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Mini Review

Relevance of the Insulinogenic Index in the Metabolic Syndrome to the Insulin Secretory Response of the Endocrine Pancreas to Extracellular Glucose

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Abstract

The insulinogenic index to the insulin secretory response of the endocrine pancreas to extracellular glucose, i.e. the ratio between body weight and the square height was measured in 20 non-obese control subjects, 20 obese control subjects, and 60 male and 40 female patients affected by the metabolic syndrome. In the latter patients, comparisons were also made between non-diabetic and diabetic, as well as overweight and obese subjects. In the light of this information, it is proposed that a decrease in the pancreatic insulin stores otherwise available to ensure a suitable release of insulin may play a role in the perturbation of the insulinogenic index. The latter perturbation may also involve a phenomenon of so-called glucotoxicity, as could be assessed in patients affected by the metabolic syndrome by occurrence or either a paradoxical early decrease in insulinemia and/or an altered anomeric specificity of the pancreatic insulin release after intravenous administration of glucose.

Introduction

The plasma insulin/glucose ratio, i.e. the insulinogenic index is not listed among the biochemical markers of the metabolic syndrome. Yet, extensive prior studies conducted in several animal models of non-insulin-dependent diabetes have validated the use of this index to assess the pancreatic islet β-cell responsiveness to glucose [1]. The aim of the present study is to investigate in one hundred young adults affected by the metabolic syndrome the possible relevance of this index to the pathogenesis of the metabolic syndrome.

Subjects, Materials and Methods

The insulinogenic index was measured in 20 non-obese and 20 obese control subjects, in 60 male and 40 female patients affected by the metabolic syndrome. In these patients, attention was also paid to the comparison between non-obese, overweight and obese subjects and between non-diabetic and diabetic subjects. The criteria used to distinguish between non-obese, overweight and obese subjects were a body mass index of 25 Kg/m^2 (non-obese *versus* overweight subjects) and 30 Kg/m^2 (overweight *versus* obese subjects). A plasma glucose concentration of 7.0 mM after 12 hours of fasting was used to distinguish between non-diabetic and diabetic subjects.

Results

Table 1 provides the mean insulinogenic index found in non-obese and obese control subjects, as well as male and female MetS patients, non-diabetic and diabetic MetS patients, and overweight and obese MetS patients. As expected such a ratio was about twice higher ($p < 0.01$) in obese than non-obese control subjects. Despite comparable values for the BMI in the 60 male MetS patients (32.67 ± 0.30 kg/m^2) and 40 female MetS patients (32.75 ± 0.45 kg/m^2), the plasma insulin/glucose ratio was, modestly but significantly ($p < 0.01$), higher in female than male patients. The overall mean value for the plasma insulin/glucose ratio in the 100 MetS patients averaged 4.31 ± 0.07 μU/mol and, as such was significantly lower in these patients than in the obese control subjects. The insulinogenic index failed, however, to differ significantly ($p=0.70$) in overweight and truly obese MetS patients. The BMI averaged 31.57 ± 0.40 kg/m^2 and 33.30 ± 0.22 kg/m^2, respectively in 25 non-diabetic and 75 diabetic MetS patients. Despite such a minor difference in BMI, the mean insulinogenic index was obviously significantly higher ($p < 0.01$) in the non-diabetic than in the diabetic patients.

In the non-diabetic patients, only the correlations between the insulinogenic index and either HbA1C ($p < 0.01$) or TNF-($p < 0.05$) provided significant positive values, whilst that concerning GLP-1 provided a significant ($p < 0.01$) negative value. In the diabetic patients, however, significant positive correlations were observed between the insulinogenic index and either body mass index ($p < 0.01$), C-peptide ($p < 0.01$), HOMA index ($p < 0.01$), leptin ($p < 0.01$), hs-CRP ($p < 0.01$), total cholesterol ($p < 0.05$), triglycerides ($p < 0.05$) and interleukin-6 ($p < 0.05$), whilst the correlation between insulinogenic index and GLP-1 reached a significant ($p < 0.01$) negative value.

Discussion

As already mentioned in the introduction of the present report, the insulinogenic index, i.e. the plasma insulin/glucose ratio, is not listed among the markers of the metabolic syndrome. Yet, the present findings reinforce the usefulness of this insulinogenic index in assessing the changes occurring in patients affected by the metabolic syndrome as far as an essential pathophysiological aspects of this syndrome is concerned, mainly the insulin secretory response of the endocrine pancreas to extracellular glucose considered as the major regulator of insulin secretion.

Thus, the present findings are compatible with the well-known higher rate of insulin release in either obese control subjects or non-

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Table 1: Plasma insulin/glucose ratio.

Subjects	Glycemia (mM)	Insulinemia (mU/ml)	Insulin/glucosev ratio (mU per ml/mM)
Non-obese control subjects (n=20)	4.78 ± 0.11	11.05 ± 0.88	2.31 ± 0.17
Obese control subjects (n=20)	5.73 ± 0.07	28.18 ± 1.08	4.91 ± 0.16
Male MetS patients (n=60)	7.56 ± 0.15	30.97 ± 0.49	4.16 ± 0.08
Female MetS patients (n = 40)	7.42 ± 0.17	33.14 ± 0.54	4.53 ± 0.09
Non-diabeticMetS patients (n=25)	6.02 ± 0.08	30.38 ± 0.37	5.19 ± 0.12
DiabeticMetS patients (n = 75)	8.00 ± 0.09	32.33 ± 0.45	4.05 ± 0.07
OverweightMetS patients (n = 20)	6.82 ± 0.23	28.27 ± 0.38	4.26 ± 0.17
Obese MetS patients (n = 80)	7.68 ± 0.12	32.73 ± 0.40	4.32 ± 0.12

Table 2: Correlation analyses between insulinogenic index and selected variables in diabetic and non diabeticMetS patients.

BMI		C Peptide		HOMA index	
Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic
0.0853	0.3856	-0.3426	0.2859	-0.1173	0.2699
(p =0.68)	(p<0.01)	(p =0.09)	(p <0.01)	(p <0.57)	(p <0.01)
Glycated hemoglobin (HbA1C)		Total cholesterol		HDL-cholesterol	
Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic
0.5669	0.1765	0.2139	0.225	0.1897	0.0866
(p <0.01)	(p =0.12)	(p =0.30)	(p <0.05)	(p =0.36)	(p =0.46)
LDL-cholesterol		Triglycerides		Leptin	
Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic
0.1786	0.0626	0.0127	0.2155	0.0666	0.3781
(p =0.39)	(p =0.59)	(p =0.95)	(p <0.05)	(p =0.83)[a]	(p <0.01)[b]
Adiponectin		Interleukin-6		TNF-α	
Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic
-0.141+	-0.0563	0.2712	0.2747	0.5941	0.0426
(p =0.67)[c]	(p =0.69)[d]	(p =0.39)[a]	(p <0.05)[d]	(p <0.05)[f]	(p =0.76)[e]
hs-CRP		GLP-1			
Non diabetic	Diabetic	Non diabetic	Diabetic		
0.3484	0.656	0.2304	-0.4838		
(p =0.29)[c]	(p <0.01)[g]	(p =0.42)[f]	(p <0.01)[h]		

[a]n=12; [b]n=54; [c]n=11; [d]n=51; [e]n=52; [f]n=14; [g]n=39, [h]n=48. n=25 non diabetic and 75 diabetic patients affected by MetS in all other cases. BMI: Body Mass Index; HOMA: Homeostasis Model Assessment of Insulin Resistance; TNF-α: tumor necrosis factor -a; hs-CRP: high sensitive C Reactive Protein; GLP-1: Glucose Like Peptide-1.

diabetic MetS patients than in non-obese control subjects. They also suggest that the insulin secretory response of pancreatic islet B-cells to glucose is modestly but significantly decreased in MetS as compared to obese control subjects. Such a difference was observed when comparing either male or female MetS patients and either overweight or obese MetS patients, as well as diabetic MetS patients to obese control subjects. It was not observed, however, when comparing non-diabetic MetS patients to obese control subjects.

The obvious difference between the mean values for the insulinogenic index found in non-diabetic *versus* diabetic MetS patients appears compatible with the hypothesis that, in patients affected by the MetS, the insulin secretory response of the endocrine pancreas to extracellular glucose is indeed perturbed in parallel with the worsening of glucose homeostasis. Although the insulinogenic index is not corrected for the threshold value of glycemia required to augment insulin release above basal value, the present finding of a much higher plasma insulin/glucose ratio in obese than non-obese control subjects is consistent with the hypothesis that obesity, as caused by an imbalance between food intake and energy expenditure, eventually leads to a rise in insulin output and, possibly, even in the insulin secretory responsiveness of the endocrine pancreas to a given hexose concentration. It should not be ignored, however, that the rate of insulin secretion by the endocrine pancreas at a given extracellular glucose concentration may also be modulated by the amount of insulin stored in the pancreatic gland. In other words, a decrease of the insulinogenic index, as observed for instance in diabetic MetS patients, does not inform on the question whether the impaired release of insulin is attributable to an alteration of the process of glucose recognition by the B-cells as an insulin tropic agent, a decreased availability of insulin in the pancreatic gland or a combination of the latter two processes. The fact that a lower insulinogenic index in MetS patients than in control obese subjects prevailed in diabetic MetS patients, but not so in non-diabetic MetS patients, apparently

argues in favour of the second hypothesis mentioned in the preceding sentence, i.e. a decrease of the pancreatic insulin stores otherwise available to ensure a suitable release of insulin.

Alternatively, however, the dramatic difference between the insulinogenic index in non-diabetic and diabetic MetS patients may be attributable to the phenomenon of so-called glucotoxicity caused by the accumulation of glycogen in the pancreatic islet B-cells [2-6]. Prior investigations have documented that such an accumulation of glycogen accounts in diabetic subjects for both the early and transient paradoxical inhibition of insulin release and anomeric perturbation of glucose-induced insulin release both observed after intravenous administration of the hexose [7,9].

In conclusion, therefore, it is proposed that relevant information could be reached by following in the same MetS patients and over a suitable period the progressive changes in the early insulin emic response to either - or -D-glucose or the hexose at anomeric equilibrium following their intravenous administration.

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