ORIGINAL RESEARCH: Chronic Hypoxia Causes Disorder of Glucose Metabolism and a Specific Type of Diabetes

Antonio Gomez-Valdes*

Department of Internal Medicine, Havana University School of Medicine, Vedado, Havana, Cuba

Abstract: *Objective*: The purpose of this study was to show the existence of a specific hypoxic diabetes and investigate the effect of prolonged hypoxia on insulin.

Research Design and Methods: 101 patients diagnosed with hypoxic chronic obstructive pulmonary disease in its different stages participated in this study. Family and personal histories as well as other causes of diabetes were excluded. Blood glucose and serum insulin response to an oral glucose load were checked during fasting, 30, 60, 120, and, 180 minutes. Plasma glucagon, piruvato, and thyroid hormones were analyzed. Pulmonary function testing was performed.

Results: Impaired glucose tolerance in COPD patients were significantly higher than normal control ($p < 0.001$). The plasma glucose and serum insulin response during oral glucose tolerance test corresponded to a diabetic profile with pronounced hyperinsulinism ($p < 0.01$).

Conclusion: Our results showed that a specific hypoxic type of diabetes occurs under long-term hypoxic condition, affecting insulin synthesis and secretion.

Keywords: Long-term hypoxia, irreversible, pathways, glucose metabolism, hyperinsulinism, autocontrol, specific type.

INTRODUCTION

In previous report it was announced my finding that chronic respiratory failure was a cause of alteration of glucose metabolism and a possible diabetic condition. Family and personal history, diabetogenic factors such as steroids use were excluded. It was the first report in literature on this metabolic disorder [1, 2]. Since then, there has been valuable publications on this current research problem that supported our finding. One of them concluded that hypoxic patients have altered glucose metabolism [3]. The Third National Health and Nutrition Examination (NHANES III) survey results, has proved our discovery [4]. Our study was conducted to investigate the effect of prolonged hypoxia on insulin, and to show the development of a specific or secondary hypoxic diabetes.

MATERIAL & METHODS

Patients

101 patients with chronic obstructive pulmonary disease (COPD) were studied. 208 healthy control subjects as a control group, were selected from the Hispanic Healthy and Nutrition Survey (Jan-Feb, 1984). The COPD patients were classified according to the degree of pulmonary dysfunction (FEV_1), and clinically based on the intensity of cyanosis, dyspnea and right ventricular dysfunction. There was not obese, BMI= 21± 4. Average age was 55 years. Patients had no family and personal history of diabetes; women had not history of macrofetus, spontaneous abortion and perinatal mortality. Other specific diabetes were excluded, as well as hypertension, stress, steroids, and beta adrenergic agonist. Blood sample for glucose and insulin measurement was obtained at fasting and, 30, 60, 120 and 180 minutes after the oral glucose load (75 gm). Criteria for the diagnosis of diabetes were according to the American Diabetes Association (ADA) [5]. Serum insulin was analyzed by radioimmunoassay, as defined by the Quest Institute of Endocrinology Test. Hematology and chemical values, amylase, lactic acid, pyruvic acid glucagon and thyroid hormones were performed. Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio were also measured. Assessment of reversion of bronchial obstruction was tested using albuterol. Arterial blood gases (PAO_2, Pa CO_2, and O_2 Sat) were tested. Patient hospitalized, condition = 37.0 C, with a plastic gas syringe the sample from the radial artery was transported and, kept at room temperature mentioned, during 30 min before analyzed. The unit of measure was mmHg. Echocardiogram (ECHO) was performed. Patients had our personal medical tertiary care and, followed during a time-period of 10 years, in the Service of Internal Medicine. There was the best physician- patient relationship. This study was based on the results of medical care and, approved by a local Ethics Committee.

*Address correspondence to this author at 401 69 Street Apt. # 603, 33141, Miami Beach, FL, USA; E-mail: antoniongomez@aol.com

E-ISSN: 2310-9971/14

Statistical Analysis (Adjusted Model)

Again the COPD group was significantly older than the HH group and had no significantly higher number of males. After adjusting for the effects of age and sex, the COPD group was now 13 times more likely than the HH group to have diabetes mellitus (DM); this association was significant. Also, the COPD group was twice as likely as the control group to have pre-DM; this association was also significant. The 0.05 level was used to determine statistical significance SAS 9.2 (SAS Institute, Inc. Cary, NC) was used for all analysis.

RESULTS

From 101 COPD patients, 50 (50 %) had diabetes mellitus; 30 (30%) had pre-diabetes; 20 (20 %) were normal (<0.001) (Table **1**) Comparison DM *vs.* Normal (< 0.001). Pre-DM *vs.* Normal (<0.001). Mean reduction in the FEV_1 was 48 ± 20 %, and mean FEV_1 **/** FVC ratio was 58 ± 5 %. Mean PaO^2 was 60 % mmHg; O2 Sat 90% for DM; Pa O2 75%; O2 Sat 92m for IGT (Table **1**). There was significant correlation between the severity of hypoxemia and the magnitude of glucose alteration (Table **1**). The response of plasma glucose and serum insulin during OGTT was performed on 36 COPD patients, resulting in 8 diabetic associated to marked hyperinsulinism specially in the latter parts of the test and initially was slower than normal (Table **2** & Figure **1**) $p < 0.01$; CI < 95%. Also ten COPD patients had hyperinsulinism despite having normal OGTT. Mean FPG was 84.2 mg/dl; mean fasting serum insulin was 22 µU/ml.

DISCUSSION

Our study showed that long-term hypoxic condition in COPD patients develop alteration of glucose regulation including a hypoxic diabetic state, with effects on insulin, that are irreversible. This disorder commonly occurs 3 to 4 years after the onset of respiratory dysfunction This time can be reduced by intercurrent acute pulmonary infection such as pneumonia which increases hypoxemia, and the injury to the endocrine pancreatic tissue is very sensitive to poor oxygenation. Therefore, for an accurate assessment of the hypoxic effect on the glucose metabolism, it is necessary to estimate the appropriate time under hypoxic condition to understand of that the alteration take place. Unfortunately, this requirement is not always observed resulting in a false result. A

Table 1: Plasma Glucose Distribution, and Correlation with the Result of Spirometry, Blood Gases, and Chronic Lung Disease Stage

Stage of glucose disorders	n (%)	Spirometry			Blood gases		CCP
		Obstruction	Lung test				
DIABETES	50 (50%)	Irreversible	FEV_1 48±20	FEV_1/FVC 58±1	PO_2 66.4%	O_2 Sat 90	62.2%
IGT	30 (30%)	Irrevers (50%)	FEV_1 69±10	FEV_1/FVC 62±3	PO_2 80%	O_2 Sat 91	10%
NORMAL	20 (20%)	No obstruct	FEV_1 95±5%	FEV_1/FVC 8%	PO_2 95%	O_2 Sat 95	

Abbreviations: FEV_1 forced expiratory volume in 1 second. FVC forced vital capacity. CCP chronic cor pulmonale.

Table 2: Plasma Glucose and Insulin Response During OGTT in Chronic Hypoxic Pulmonary Disease. COPD Chronic Obstructive Pulmonary Disease. CCP Chronic Cor Pulmonale

Name	Sex	Age	Cyanosis	Diagnosis	Oral glucose tolerance test (mg/dl)					Insulinemia (µU/ml)				
					Fasting	30 m	60 m	120 m	180 m	Fasting	30 m	60 m	120 m	180 m
FC	F	42	+ +	COPD	72	144	202	213	210	15.6	30.6	192	78	213
TRP	F	57	+ + +	COPD	90	214	261	202	66	31.7	95.2	234	402.0	175.6
VPM	F	34	+ +	CCP	67	108	128	212	238	17.0	39.3	71.7	159.5	185.0
DGJ	M	68	+ + +	CCP	105	164	297	361	261	39.9	102.6	186.6	146.4	150.9
LSG	M	52	+	COPD	61	104	199	220	81	5.4	27.9	45.9	92.1	24.9
AQS	F	53	+ +	COPD	104	172	261	236	186	21.2	68.5	65.7	102.3	80.4
LPI	F	67	+ +	COPD	92	172	138	238	30	6.3	8.7	48.1	135.4	154
GRA	F	68	+ + +	CCP	83	150	218	210	97	44.8	127.3	191.7	295.8	142.21

Abbreviation: COPD chronic obstruction pulmonary disease. CCP chronic cor pulmonale.

significant high percentage of alteration of glucose metabolism was found in the population of our study'.

However, it can be deducted that all patients with COPD will develop timely metabolic disorder of glucose. Also, It was possible to note a positive correlation between the stage of glucose alteration and the degree of hypoxemia. Thus, when hypoxic COPD patients progress and reach the stage of chronic cor pulmonale (CCP) or chronic respiratory failure is associated with hyperglycemia. Our patients were not overweight but with tendency to lose weight. The exposure of young rats to hypoxia for 7 days led to loss of the body weight, due to hypoxic anorexia [7].

The response of blood glucose and serum insulin during OGTT performed to a group hypoxic COPD patients had the diagnostic criteria of diabetes associated to a marked hyperinsulinism. The insulin response was typical with the initial poor reaction of the pancreatic beta cells combined with exaggerated response in the latter part of the test (Figure **1**). This result is an objective evidence of the existence of a specific hypoxic diabetes. The influence of other causal factors was excluded. We propose that this hyperinsulinism is due, in part, to a compensatory response of the beta cells less affected by the hypoxic agent and the regenerated beta cells possibly, but unrelated with insulin resistance. Study in transgenic mice suggests that the presence beta cells, less injured lead to incomplete suppression of K_{ATP} channels activity can give rise to a maintained hyperinsulinism [8]. The regeneration of pancreatic beta cells can occur through several pathways [9]. The finding of hyperinsulinism in a group of 10 COPD patients with normal OGTT might be a predictable index of glucose intolerance. In these euglycemic COPD patients, our strategy was to follow the glucose regulation making periodic testing until the metabolic alteration, noticing the hypoxic degree.

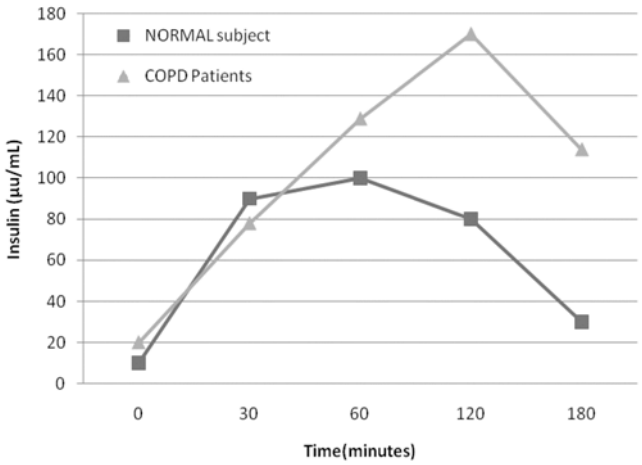

Figure 1: Serum insulin response to oral glucose (75 gm) in normal subject ■ and in hypoxic chronic obstructive pulmonary disease ▲.

It is well known that in many patients, the IGT in type II diabetes does not progress to overt diabetes or revert to normal. Conversely, once IGT or hyperglycemia by hypoxemia in COPD patients appears, it never reverts despite the improvement of the respiratory function. Also, it is well known that type 2 diabetes, its IGT and, obesity have insulin resistance, contrary to hypoxic diabetes in which insulin sensitivity is increased, as we have found in the research study and, in our medical practice. The hypersensitivity to the insulin has been shown at moderate and extreme altitudes [10, 11]. It is a controversial field, since for some researcher is normal [12] and for other is increased [13, 14]. It is important to emphasize that the effect of short-term hypoxia on glucose metabolism is temporal, reversible, as has been shown at altitudes and experimentally in the perfused pancreatic islets exposed to specific hypoxic level (9 min), insulin secretion was suppressed [15] and the second phase of insulin secretion was reduced by hypoxia [16]. Both alterations returned to normal function after the perfused pancreas was re-exposed to oxygenated solution.

Our finding or idea consider that long-term hypoxia in COPD patients causes the metabolic disorder of glucose and the effects on insulin that are irreversible. Chronic hypoxia has a central role in the pathogenesis of the disturbance, acting in two main ways: the direct action on beta cells and under long-term hypoxic condition. The former causes injury and damage to a cellular mass. This effect was clearly demonstrated in restricted area of insulin production with the HIT-1α expression [17]. Reasonably, this morphological alteration would decrease the intracellular ATP generation, decrease of glucose uptake, associated to the defect of insulin secretion. This change in the beta cell function can be expressed by membrane potential [8]. In the second way, when oxygen supply is poor as in hypoxic COPD, the oxidative decarboxylation of pyruvate to acetyl CoA is affected. The latter appears to be essential for insulin biosynthesis [18].

The clinical manifestations of hypoxic diabetes state is peculiar. It is a mild form, hyperglycemia is moderate, well tolerate, and easily controlled without insulin, anorexia and tendency to weight loss. There is

no ketosis prone, but diabetic state can complicate by an acute pulmonary infection commonly pneumonia, developing severe hyperglycemia and lactoacidosis. Then, if insulin is needed physician should be cautelous for avoid a fatal hypoglycemia as unfortunately has happened, due to marked hypersensitivity to insulin. This is one of the reason, it is imperative to know this variety of specific diabetes. We explain the characteristic of this variety of secondary diabetes through the autocontrol based on the compensatory mechanism of the hypoxic glycolysis and the hypersensitivity of the insulin. This mechanism could be adapted to the treatment of type 2 diabetes

Regarding to chronic complication, we have long observed the acceleration of coronary atherosclerosis in the course of the hypoxic COPD patients. It was recently shown *in vitro* [19]. The link between COPD and cardiovascular disease is not fully understood although the intake is possibly due to inflammation [20]. Thus, we propose that chronic hypoxemia and its diabetes play an important pathogenic role in coronary atherosclerosis.

Our results showed with direct evidence that chronic hypoxia causes disorder of glucose metabolism including a genuine hypoxic diabetes state accompanied with the effect on the synthesis and secretion of insulin. This conclusion has direct support of valuable experimental research work referred. It is crucial to know this specific diabetes by the implications in the medical practice and future research.

ACKNOWLEDGEMENT

Thank Prof. K. Arheart for his masterly statistical work. Thank Prof. Mateo de Acosta and his colleagues for the support and the assay of hormones. I am grateful to Profs; Jose Buchaca, Virgilio Beato (Internal Medicine) for support; A. Becerra Fdez and Julio Pita (Endocrinologits) who reviewed critically the manuscript. Thank Milly Millet, Loudes Blanco and my daughter Audrey for their help such as language advise. Thank Calder Library of Miami University in the person of J.Garcia-Barcena. I dedicate this research work to the memory of my teacher Prof Antonio San Martin Marichal.

FUNDING

This study did not have specific funding, It was the cost incurred those corresponding to the medical care as impatient and outpatient. All was funded by universitary hospital.

COMPETING INTERESTS

The author has no competing interests that might be perceived to influence the results of the research. This manuscript is unpublished.

REFERENCES

[1] Gómez-Valdés A. Insuficiencia respiratoria cronica: otra causa de diabetes. Cuban J of Med 1971; Vol. 10: 43-64. (In Spanish).

[2] Gomez-Valdes A. Chronic hypoxia: Another cause of Diabetic State Memories of XIII International Congress of Internal Medicine. Helsinki Find 1976.

[3] Hjalmarsen A, Assebo U, Birkeland K. Impaired glucuse tolerance in patients with chronic hypoxic pulmonary disease. Diabetes Metab 1998; 22: 32-42.

[4] Third National Health and Nutrition Examination Survey (NHANES III) 1988-94

[5] Am Diabetes Ass (ADA) & WHO: Diabetes Care Vol. 26. Supplement 2003.

[6] Quest Diagnostic and Nichols Institute. 1998. (Second edition).

[7] Raff H, Burden ED, Jankouski BM. The effect of hypoxia on plasma insulin and lepsin in newborn and juvenile rats. Endocrine J 1999; 11: 37-39. http://dx.doi.org/10.1385/ENDO:11:1:37

[8] Koster JC, Remedi MS, Flagg TP, *et al*. Hyperinsulinism induced by targeted suppression of beta cell KATP channels. Proc Natl Acad Sci USA 2002; 96: 16992-7. http://dx.doi.org/10.1073/pnas.012479199

[9] Oyama K, Minami K, Ichsaki K, Fuse M, Miki T, Seino S. Spontaneous recovery from hyperglycemia by regeneration of pancreatic β Cells in Kir6.2G132S transgenic mice. Diabetes 2006; 55: 1930-8. http://dx.doi.org/10.2337/db05-1459

[10] Lechleitner M, Insulin sensitivity increases at moderate altitudes. 11 ECO) Europe Congress 2000.

[11] Moore K, Vizzard N, Coleman, McMahon J, Hayes R, Thompson CJ. Extreme altitude mountaineering in Type I diabetes; the Diabetes Federation of Ireland Kilimanjaro Expedition Diabetes. Diabet Med 2001; 18: 749-55. http://dx.doi.org/10.1046/j.0742-3071.2001.00568.x

[12] Jakobsson P, Jorfeldt L, Von Schenck. Insulin resistance is not exhibited by advance chronic pulmonary disease patients. Clin Physiol 1995; 15: 547-55. http://dx.doi.org/10.1111/j.1475-097X.1995.tb00543.x

[13] Suerwein HP, Schols AMWJ. Glucose metabolism in chronic lung disease. Clin Nutr 2002; 21: 367-71. http://dx.doi.org/10.1054/clnu.2002.0561

[14] Gamboa JL, Garcia-Casarin ML, Andrade FN. Chronic hypoxia increases insulin-stimulated glucose uptake in mouse soleus muscle. Am J Physiol 2010; 100: R85-91.

[15] Narimiya M, Yamada H, Matsuba I, Ikeda YU, Tanese T, Abe M. The effect of hypoxia on insulin and glucagon secretion in the perfused pancreas of the rat. Endocrinology 1982; 111: 1010-4. http://dx.doi.org/10.1210/endo-111-3-1010

[16] Dionne KE, Colton CK, Yarmush ML. Effect of hypoxia on insulin secretion by isolated rats and canine islets. Diabetes 1993; 42: 12-21. http://dx.doi.org/10.2337/diab.42.1.12

[17] Moritz W, Meier F, Stroka DM, *et al*. Apoptosis in human pancreatic islets correlates with HIF-1alpha expression. FASEB J 2002; 16: 745-7.

[18] Alarcon C, Wicksteed B, Prentki M, Corkey BE, Rhodes CJ. Succinate is a preferential metabolic stimulus-coupling signal for glucose-induced proinsulin biosynthesis translation. Diabetes 2002; 51: 2496-504. http://dx.doi.org/10.2337/diabetes.51.8.2496

[19] Humar R, Kiefer FN, Berns H, Resink TJ, Battegay EJ. Hypoxia enhances vascular cell proliferation and angiogenesis *in vitro via* rapamycin (mTOR)-dependent signaling. FASEB J 2002; 16: 771-80. http://dx.doi.org/10.1096/fj.01-0658com

[20] Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. Eur Respir J 2006; 28: 1245-57. http://dx.doi.org/10.1183/09031936.00133805

Received on 23-04-2014 Accepted on 12-06-2014 Published on 14-07-2014

DOI: http://dx.doi.org/10.12970/2310-9971.2014.02.02.3