.38[d,e]	<.01
PG 2 h_c after LGTT (mmol/L)	6.67 ± 1.36	8.90 ± 2.00[f]	15.24 ± 6.10[d,e]	<.01
HbA_{1c}[c] (%)	5.3 ± 0.3	5.6 ± 0.5	7.1 ± 1.0[d,e]	<.01
Glucagon, fasting (pmol/L)	37.86 ± 9.18	48.05 ± 16.17[f]	42.19 ± 10.67	.03
Insulin, fasting[c] (pmol/L)	60.00 ± 22.20	85.73 ± 51.82	93.59 ± 77.98	NS
Proinsulin, fasting[c] (pmol/L)	2.99 ± 1.98	3.49 ± 2.82	7.36 ± 6.39[a]	.01
FFA, fasting (μmol/L)	0.49 ± 0.20	0.51 ± 0.22	0.58 ± 0.21	NS
Total cholesterol (mmol/L)	5.50 ± 0.70	5.05 ± 0.84	5.13 ± 0.84	NS
TG (mmol/L)	1.43 ± 0.75	1.37 ± 0.59	1.99 ± 1.02[a,b]	.03
HDL-C (mmol/L)	1.19 ± 0.26	1.08 ± 0.26	0.98 ± 0.22[a]	.02

Values are expresse as mean ± SD. NS indicates not significant; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol.

[a] $P < .05$, T2DM vs NGT.

[b] $P < .05$. T2DM vs IGT.

[c] Logarithmically transformed values in analysis of variance.

[d] $P < .001$, T2DM vs NGT.

[e] $P < .001$, T2DM vs IGT.

[f] $P < .05$, IGT vs NGT.

within 5 minutes. Glucagon was measured in the fasting state and at 30 minutes and 2 and 4 hours after the load.

2.3. Laboratory examinations

Plasma glucose was measured by the hexokinase method. Glycated hemoglobin (HbA_{1c}) was determined by high-performance liquid chromatography. Plasma glucagon was measured by radioimmunoassay (IBL, Hamburg, Germany; coefficient of variation [CV] = 8.9%); serum insulin level, by microparticle enzyme immunoassay (Abbott, Wiesbaden, Germany; with an interassay CV of <5%); and serum proinsulin level, by enzyme immunoassay (DRG Instruments GmbH, Germany; CV = <6%). Free fatty acids (FFA) were measured by microtiter analysis (ANTHOS II, Anthos Labtec Instruments, Salzburg, Austria).

2.4. Statistical analysis

Data evaluation was performed using the SPSS 11.0 program (SPSS, Inc, Chicago, Ill). The distribution of values was assessed by the Kolmogorov-Smirnov test for homogeneity of variances, and parameters were transformed logarithmically if necessary. The correlations between variables were assessed using the Pearson correlation coefficient. Metabolic parameters of the 3 groups were compared by analysis of variance. The level of significance was set to $P < .05$. Data are presented as mean ± SD.

The pp excursion of PG, insulin, proinsulin, triglycerides, and FFA was calculated as AUC for 6 hours after the meal intake.

The early glucose increment (ΔPG at 30 minutes) was calculated as the difference between the glucose at 30 minutes and the fasting glucose, and 2-hour PG increment (ΔPG at 2 hours) as glucose at 2 hours minus fasting glucose. The same refers to early insulin and early glucagon increment.

The pp excursion of glucagon was calculated as AUC for 2 and 4 hours after the load, respectively.

The early insulin response was defined as change in insulin at 30 minutes divided by change in PG at 30 minutes by analogy from previous literature data [27]. The 2-hour insulin response was quantified as 2-hour insulin increment divided by 2-hour PG increment.

A multiple linear regression analysis was conducted to obtain correlation coefficient (R) and regression coefficient (β) of independent variables that predict the dependent variable.

Insulin resistance was calculated by HOMA [28].

3. Results

The baseline characteristics of our study population are shown in Table 1. The subgroups were well balanced for age, BMI, waist-to-hip ratio, blood pressure, cholesterol, and FFA. Triglycerides were somehow higher and high-density lipoprotein cholesterol lower in T2DM. The HbA_{1c} of 7.1% in T2DM is indicative of good diabetic control. Fasting glucagon was significantly increased in IGT vs NGT. Fasting proinsulin was significantly higher in T2DM than in IGT, and there was a trend toward higher fasting insulin levels in diabetes as well. Fig. 1A displays the changes in PG concentration after the test drink. In patients with NGT, glucose experiences a rapid increase, reaching its peak at 30 minutes and returning to baseline after 4 hours. In contrast, patients with IGT and T2DM reach their peak later, at 2 hours, and return to baseline at 4 and 6 hours, respectively. The 2-hour PG levels were significantly different in the 3 groups ($P < .001$), and they increased along with the AUC after the LGTT (Fig. 1A; Table 2).

Six subjects with IGT (40%) had an impaired fasting glucose (between 6.1 and 7.0 mmol/L) on the day of the mixed load.

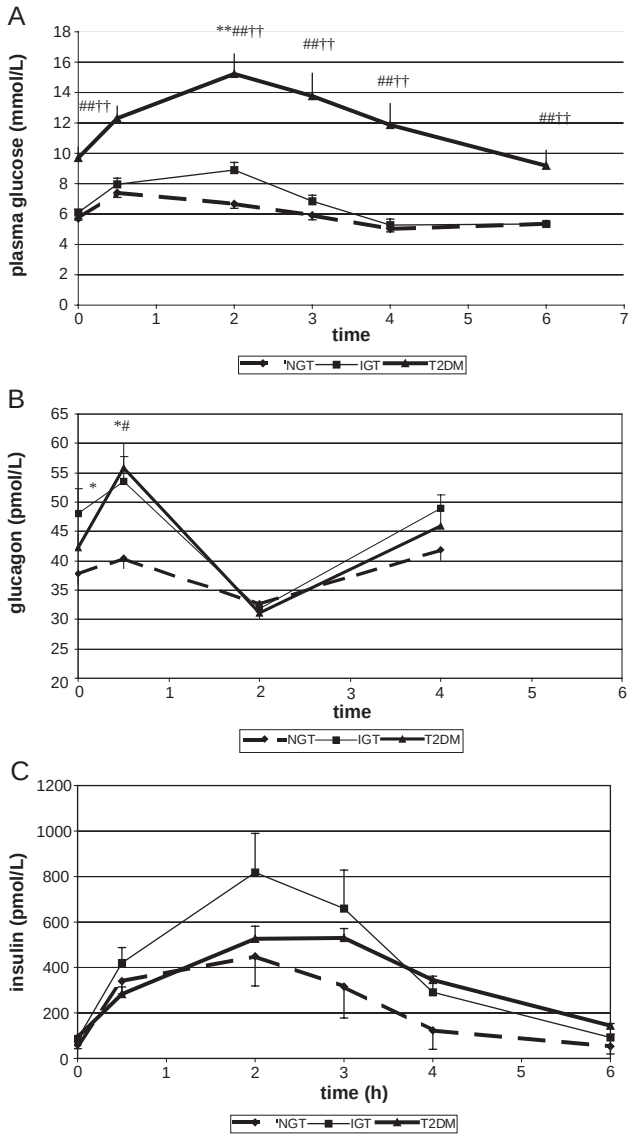

Fig. 1. Plasma glucose (A), glucagon (B), and insulin (C) excursion after lipid-glucose-protein load in subjects with NGT (n = 27), IGT (n = 15), and T2DM (n = 22). Data are expressed as mean ± SEM between 0 and 6 hours. $^{*}P < .05$, IGT vs NGT; $^{\#}P < .05$, T2DM vs NGT; $^{\#\#}P < .001$, T2DM vs NGT; $^{\dagger}P < .05$, T2DM vs IGT; $^{\dagger\dagger}P < .001$, T2DM vs IGT.

Table 2
Metabolic parameters in study groups with NGT, IGT, and T2DM

	NGT	IGT	T2DM	*P*
n	27	15	22	
6-h AUC of PG[a] (mmol/L × 6 h)	36.01 ± 4.24	40.71 ± 5.13	74.53 ± 31.78[b,c]	<.01
Early glucagon increment (pmol/L)	2.7 ± 9.0	5.6 ± 5.9	13.5 ± 15.8[de]	.01
2-h AUC of glucagon (pmol/L × 2 h)	73.14 ± 11.5	85.41 ± 16.6[f]	86.00 ± 17.4[d]	.03
4-h AUC of glucagon (pmol/L × 4 h)	146.6 ± 17.6	167.8 ± 21.6	161.5 ± 29.2	.05
Early insulin increment (pmol/L)	279.6 ± 158.3	334.0 ± 229.4	189.7 ± 209.6	NS
2-h insulin increment[a] (pmol/L)	388.9 ± 278.9	732.0 ± 646.9[f]	432.6 ± 559.9[e]	<.05
Early insulin response[a]	164.9 ± 176.5	202.2 ± 155.0	86.4 ± 94.6[b,c]	<.01
2-h insulin response[a]	486.3 ± 1657.4	393.6 ± 794.0	145.7 ± 230.3[b,e]	<.01
6-h AUC of insulin[a] (pmol/L × 6 h)	1469.05 ± 581.7	2643.0 ± 1768.2	2155.9 ± 2062.9	NS
6-h AUC of proinsulin (pmol/L × 6 h)	86.4 ± 58.4	129.4 ± 107.2	132.5 ± 82.9	NS
Insulin resistance[a] (HOMA)	15.4 ± 6.1	23.8 ± 15.9	41.0 ± 37.7[d]	<.01
6-h AUC of FFA[a] (μmol/L × 6 h)	2.06 ± 0.62	2.09 ± 0.61	2.48 ± 0.79	NS
6-h AUC of TG (mmol/L × 6 h)	13.95 ± 6.74	12.22 ± 4.27	18.05 ± 8.56[d,e]	.03

Values are expresse as mean ± SD.
[a] Logarithmically transformed values in analysis of variance.
[b] $P < .001$, T2DM vs NGT.
[c] $P < .001$, T2DM vs IGT.
[d] $P < .05$, T2DM vs NGT.
[e] $P < .05$, T2DM vs IGT.
[f] $P < .05$, IGT vs NGT.

A rapid and significant rise in glucagon can be observed after 30 minutes in IGT and T2DM but not in NGT (Fig. 1B). The peak levels at 30 minutes are significantly increased in T2DM (Fig. 1B; Table 2). Glucagon drops below baseline levels after 2 hours and returns to baseline level after 4 hours in all groups. The glucagon concentration 2 hours after the load but not after 4 hours was increased in IGT and T2DM vs NGT ($P = .052$).

Early insulin and 2-hour insulin response were considerably reduced in T2DM (Fig. 1C; Table 2). The difference in pp insulin (6-hour AUC of insulin) and proinsulin (6-hour AUC of proinsulin) concentration between the 3 study groups did not reach statistical significance ($P = .056$ and $P > .05$, respectively). Insulin resistance calculated by homeostasis model assessment (HOMA) was significantly higher in T2DM, with a tendency also for IGT. The AUC of FFA for 6 hours was similar in all 3 groups, whereas the 6-hour AUC of triglycerides was significantly higher in T2DM (Table 2).

Table 3 shows the correlation of different variables with the 6-hour AUC of PG. Glucagon increment and the 2-hour AUC of glucagon were strongly correlated to pp glucose excursion. An inverse correlation was observed between pp hyperglycemia and early insulin response and 2-hour insulin response, and a positive correlation, between pp hyperglycemia and insulin resistance. A significant correlation was

Table 3
Univariate correlation of the 6-hour AUC of PG to metabolic parameters in LGTT in total (n = 64)

	6-h AUC of PG (mmol/L × 6 h)
	r (*P*)
BMI (kg/m^2)	0.29 (.02)
Glucagon, fasting (pmol/L)	NS
Early glucagon increment (pmol/L)	0.49 (<.01)
2-h AUC of glucagon (pmol/L × 2 h)	0.44 (<.01)
Insulin, fasting (pmol/L)	NS
6-h AUC of insulin (pmol/L × 6 h)	NS
Early insulin response	−0.55 (<.01)
2-h insulin response	−0.74 (<.01)
Proinsulin, fasting (pmol/L)	0.59 (<.01)
6-h AUC of proinsulin (pmol/L × 6 h)	0.37 (<.01)
Insulin resistance (HOMA)	0.50 (<.01)
FFA, fasting (μmol/L)	0.30 (.02)
6-h AUC of FFA (μmol/L × 2 h)	0.44 (<.01)
Triglycerides, fasting (mmol/L)	0.42 (<.01)
6-h AUC of TG (mmol/L × 6 h)	0.38 (<.01)

Table 4
Multiple linear regression analysis

	β	*P*	R
Independent determinants of 6-h AUC of PG in NGT			
6-h AUC of proinsulin	.78	<.01	0.78
Independent determinants of 6-h AUC of PG in IGT			
2-h insulin response	.56	.02	0.79
Early glucagon increment	.45	<.05	
Independent determinants of 6-h AUC of PG in T2DM			
2-h insulin response	.58	<.01	0.87
Insulin resistance (HOMA)	.40	<.01	
Early glucagon increment	.30	.04	
Independent determinants of 6-h AUC of PG in NGT, IGT, and T2DM			
2-h insulin response	.42	<.01	0.87
Insulin resistance (HOMA)	.35	<.01	
Early insulin response (30 min)	.21	.02	
Early glucagon increment	.20	.02	
BMI	.17	.04	

R indicates regression coefficient. Dependent determinant: 6-hour AUC of PG; independent variables: BMI, early glucagon increment, early insulin response (30 minutes), 2-hour insulin response, 6-hour AUC of proinsulin, 6-hour AUC of triglycerides, 6-hour AUC of FFA, insulin resistance (HOMA).

also found for BMI, triglycerides, and FFA. An inverse correlation was observed between early glucagon increment and early insulin response ($r = -0.287$, $P = .026$), and between early glucagon increment and 2-hour insulin response ($r = -0.435$, $P = .001$), respectively. The 2-hour AUC of glucagon after the meal was significantly associated with insulin resistance calculated according to HOMA ($r = 0.354$, $P = .020$).

Multivariate analysis for pp hyperglycemia (6-hour AUC of PG) reveals proinsulin AUC in NGT ($R = 0.784$); 2-hour insulin response and early glucagon increment in IGT ($R = 0.787$); and 2-hour insulin response, insulin resistance, and early glucagon increment in T2DM ($R = 0.867$) (Table 4). Two-hour insulin response, insulin resistance, early insulin response, early glucagon increment, and BMI were the independent determinants of pp glucose excursion in all study groups.

4. Discussion

In our study in a homogenous population of 64 middle-aged men with different levels of glucose intolerance, we found an important role for the irregularities in glucagon response in the pp glucose excursion after the ingestion of a standardized mixed meal.

Our data, in principle, confirm abnormal glucagon release in IGT and T2DM after a standardized LGTT with a glucose amount corresponding to 75-g OGTT. A diminished suppression of glucagon increment after an oral glucose and mixed meal load, respectively, has been reported for IGT [5-11] and T2DM [15-18].

Previously published data in IGT may include many cases of diabetes [5,7-10] because the updated classification for glucose tolerance stages was not used [25,26]; furthermore, studies using IV glucose do not include enteroinsulinar axis, eliciting a different response from the physiologic [6,11]. The early glucagon excursion in our study was positive in the 3 groups in contrast to previously reported data with OGTT alone or IV glucose.

This suggests that the pp response after a mixed meal is different from that elicited with 75-g OGTT load and can be considered as a more physiological model to evaluate the bihormonal situation in the pp phase.

In studies with 75-g OGTT, insulin peak in IGT was observed after 30 minutes [2,3]. In our model with LGTT, plasma and insulin peaks in subjects with IGT were observed after 2 hours. A deficit in early insulin response in IGT has been demonstrated [2,3]. We have not found any significant deficit in insulin response in IGT after LGTT (Table 2).

As shown in Fig. 1B and Table 2, a significant difference in the pp glucagon excursion 2 hours after LGTT exists already in IGT and also in T2DM compared with control. It is of interest to note that the alpha cells' response to LGTT in IGT was already impaired, whereas beta cells still retained sufficient secretory capacity. In contrast to previous published data [29], this observation suggests that abnormal glucagon response in subjects with IGT can exist under a condition of insignificantly impaired insulin secretion.

As already mentioned, this divergence may be explained by the inclusion of subjects with diabetes in previous studies by the use of a cutoff level of 7.8 mmol/L or higher fasting PG.

We have found a close association between glucagon excursion and an impaired insulin secretion. An inverse correlation was observed in our study between glucagon rise and insulin secretion, as well as a positive correlation between pp glucagonemia and insulin resistance. This confirms the close interactions of irregularities in pp glucagon and insulin secretion with insulin resistance.

After 2 hours in the pp phase, the glucagon concentrations in all 3 study groups reached the premeal level, whereas PG and insulin concentrations remained considerably longer and increased. Probably, early glucagon secretion is particularly important for pp glucose regulation.

As shown by regression analysis (Table 4), 2-hour insulin response was the strongest determinant for the AUC of PG, followed by early glucagon increment in IGT. Multivariate data analysis is not intended to prove causal association between the dependant variable (pp hyperglycemia) and independent determinants. As this is a cross-sectional study, the abnormalities seen in glucagon secretion could be the consequence and not the cause of pp hyperglycemia. Future longitudinal studies should address this issue.

However, there was also a significant contribution of insulin resistance in the diabetic patient group. Both 2-hour insulin response and early insulin response, as well as insulin resistance, early glucagon increment, and BMI, were significant for pp hyperglycemia in total study population, which is rather strong, amounting to 86.9% of the variance.

Proinsulin excursion was a significant determinant for pp glycemia only in subjects with NGT. Previous studies have indicated that proinsulin is a marker for the development of T2DM [30,31].

In conclusion, our data show a diminished suppression of early glucagon release already in IGT. According to our data, a bihormonal imbalance starts before diabetes is diagnosed. Apparently, glucagon secretion anomalies are not only a phenomenon of advanced diabetes stage because of impaired paracrine effects by beta cells but also a primary disorder.

Prospective studies are needed to evaluate the impact of glucagon on the progression of glucose intolerance and the possible effects of medicinal suppression of glucagon to prevent the progression of glucose tolerance.

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